inflammation.life

Compiled by Jason Howard

"So we're combating inflammation throughout our lives, you can basically think of life and diet as a fight against inflammation, adequate nutrition while we try to minimize inflammation, because inflammation is just constantly wearing and tearing on our tissues, it's breaking us, it's breaking us down. And eventually, it's why we age. So we're always putting out the fire of inflammation."

-Dr. James Kneller M.D.

https://www.youtube.com/watch?v=lnCkSRHqdZc
http://bit.do/drkneller

"Understanding the process' of inflammation, is paramount to maintaining health." - J.H

FOR EDUCATIONAL PURPOSE ONLY

★

4st Edition - 8/22/2022

"Man is what he eats"

—(Ludwig Feuerbach, 1826)

Dedication

✧

This book is dedicated to

★★★★★

Michael James "Jim" Harris

to Papa, you will always be on our mind and in our hearts.

★★★★

Sgt. Chad Lane Williams

Dedicated soldier, leader, mentor and warrior who will always be remembered.

★★★

EJ.G.H

May you dedicate your life to knowledge, positive energy, and helping others.

★★

My Family

Thank you for your support and encouragement.

★

The Researchers

For without the scientists and medical doctors involved in these discoveries, none of this would have been possible.

About this Book

I joined the U.S Army in 2006 and after training in Germany, I deployed to Iraq in 2008. In July of that year I had a run in with 2 landmines in one week. This sent me down a journey of experiencing the effects of a traumatic Brain injury, migraines, PTSD, memory loss, gut issues and sleeping issues. I was prescribed many medications over the course of the coming years following those injuries but eventually the side effects from them became too much and seem to further dysregulate my body. So I wanted to find other options that wouldn't cause so many stomach issues and withdrawal symptoms. It wasn't until much later that I realized that inflammation was further progressing my health issues and that it was crucial to figure out how to regulate inflammation in my body, otherwise I would feel much worse.

Shortly after starting down this path of reading medical research about the body. I found out that my squad leader Sgt. Williams committed suicide. This really pushed me even further to read as much as I could find on mental health and other conditions affecting veterans and active military. A family member at that time, was also dealing with cancer which was another driving force that made me look into all aspects of human health. These events in my life were the catalyst of this project, now I hope to pass on this information on to anyone who is interested in learning more about health.

The layout

I have attempted to compile as many conditions and topics with a focus on inflammation and the systems or compounds which regulate or cause inflammation in the body. You will see some, but not all, categories linked with double blue underline, these links are still being developed, and unfortunately these clickable links currently only work in epub format, but future updates may fix this issue in other formats. The table of contents is clickable and should navigate to the category in the book in most common PDF readers.

Insights from the Research

What I have come to realize from reading a vast amount of medical research over many years as well as what other medical professionals are saying, is that many common conditions considered as "Diseases of Civilizations" as well as the conditions veterans and active military are

facing, involve ongoing dysregulated inflammation that isn't being addressed which can lead to chronic diseases and further mental health issues or age related neurological diseases. An injury, ongoing stress, or infection maybe the catalyst which initiates the inflammation. In other cases, diet can play crucial role in promoting an inflammatory state in the body over time and can become a major problem even in childhood. Various combinations of medications, alcohol or other vices can also cause inflammation. Inflammation in aging, known as "Inflammaging", refers to the the chronic low grade inflammation seen in aging. In any case it is imperative that people learn how to regulate the inflammation in the body through understanding the way the body regulates inflammation and which foods are inflammatory, otherwise it can be deadly, leading to wide range of potential medical conditions as the research is showing throughout this book.

This collection of research is an attempt to consolidate a fraction of the research out there, in hopes that it may somehow help someone, somewhere in the world. This project is ongoing so please check back online at inflammation.life for updates and consider adding your email to our email newsletter so you can be notified of major updates.

Regulating Inflammation

The body initiates inflammation and regulates it, through a wide range of lipids as part of the bodies healing process. These lipids[1], receptors, and enzymes which recycle these lipids, function universally throughout the body and make up the The Endocannabinoid System(ECS). This system is a bi-directional lipid signaling system and the universal regulator[2] of all mammals. It is the largest neurotransmitter system in the human body[3], however, it is not being taught in medical school at all, or in any great detail,[4,5,6,7] despite its crucial role in maintaining human health.[8] While mammalian cells contain between 1000-2000 lipids species[9], we will be discussing a select few crucial lipids in this book to understand the bodies pro-inflammatory &

[1] also referred to as endogenous ligands - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770351/

[2] https://www.jyi.org/2018-june/2018/6/1/the-endocannabinoid-system-our-universal-regulator

[3] Dr. Michelle Ross Ph.D - Neuroscientist - http://bit.do/drross2

[4] Dr. Robert Melamede PhD - https://www.youtube.com/watch?v=3qkhwaETnjw

[5] Dr. Uma Dhanabalan M.D MPH FAAFP MRO - http://bit.do/druma

[6] Dr. David B. Allen, M.D - Retired Heart Surgeon - http://bit.do/ecssurvey

[7] Dr. Bradstreet, M.D - http://bit.do/drbradstreet

[8] See Endocannabinoid System and other categories throughout this book

[9] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2293298/

anti-inflammatory regulatory process. Our ECS requires a balance of these pro-inflammatory lipids, otherwise it becomes overactive in a pro-inflammatory manner which can be destructive to the bodies tissues, gut, organs and brain, and can be detrimental to mental health and speed up the aging process.

To maintain an anti-inflammatory state, the body must obtain adequate daily amounts of the correct ratio of omegas while also avoiding inflammatory foods. You are probably familiar with the two main omegas, omega-3s and omega-6s these are known as Polyunsaturated fatty acids (PUFAs). In regards to omega-3s there are three main omega-3 fatty acids derivatives. They are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). These three omega-3s are essential to the body, meaning the body is unable to make them on its own and must be acquired from diet.[10] ALA is found mostly in plants, nuts and seeds in varying amounts. DHA and EPA are found primarily in fatty fish, which eat algae and other aquatic plant-life which contains DHA and EPA.[11] ALA is by far the most common omega-3 found in nature, and is not biologically active until its converted into EPA or DHA by the body. The body can convert approximately 1 - 10% of ALA into EPA and only about 0.5% - 5% of ALA can be converted into DHA.[12,13,14,15] This conversion rate also is dependent on the levels of other nutrients in the body such as vitamin B6, B7, calcium, copper, iron, magnesium, and zinc.[16] In healthy young women the conversion rate tends to be slightly higher than men, due to estrogen.[17,18,19] From omega-3s the body can produce a wide range of mostly anti-inflammatory lipids; endocannabinoids, resolvins, protectins, and maresins. All of which have have a wide range of functions throughout the body and brain. These resolving mediators are critical during the resolution phase of acute inflammation and are important at stopping the inflammation once the problem is eliminated.[20] Ultimately the brain and body are trying to maintain adequate amounts of DHA & EPA in order to maintain the high amount of DHA found in the brain so that it can produce enough on-demand lipids to maintain an anti-inflammatory state and be

[10] https://ods.od.nih.gov/factsheets/Omega3FattyAcids-Consumer

[11] https://www.health.harvard.edu/heart-health/omega-3-rich-foods-good-for-your-heart

[12] https://pubmed.ncbi.nlm.nih.gov/11844977/

[13] https://pubmed.ncbi.nlm.nih.gov/9637947/

[14] https://pubmed.ncbi.nlm.nih.gov/17622276/

[15] https://pubmed.ncbi.nlm.nih.gov/12323090/

[16] https://www.healthline.com/nutrition/3-types-of-omega-3

[17] https://pubmed.ncbi.nlm.nih.gov/12323090/

[18] https://pubmed.ncbi.nlm.nih.gov/15075703/

[19] https://pubmed.ncbi.nlm.nih.gov/15531662/

[20] https://www.sciencedirect.com/science/article/abs/pii/S1388198114001619

prepared for various injuries that may occur throughout our life. It can however, be difficult to acquire higher amounts of DHA with western diets, due to the higher amounts of omega-6s.

The most common omega-6 is linoleic acid (LA), which the body is able to convert into the longer omega-6 fats such as arachidonic acid (AA) which are then converted into mostly pro-inflammatory lipids. The major problem with western diet is that it is very high in omega-6s and low in omega-3s.[21] Omega-6 (LA) use the same conversion enzymes as omega-3 (ALA). With western diet no longer having an omega 6/3 ratio of 1:1 this causes the body to eventually overproduce pro-inflammatory lipids due to over consumption of AA and LA, this can lead to chronic inflammation and an over active ECS. This is a problem because chronic disease is driven by inflammation.[22] Many of the over counter anti-inflammatory medications and a number of prescriptions target the omega-6 pathway to regulate inflammation in various diseases and mental health.[23,24,25] However inhibiting pro-inflammatory lipids are having detrimental consequences to human health.[26] Because pro-inflammatory lipids are an important part of cellular functions and healing. Concentrations of LA can stick around in adipose tissue[27] for approximately 2 years, the increase in the amount of LA paralleled the increase in prevalence of diabetes, obesity, coronary artery disease and asthma. This provides compelling evidence that Omega-3 (DHA/EPA) protect, and excessive omega-6 (LA/AA) promotes heart disease, obesity, diabetes, pain, non-alcoholic fatty liver disease and more.[28,29]

Drugs specifically targeting the omega-6 pro-inflammatory pathways make up over 25% of pharmaceutical companies annual sales.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3583533/

[21] see Omega Ratio

[22] Dr. Barry Sears - https://pubmed.ncbi.nlm.nih.gov/26400429

[23] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3583533

[24] https://www.ncbi.nlm.nih.gov/pubmed/29610056

[25] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537720

[26] See NSAIDs, Interstitial Nephritis, Prostaglandins

[27] commonly known as body fat

[28] https://openheart.bmj.com/content/5/2/e000898

[29] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6274989/

The Endocannabinoid System (ECS) & Healing

Exercise has long been shown to increase wound healing, improve inflammatory markers, and many other benefits.[30] Exercise can also be damaging to our joints, muscles and bones. For this reason, mammals have the ECS which is activated when we exercise. Our body has cannabinoid receptors in essentially all cells of the human body.[31] These receptors are known as Cannabinoid Receptor type 1 (CB1) and Cannabinoid Receptor type 2 (CB2) which are excited during movement and exercise. When these receptors are excited, the body releases **endo**genous[32] cannabinoids also known as **endo**cannabinoids these are fat like lipids our body makes from the correct ratio of omegas.[33] Cannabis is a plant that contains over 80 different **phyto**cannabinoids. These fat like lipids interact with our ECS in various way to promote homeostasis.

THC [Tetrahydrocannabinol] is a phytocannabinoid which sticks to our cannabinoid receptors, exciting them causing a longer release of endocannabinoids. This is one of the major reasons that exercise and cannabis both induce a runner's high.[34,35] ECS is how the body regulates body temperature, immune system, inflammation, pain, stress, healing, senses, cardiovascular system, nervous system, digestive system, endocrine system, skin, gut, skeleton, oxidative stress, cell signaling and much more. If the body has the right omegas and nutrients then the body can produce its own cannabis like cannabinoids. In fact, anandamide an endocannabinoid made by the body mimics many of same effects as the phytocannabinoid THC. But as we get older and move around less an less, this "runner's high" doesn't occur as much. With less exercise induced endocannabinoid signaling this can lead to a wide range of problems due to importance of activating this cell signaling in the body and to maintain an anti-inflammatory state in the body and cell signaling.[36] It is important to note, that some injuries can also make it more difficult to produce lipids efficiently.[37]

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[30] https://digitalcommons.wku.edu/cgi/viewcontent.cgi?article=1272&context=ijes

[31] https://bit.ly/3T1h74p (short list)

[32] having an internal cause or origin. - Oxford languages / Google

[33] https://www.sciencedaily.com/releases/2017/07/170718142909.htm

[34] https://jeb.biologists.org/content/215/8/1331

[35] See Exercise

[36] https://pubmed.ncbi.nlm.nih.gov/12044936/

[37] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2293298/

> "Our Endocannabinoid System [ECS] regulates everything in our body. Our Immune system, digestive system, cardiovascular system, nervous system, endocrine system, skin, skeleton, everything in our body is homeostatically regulated by our Endocannabinoid System. And yet it's not taught in medical schools? There's something a little flawed here..."
>
> - Dr. Robert Melamede Ph.D
> bit.do/drbob

Clinical Endocannabinoid Deficiency (CECD)

Often times the root of a medical condition tends to be overlooked in favor of treating the symptoms rather than the cause. [38] Many conditions in the future maybe considered as CECD.[39] Many conditions have already been linked to CECD such as Post traumatic stress disorder (PTSD), Irritable bowel syndrome (IBS), autism, Chronic traumatic encephalopathy (CTE), Major Depression, Bipolar, Autism and more. There are many more have yet to be classified as CECD. This doesn't include the many conditions linked to high omega-6/3 ratio which is crucial to maintaining adequate amount of anti-inflammatory lipids such as endocannabinoids etc and maintaining our ECS and an anti-inflammatory state. So its is absolutely circuital to human health to maintain our Endocannabinoid System to avoid CECD and the cascade of medical problems that come with it.

Omega-3 Supplementation Warning

Due to the low conversion rate for omega-3 (ALA) as discussed above, most American's are probably deficient in Omega-3s (DHA & EPA).[40] It is also alarming that most clinicians do not currently check the omega-3s status and omega ratios as standard practice of care.[41] This is especially concerning considering that DHA is suppose to be highly concentrated in the brain and

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[38] Dr. Habib - https://www.youtube.com/watch?v=m-2zWeiyFS8

[39] Dr. Michelle Ross Ph.D - Neuroscientist - http://bit.do/drross2

[40] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645

[41] https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional

eyes and critical for normal brain development and eye sight.[42] A number of research papers which use omega-3s supplements tend to have varying results and this is dependent on the source of the supplements. It is important to acquire you omega-3s in the form of ALA, DHA, and EPA from diet. Such as kale, chia seeds, flax, walnuts, fatty (non-farmed) fish to name a few. Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol.[43] Unfortunately, there are no shortcuts to health, but a healthy meal plan.

Western Diet

Due to over consumption of cooking oils, animal products, wheat, processed foods, high carbohydrates consumption and Genetically Modified Organisms (GMO) foods all tend to push inflammation and overload the body with toxins. This can affect people at various periods in their life from childhood to adulthood.

Cooking oils have became quite popular over the last 100 years. However most of them have a high omega-6 to omega-3 profile (even olive oil) and can contain heavy metals.[44,45]

Animal products have various problems when it comes to inflammatory components. When it comes to dairy, a major concern is casein protein which is makes up 80% of the protein in cow milk has been found to be cancerous.[46,47] Casein has also been found to be a casual trigger for type 1 diabetes.[48] It has also been found to promote intestinal inflammation and exacerbated gastrointestinal symptoms.[49]

Animal products contain Neu5Gc, which has been linked to inflammation and cancer.[50] There has also been a number of studies which has linked meat consumption to various conditions such as a diabetes[51], atherosclerosis[52], cardiometabolic health[53], heart disease[54] and various

[42] https://www.karger.com/Article/Fulltext/448262

[43] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5596017

[44] See Cooking Oils

[45] https://www.ocl-journal.org/articles/ocl/full_html/2014/01/ocl130041/ocl130041.html

[46] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5149046/

[47] Dr. T. Colin Campbell, PhD - https://www.youtube.com/watch?v=xEWAf6sOGv0

[48] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5518798

[49] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5657040/

[50] See Neu5gc

[51] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3942738/

[52] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315380/

cancers.[55] Consumption of organic meat does not diminish the carcinogenic potential associated with the intake of persistent organic pollutants (POPs).[56] High omega-6 is another factor to consider when consuming animal products.

GMO foods often contain high amounts of of glyphosate, a herbicide, which affects gut bacteria, and inhibits the body to uptake nutrients.[57]

Final Thoughts

This project was started to get the conversation going on an important topic in health, regulating inflammation and how our ECS regulates the body. One review suggested that it takes an average of up to 17 years for research to be integrated into a physicians practice.[58] After my injuries the topic of diet, omegas, & inflammation was never a conversation with any medical professional, I visited, up until I went to a functional medicine office and the nurse practitioner knew more about omega ratio and inflammation than any doctor I had ever met. My hopes is that you will share this information with other medical professionals, friends and family, so we can share more knowledge about the body manages inflammation and avoid inflammatory complications and oxidative stress when our ECS isn't functioning at 100%. If you have any feedback, suggestions or fixes, please contact me at inflammation.life@gmail.com

Treating the Root of the Disease not the Symptom

"I'd like to challenge you with a couple of questions. Would you like to have the best cardiac doctor, or the best cancer doctor? Or would you rather prevent it? That's an interesting concept. Well, let's look at how we practice medicine right now. If you have high cholesterol, and you use a pill to lower it, what happens when you stop the pill? If you have high blood pressure, and you stop the blood pressure pill? What happens to the blood pressure? If you use a diabetic pill to lower the sugar? What happens when you stop the blood sugar? If the answer is that the

[53] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3483430/

[54] https://www.ncbi.nlm.nih.gov/m/pubmed/21912836/

[55] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769029/

[56] https://www.ncbi.nlm.nih.gov/m/pubmed/25893622/

[57] See Genetically Modified Organisms (GMO)

[58] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1497798

problem didn't go away? Did you merely control it? Or did you actually treat it? That's a fundamental question. Because to me, treatment means fixing the root cause. Let me give you a second challenge, which might help bring out the concept of the root cause. Did you know that 50% of patients who had had a heart attack had normal cholesterol ? Did you know that diabetics whose sugars are under control had twice as many heart attacks. That should shock you. Well, let me tell you what the underlying problems are to almost all diseases. It's oxidation, inflammation, immune dysregulation, from two dimensional medicine of merely controlling numbers, we now move into three dimensional medicine, dealing with the underlying cause where all the organ systems are communicating with each other. And as a result, there are markers that are leading to diseases, a concept that may make sense for you is as we get older, our function goes down. That's logical. Correct. And in medicine, we have a term. It's called age related diseases, namely, dementia, arthritis, mature onset diabetes, even heart disease and cancer come later in life. Wouldn't it make sense, therefore, to understand the five stages of cell decline, where most doctors are identifying disease at stages three, and four? I'd like to understand stages one and two. That's a fundamental concept of predicting, preventing and prolonging life."....

- Dr. Habib M.D

https://www.youtube.com/watch?v=m-2zWeiyFS8

nexthealthmed.com

Table of Contents

Relax, Eat, Sleep, Forget

….“It was about six years ago that i started to learn that I knew nothing nothing about a system known as the endocannabinoid system. Today I say that system is life, homeostasis balance, later I learned Dr. Dimarzio describes a system in five beautiful words he said that this system is meant for us to relax, eat, sleep, forget and protect that has become my mantra about the system when i look at these five beautiful words an imbalance in these words could cause illnesses or diseases if someone muscle could not relax and they were in a constant spasticity or their muscle hang and placid, imbalance, if they ate too much in obesity or they couldn't eat enough as in anorexia or if they slept too much as in depression or they couldn't sleep as an insomnia if they forgot too much as in Alzheimer's or in dementia where or they didn't forget enough as in patients with PTS [aka PTSD] and protection, if your body is overprotected you had autoimmune illnesses like lupus, MS, cystic fibrosis, just to name a few, or if you couldn't fight off an infection like people that have diabetes or people that have been treated with cancer. So these five words mean a lot to me, relax, eat, sleep, forget and protect and that's what I look at the endocannabinoid system. In all my years of education I had never learned about it and to this day only 15% of the medical schools even teach it. It was after my mother died and my contract ended that i became involved and started to pursue This is my career. Today I'm proud to say I am a cannabis therapeutics specialist that's been certified with the American Academy of cannabinoid medicine. I Dr. Ouma danabol and does not contribute to the opioid epidemic. I have not written an opioid prescription in over eight years, I have seen several 1000s of patients. And I make the statement. cannabis is not an entrance drug. It's an exit drug from pharmaceuticals and narcotics.”…

-Dr. Uma Dhanabalan M.D MPH FAAFP MRO
http://bit.do/druma

Acetaminophen

Acetaminophen (Paracetamol, Tylenol etc) is an analgesic drug used to relieve mild or chronic pain and to reduce fever, often as an alternative to aspirin. Proprietary names include Tylenol.

-Oxford/Google

Acetaminophen **(Paracetamol, Tylenol etc)** has many brands and variants to include over the counter and over 600 prescriptions contain some variation of this medication. Please consult a medical professional to see if a particular medication contains any variant of Acetaminophen. AM404 **is an active metabolite of Acetaminophen, which is a synthetic re-uptake inhibitor and a synthetic lipid similar to** Anandamide (AEA)

See also: Partial List of Acetaminophen Containing Brands

…"These data suggest that paracetamol use is a risk factor for fracture, although the mechanism of action remains unclear."

-School of Medicine, Deakin University, Australia; Department of Psychiatry, University of Melbourne, Australia.
https://pubmed.ncbi.nlm.nih.gov/21396491

Paracetamol has been shown in research to reduces the amount of prostaglandins the body is producing. These lipids are derived from omega-6 (Arachidonic Acid). This could explain why Paracetamol is a risk factor for bone fractures and other medical issues, due to potential prostaglandins deficiency, Interstitial Nephritis and liver injures.

…"One class of factors that could mediate certain events of fracture healing is the prostaglandins. The effects of prostaglandins on bone metabolism are complex because prostaglandins can stimulate bone formation as well as bone resorption.[6] Prostaglandins are synthesized by osteoblasts, and different cell stimuli can alter the amount and possibly the spectrum of prostaglandins produced by osteoblasts.[7-9] Therefore, signal transduction, mechanical perturbations, or other physiological signals can affect bone metabolism through alteration of prostaglandin production."…

-Department of Orthopaedics, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark 07103, USA.
https://asbmr.onlinelibrary.wiley.com/doi/full/10.1359/jbmr.2002.17.6.963

"Acetaminophen (APAP), a major cause of acute liver injury in the Western world, is mediated by metabolism and oxidative stress. "…

-Department of Pharmacology and Toxicology, Radboud University Nijmegen Medical Centre, Nijmegen, The

Netherlands.
https://pubmed.ncbi.nlm.nih.gov/22610607

Effect of Paracetamol (Acetaminophen) On Haematological and Reproductive Parameters in Male Albino Rats

"Paracetamol (acetaminophen) is a widely used over-the-counter analgesic and antipyretic drugs. Several studies have reported the toxic, gastrointestinal and musculoskeletal effect of this drug, but there is scanty information on its effect on blood chemistry and reproduction in albino rats. This study was designed to investigate the effect of this drug on haematological and reproductive parameters in male albino rats. Paracetamol (7. 5 mg/kg BW) was administered to the rats for 42 days (six weeks) for haematological and andrological study. Distilled water (0. 5 ml) served as control. Red Blood Cell (RBC) and Total White Blood Cell (TWBC) counts were determined using haemocytometer. PCV was determined by micro-haematocrit method. Semen analyses were done microscopically. Data were analysed using student's t-test at $p<0.05$. Treatment of rats with paracetamol caused decrease in PCV and RBC counts relative to the controls. Treatment of rats with paracetamol also caused significant decrease in sperm motility and sperm count, but did not produce any pathological lesions on the testes. These findings indicate that paracetamol caused deleterious effect on the blood chemistry and reproductive parameters in male albino rats."…

-Department of Physiology, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology
-Department of physiology, College of Medicine, University of Ibadan, Ibadan, Nigeria.
http://www.iosrjournals.org/iosr-jpbs/papers/Vol4-issue6/O0466570.pdf

See also Interstitial Nephritis , prostaglandins

Abdominal Aortic Aneurysm (AAA)

"An abdominal aortic aneurysm (AAA) is a blood-filled bulge or ballooning in a part of your aorta that runs through your abdomen. Over time, this bulge in your aorta can become weak, and the force of normal blood pressure can cause it to rupture. This can lead to severe pain and massive internal bleeding, or hemorrhage."

-Medtronic

https://www.medtronic.com/us-en/patients/conditions/abdominal-aortic-aneurysm.html

Arachidonic Acid, but Not Omega-3 Index, Relates to the Prevalence and Progression of Abdominal Aortic Aneurysm in a Population-Based Study of Danish Men

"Animal models support dietary omega-3 fatty acids protection against abdominal aortic aneurysm (AAA), but clinical data are scarce. The sum of red blood cell proportions of the omega-3 eicosapentaenoic and docosahexaenoic acids, known as omega-3 index, is a valid surrogate for long-term omega-3 intake. We investigated the association between the omega-3 index and the prevalence and progression of AAA. We also investigated associations between AAA and arachidonic acid, an omega-6 fatty acid that is a substrate for proinflammatory lipid mediators."…

Conclusions

"Omega-3 index is unrelated to men with AAA from a country in which fish consumption is customarily high. Arachidonic acid is associated with AAA presence and progression."…

-Elitary Research Centre of Individualized Medicine in Arterial Disease (CIMA), Department of Cardiothoracic and Vascular Surgery, Odense University Hospital, Odense, Denmark,

-CIBERCV, Instituto de Salud Carlos III (ISCIII), Madrid, Spain,

-Vascular Research Lab., FIIS-Fundación Jiménez Díaz, Autónoma University, Madrid, Spain,

-CIBEROBN, Instituto de Salud Carlos III (ISCIII), Madrid, Spain,

-Lipid Clinic, Endocrinology and Nutrition Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850259

Low Serum Levels of EPA are Associated with the Size and Growth Rate of Abdominal Aortic Aneurysm

"Omega-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been reported to reduce the risk of cardiovascular disease. However, whether omega-3 PUFAs are involved in the pathogenesis of abdominal aortic aneurysms (AAA) remains unclear."…

"EPA levels in patients with AAA were relatively low. Low serum EPA levels and EPA/AA ratio were associated with the size and growth rate of AAA."…

-Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

-Department of Cardiovascular Surgery, Juntendo University Graduate School of Medicine, Tokyo, Japan

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5587517

Activation of Endocannabinoid System Is Associated with Persistent Inflammation in Human Aortic Aneurysm

…"Several studies investigated mechanisms in pathogenesis of human aortic aneurysm. Beside the genetically well-described diseases [3, 4], there are a growing number of studies reporting molecular mediators and cellular interactions in the aortic aneurysmatic wall. Inflammation has been postulated as a major factor during development of abdominal aortic aneurysms [7] and has not yet been reported in aneurysms of the ascending aorta. Since regulation of inflammatory response and tissue remodeling are the major effects mediated by the endocannabinoid system [14, 15], we investigated it in aneurysms of ascending aorta.

With respect to the published data, we here provide novel evidence for the activation of the endocannabinoid system in human aortic aneurysms. The higher mRNA levels of the four receptors (CB1, CB2, TRPV1, and GRP55) show together with differential levels of their ligands in the tissue an activated endocannabinoid system in human aneurysms. The lower tissue amount of arachidonic acid, a degradation product of both endocannabinoids, also supports this assumption, indicating prolonged demand for endocannabinoids in aneurysmatic tissue. Since the published data suggest a regulatory role of AEA in inflammatory response, the lower AEA tissue amount could be associated with lower expression of IL-6 and CCL2. Still, our data also show higher M-CSF and PPARγ expression, and in the lack of experimental evidence we can only speculate whether this finding is linked to the increased 2-AG tissue amount. To our knowledge, a distinct association of the two known endocannabinoids with specific mediators of inflammatory response has not yet been dissected. The endocannabinoid-mediated fine-tuning of inflammatory reaction involves several mediators acting on different cell types [14]. Our data on the newly recruited leukocytes show no difference between aneurysms and controls but reveal a constant low-level infiltration of them into the adventitia of the aortic wall. This action of inflammatory cells underlines their role in homeostatic regulation of the aortic wall tissue, representing not only inflammation, but also tissue remodeling or regeneration. "…

-Department of Cardiac Surgery, University Clinical Centre Bonn, Sigmund-Freud Street 25, Bonn, Germany

-Institute of Molecular Psychiatry, Life & Brain Center, Sigmund-Freud Street 25, Bonn, Germany

-Institute of Physiological Chemistry, University Medical Centre of the Johannes Gutenberg University Mainz, Duesbergweg 6, Mainz, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619808/

See also Tissue Remodeling

Abdominal Adhesions (Scar Tissue)

Unraveling the Complexities of Cannabinoid Receptor 2 (CB2) Immune Regulation in Health and Disease

…"In the TNBS-induced [trinitrobenzene-sulfonic acid] mouse model of colitis, intraperitoneal administration of the CB2-selective agonists JWH-133 or AM1241 given just before or after colitis induction, resulted in a significant reduction in macroscopic damage, as determined by the presence of ulcers, adhesions, shortening of the colon, hemorrhage, fecal blood and diarrhea, as well as microscopic damage as assessed by histology of colon sections [78]."…

-Blood Research Institute, BloodCenter of Wisconsin, Milwaukee
-Department of Microbiology and Molecular Genetics, Medical College of Wisconsin
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624216/

Abdominal Aortic Aneurysm

"An abdominal aortic aneurysm (AAA) is a blood-filled bulge or ballooning in a part of your aorta that runs through your abdomen. Over time, this bulge in your aorta can become weak, and the force of normal blood pressure can cause it to rupture. This can lead to severe pain and massive internal bleeding, or hemorrhage."

- Medtronic
https://www.medtronic.com/us-en/patients/conditions/abdominal-aortic-aneurysm.html

Activation of Endocannabinoid System Is Associated with Persistent Inflammation in Human Aortic Aneurysm

"Human aortic aneurysms have been associated with inflammation and vascular remodeling. Since the endocannabinoid system modulates inflammation and tissue remodeling, we investigated its components in human aortic aneurysms. We obtained anterior aortic wall samples from patients undergoing elective surgery for aortic aneurysm or coronary artery disease as controls. Histological and molecular analysis (RT-qPCR) was performed, and endocannabinoid concentration was determined using LC-MRM. Patient characteristics were comparable between the groups except for a higher incidence of arterial hypertension and diabetes in the control group. mRNA level of cannabinoid receptors was significantly higher in

aneurysms than in controls. Concentration of the endocannabinoid 2-arachidonoylglycerol was significantly higher, while the second endocannabinoid anandamide and its metabolite arachidonic acid and palmitoylethanolamide were significantly lower in aneurysms."….

"Our data provides evidence for endocannabinoid system activation in human aortic aneurysms, associated with persistent low-level inflammation and vascular remodeling."

-Department of Cardiac Surgery, University Clinical Centre Bonn, Sigmund-Freud Street 25, Bonn, Germany
-Institute of Molecular Psychiatry, Life & Brain Center, Sigmund-Freud Street 25, Bonn, Germany
-Institute of Physiological Chemistry, University Medical Centre of the Johannes Gutenberg University Mainz, Duesbergweg 6, Mainz, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619808/

Abdominal Migraines in Children and Adults

"Abdominal migraine is a sub-type of migraine seen mainly in children. It consists of episodes of abdominal pain with nausea, vomiting, loss of appetite or pallor. Between episodes, there should be no symptoms. Children with abdominal migraine generally go on to develop migraine headaches later in life."

- American Migraine Foundation
https://americanmigrainefoundation.org/resource-library/abdominal-migraine/

See also Gastrointestinal Diseases

Achilles Tendon

Increased expression of cannabinoid CB_1 receptors in Achilles tendinosis.

…"Expression of cannabinoid receptor 1 is increased in human Achilles tendinosis suggesting that the cannabinoid system may be dysregulated in this disorder."

Pharmacology Unit, Department of Pharmacology and Clinical Neuroscience, Umeå University, Umeå, Sweden.
http://www.ncbi.nlm.nih.gov/pubmed/21931835

Achondroplasia

"Achondroplasia is a hereditary condition in which the growth of long bones by ossification of cartilage is retarded, resulting in very short limbs and sometimes a face that is small in relation to the (normal-sized) skull."

-From Oxford / Google

Tissue Engineering of Cartilage; Can Cannabinoids Help?

"This review discusses the role of the cannabinoid system in cartilage tissue and endeavors to establish if targeting the cannabinoid system has potential in mesenchymal stem cell based tissue-engineered cartilage repair strategies. The review discusses the potential of cannabinoids to protect against the degradation of cartilage in inflamed arthritic joints and the influence of cannabinoids on the chondrocyte precursors, mesenchymal stem cells (MSCs). We provide experimental evidence to show that activation of the cannabinoid system enhances the survival, migration and chondrogenic differentiation of MSCs, which are three major tenets behind the success of a cell-based tissue-engineered cartilage repair strategy. These findings highlight the potential for cannabinoids to provide a dual function by acting as anti-inflammatory agents as well as regulators of MSC biology in order to enhance tissue engineering strategies aimed at cartilage repair."

…"Although knowledge of the role of the cannabinoid system on bone and osteogenesis is well documented, and continues to become further insightful, the role of the cannabinoid system in cartilage tissue has lagged behind. This review aimed to assess the potential application of cannabinoids in enhancing MSC-based tissue-engineered cartilage regeneration strategies. Overall we have shown that modulation of the cannabinoid system can affect the major facets of MSC cell biology: survival, migration and differentiation. We conclude that there is sufficient evidence from the past literature and from our experimental evidence to support the potential of cannabinoid-based drugs in tissue-engineered applications aimed at reducing cartilage degradation and facilitating cartilage repair."

-Trinity College Institute of Neuroscience and Department of Physiology, School of Medicine, University of Dublin, Trinity College, Dublin 2, Ireland

-Trinity Centre for Bio-Engineering, School of Engineering, University of Dublin, Trinity College, Dublin 2, Ireland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4034107/

Acid reflux (Gastro-esophageal Reflux Disease (GERD))

See Gastrointestinal Diseases

Acne

"A common, multi-etiological skin condition characterized by increased sebum production and inflammation of the sebaceous glands; acne can be induced and/or aggravated, for example, by stress, endocrine conditions (adolescence), immune/inflammatory factors, bacterial infection of the skin, diet, and so on."

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ 07103, USA
-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck 23538, Germany
-School of Translational Medicine, University of Manchester, Manchester, M13 9PL, UK
-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes

…"Collectively, our findings suggest that, due to the combined lipostatic, antiproliferative, and antiinflammatory effects, CBD has potential as a promising therapeutic agent for the treatment of acne vulgaris."…

"We also tested its effect on actions of other lipogenic substances, which were shown previously to act through different, ECS-independent signal transduction mechanisms. Indeed, CBD effectively inhibited lipid synthesis induced by either arachidonic acid (AA) (21) or the combination of linoleic acid and testosterone (LA-T) (ref. 22 and Figure Figure1F),1F), indicating that the effect of CBD is not "ECS specific" but a "universal" lipostatic action."…

-DE-MTA "Lendület" Cellular Physiology Research Group, Department of Physiology, University of Debrecen, Debrecen, Hungary.
-Laboratory for Ion Channel Research and TRP Research Platform Leuven, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium.
-Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan.
-Department of Dermatology, University of Lübeck, Lübeck, Germany.
-Neurobiology Research Group, Department of Physiology, University of Debrecen, Debrecen, Hungary.

-Laboratory of Cutaneous Physiopathology and Integrated Center of Metabolomics Research, San Gallicano Dermatologic Institute, IRCCS, Rome, Italy.
-Departments of Dermatology, Venereology, and Allergology and Immunology, Dessau Medical Center, Dessau, Germany.
-School of Translational Medicine, University of Manchester, Manchester, United Kingdom.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151231/

■■■

"Acne vulgaris (or acne) [is] a common, multi-etiological skin condition characterized by increased sebum production and inflammation of the sebaceous glands; acne can be induced and/or aggravated, for example, by stress, endocrine conditions (adolescence), immune/inflammatory factors, bacterial infection of the skin, diet, and so on."

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ, USA
-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck, Germany
-School of Translational Medicine, University of Manchester, Manchester, UK
-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

Antimicrobial Property of Lauric Acid Against Propionibacterium acnes: Its Therapeutic Potential for Inflammatory Acne Vulgaris

"The strong bactericidal properties of lauric acid (C12:0), a middle chain-free fatty acid commonly found in natural products, have been shown in a number of studies. However, it has not been demonstrated whether lauric acid can be used for acne treatment as a natural antibiotic against Propionibacterium acnes (P. acnes), which promotes follicular inflammation (inflammatory acne). This study evaluated the antimicrobial property of lauric acid against P. acnes both in vitro and in vivo. Incubation of the skin bacteria P. acnes, Staphylococcus aureus (S. aureus), and Staphylococcus epidermidis (S. epidermidis) with lauric acid yielded minimal inhibitory concentration (MIC) values against the bacterial growth over 15 times lower than those of benzoyl peroxide (BPO). The lower MIC values of lauric acid indicate stronger antimicrobial properties than that of BPO. The detected values of half maximal effective concentration (EC50) of lauric acid on P. acnes, S. aureus, and S. epidermidis growth indicate that P. acnes is the most sensitive to lauric acid among these bacteria. In addition, lauric acid did not induce cytotoxicity to human sebocytes. Notably, both intradermal injection and epicutaneous application of lauric acid effectively decreased the number of P. acnes colonized with mouse ears, thereby relieving P. acnes-induced ear swelling and granulomatous

inflammation. The obtained data highlight the potential of using lauric acid as an alternative treatment for antibiotic therapy of acne vulgaris."…

-Division of Dermatology, Department of Medicine, University of California, San Diego, California, USA

-VA San Diego Healthcare Center, San Diego, California, USA

-Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, Kweishan, Taoyuan, Taiwan

-Department of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany

-Department of Nanoengineering, University of California, San Diego, California, USA

-Moores Cancer Center, University of California, San Diego, California, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2772209/

Acquired Immunodeficiency Syndrome (AIDS)

Omega-3 fatty acids as coadjuvant treatment in AIDS

"Human immunodeficiency virus (HIV), is able to replicate in many human cells such as helper lymphocytes, monocytes/macrophages and glial cells. Monocytes/macrophages must be considered an important reservoir of HIV in vivo and a producer of cytokines such as Interleukin-1 (IL1) and tumor necrosis factor (TNF). These substances lead to an autocrine feedback loop that produces an increased virus replication and a secondary induction of other cytokines such as Interleukin 6 (IL6) and granulocyte-macrophage colony stimulating factor (GM-CSF). These cytokines all together may be responsible for many clinical aspects of the disease such as headache, fever, anorexia, subtle cognitive changes, motor disfunctions and cachexia. The future strategies in the treatment of AIDS must be a combination of drugs acting on different points of viral replication and with synergistic potential. Omega 3 polyunsaturated fatty acids (omega-3) can be considered a candidate for their pleiotropic effects on immunological and metabolic systems. In particular, their use is considered for their ability to decrease IL1 and TNF production by monocytes/macrophages, as demonstrated by many authors. The decreased induction of these cytokines and consequently of IL6 and acute phase proteins may have beneficial effects on many clinical manifestations of AIDS such as cachexia."

-Department of Infectious Diseases, IRCCS Pol San Matteo, University of Pavia, Italy.

https://pubmed.ncbi.nlm.nih.gov/8289691

Immunopathogenesis of HIV infection in cocaine users: role of arachidonic acid

"Arachidonic acid (AA) is known to be increased in HIV infected patients and illicit drug users are linked with severity of viral replication, disease progression, and impaired immune functions. Studies have shown that cocaine accelerates HIV infection and disease progression mediated by immune cells. Dendritic cells (DC) are the first line of antigen presentation and defense against immune dysfunction. However, the role of cocaine use in HIV associated acceleration of AA secretion and its metabolites on immature dendritic cells (IDC) has not been elucidated yet. The aim of this study is to elucidate the mechanism of AA metabolites cyclooxygenase-2 (COX-2), prostaglandin E2 synthetase (PGE2), thromboxane A2 receptor (TBXA2R), cyclopentenone prostaglandins (CyPG), such as 15-deoxy-Δ12,14-PGJ2 (15d-PGJ2), 14-3-3 ζ/δ and 5-lipoxygenase (5-LOX) mediated induction of IDC immune dysfunctions in cocaine using HIV positive patients. The plasma levels of AA, PGE2, 15d-PGJ2, 14-3-3 ζ/δ and IDC intracellular COX-2 and 5-LOX expression were assessed in cocaine users, HIV positive patients, HIV positive cocaine users and normal subjects. Results showed that plasma concentration levels of AA, PGE2 and COX-2, TBXA2R and 5-LOX in IDCs of HIV positive cocaine users were significantly higher whereas 15d-PGJ2 and 14-3-3 ζ/δ were significantly reduced compared to either HIV positive subjects or cocaine users alone. This report demonstrates that AA metabolites are capable of mediating the accelerative effects of cocaine on HIV infection and disease progression."…

"Previous studies have shown that AA and its metabolites play a wide role in immune dysfunction, behavioral impairments as well as viral replication and disease progression in HIV-infection and substance abuse [9], [18], [23]. The increasing AA metabolites COX-2 and 5-LOX are associated with HAD or HAND. COX-2 enzyme is an important player in the regulation of immune functions (e.g. immune tolerance) of antigen-presenting cells such as macrophages or DC [31], [32]. An increase in AA secretion by HIV infection and their metabolites COX-2, PGE2, TBXA2 and 5-LOX are found in cerebrospinal fluid (CSF) of HAD-patients [33]–[35]. However, overstimulation of AA leads to increase in its metabolites COX-2 and PGE2 [36], [37], and subsequently decreased the level of 15d-PGJ2 and 14-3-3 ζ/δ, which may play a vital role in immune dysfunction and disease progression [38], [39] in HAD patients [26]. The DC differentiation, maturation, migration, and antigen presentation function are modulated by COX-2 induced prostaglandins (PGs) [15], [40], [41]. However, there are no reports on the impact of cocaine on AA metabolites in HIV positive cocaine users. The present study provides new insights into the functional role of COX-2 in AA metabolites TBXA2 which subsequently affects 5-LOX in HIV infection and cocaine use. Our previous in vitro study has shown that the HIV-1 gp120 protein induces the COX-2 mRNA expression and protein modification implicated in neuro-AIDS [42].

In the present study, we have demonstrated for the first time that cocaine users, HIV positive and HIV positive cocaine users have increased levels of AA and mRNA expression of metabolites COX-2, TBXA2, 5-LOX (Fig. 1), and the levels of AA and PGE2 (Fig. 2) are associated with reduction in 15d-PGJ2 compared to normal subjects. It is known that AA metabolites PGE2, COX-2, TBXA2 and 5-LOX are the major players in immune dysfunction [43]–[45], and reduced level of 15d-PGJ2 and 14-3-3 ζ/δ, may enhance viral replication and disease progression. These studies suggest that cocaine abusing HIV positive subjects may have an enhanced role of COX-2 and AA metabolites compared to normal subjects. This is consistent with earlier reports of gp120 induced neuroblastoma cells and HIV infected pulmonary hypertension, where activation of the COX-2 and 5-LOX pathways has been observed [36], [46]. "…

-Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Modesto A. Maidique Campus, Miami, Florida, USA.

-Department of Biostatistics, Robert Stempel College of Public Health and Social Work, Florida International University, Modesto A. Maidique Campus, Miami, Florida, USA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4149565/

…"Sepsis left untreated will result in a high mortality rate. As illicit drug use increases, sepsis cases will increase. Further research is needed to understand the continued relationship between drug use and the incidence of sepsis. Based on the current evidence, sepsis appears to be slightly affected by drug use and seems to be influenced by sedatives and opiates but only at a marginal level."…

- Cardiology, Charleston Area Medical Center, Charleston, USA

- Miscellaneous, Florida State University, Tallahassee, USA

- Internal Medicine, Charleston Area Medical Center, Charleston, USA

- Pharmacy, University of Charleston School of Pharmacy, Charleston, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6318118/

"Sepsis remains the primary cause of death from infection in hospital patients, despite improvements in antibiotics and intensive-care practices. Patients who survive severe sepsis can display suppressed immune function, often manifested as an increased susceptibility to (and mortality from) nosocomial infections. Not only is there a significant reduction in the number of various immune cell populations during sepsis, but there is also decreased function in the remaining lymphocytes. Within the immune system, CD4 T cells are important players in the proper development of numerous cellular and humoral immune responses. Despite sufficient

clinical evidence of CD4 T cell loss in septic patients of all ages, the impact of sepsis on CD4 T cell responses is not well understood. Recent findings suggest that CD4 T cell impairment is a multipronged problem that results from initial sepsis-induced cell loss. However, the subsequent lymphopenia-induced numerical recovery of the CD4 T cell compartment leads to intrinsic alterations in phenotype and effector function, reduced repertoire diversity, changes in the composition of naive antigen-specific CD4 T cell pools, and changes in the representation of different CD4 T cell subpopulations (e.g., increases in Treg frequency). This review focuses on sepsis-induced alterations within the CD4 T cell compartment that influence the ability of the immune system to control secondary heterologous infections. The understanding of how sepsis affects CD4 T cells through their numerical loss and recovery, as well as function, is important in the development of future treatments designed to restore CD4 T cells to their presepsis state."....

-Microbiology, Immunology, and Cancer Biology Graduate Program
-Medical Scientist Training Program
-Center for Immunology, and
-Department of Urology, University of Minnesota Medical School, Minneapolis, Minnesota, USA;
-Minneapolis Veterans Administration Health Care System, Minneapolis, Minnesota, USA; and
-Department of Pathology and
-Interdisciplinary Program in Immunology, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4197564/

See also Sepsis

Acupuncture

The endocannabinoid system, a novel and key participant in acupuncture's multiple beneficial effects.

"Acupuncture and its modified forms have been used to treat multiple medical conditions, but whether the diverse effects of acupuncture are intrinsically linked at the cellular and molecular level and how they might be connected have yet to be determined. Recently, an emerging role for the endocannabinoid system (ECS) in the regulation of a variety of physiological/pathological conditions has been identified. Overlap between the biological and therapeutic effects induced by ECS activation and acupuncture has facilitated investigations into the participation of ECS in the acupuncture-induced beneficial effects, which have shed light on the idea that the ECS may be a primary mediator and regulatory factor of acupuncture's beneficial effects. This review seeks to provide a comprehensive summary of the existing literature concerning the role of endocannabinoid signaling in the various effects of acupuncture, and suggests a novel notion

that acupuncture may restore homeostasis under different pathological conditions by regulating similar networks of signaling pathways, resulting in the activation of different reaction cascades in specific tissues in response to pathological insults."

-Department of Anesthesiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China; Department of Anesthesiology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China.
-Department of Anesthesiology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China.
-Department of Anesthesiology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China.
-Department of Anesthesiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China.
https://www.ncbi.nlm.nih.gov/pubmed/28412017

…"Clinical interventions characterized as "complementary and alternative medicine" also upregulate the eCB system: massage and manipulation, **acupuncture**, dietary supplements, and herbal medicines. Lifestyle modification (diet, weight control, exercise, and the use of psychoactive substances—alcohol, tobacco, coffee, cannabis) also modulate the eCB system."…

- GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom,
- Department of Family Medicine, University of Vermont, Burlington, Vermont, USA,
- Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951193/

Acute Coronary Syndrome

Reduced ratio of eicosapentaenoic acid and docosahexaenoic acid to arachidonic acid is associated with early onset of acute coronary syndrome

"The hospitalization rate for acute coronary syndrome (ACS) for people aged ≤50 has remained stable over the past decade. Increased serum levels of n-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are associated with a decreased incidence of cardiovascular events and mortality in older patients; however, it is currently unknown whether reduced serum levels of n-3 PUFAs is also a risk factor for ACS in patients aged ≤50 years."….

"Decreased EPA/AA and DHA/AA ratios may be risk factors for early onset of ACS, suggesting that reduced EPA/AA and DHA/AA may represent targets for preventing ACS in Japanese young people."…

-Department of Cardiovascular Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, Japan
-Dept. of Hematology, Endocrinology & Metabolism, Institute of Biomedical Sciences, Tokushima University Graduate School, Japan

-Department of Nutrition and Metabolism, Institute of Biomedical Sciences, Tokushima University Graduate School, Japan
-Department of Cardio-Diabetes Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, Japan
-Department of Medical Education, Institute of Biomedical Sciences, Tokushima University Graduate School, Kuramoto, Japan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4627394/

Acute Flaccid Myelitis (AFM)

Acute Flaccid Myelitis: A Clinical Overview for 2019

"Acute flaccid myelitis (AFM) is characterized by flaccid paralysis of one or more limbs, often following a viral illness, with magnetic resonance imaging findings consistent with inflammation of the spinal cord gray matter. It is unclear whether all patients with AFM will have full recovery of neurologic function. Since 2014, there have been several clusters of AFM in the United States, with a 3-fold increase in reported AFM cases recorded in 2018 compared with the previous year. Epidemiological evidence supports a temporal association between respiratory enteroviral illness, particularly with enteroviruses D68 and A71, and clustering of AFM cases. However, causality has yet to be established. Treatment of AFM is primarily supportive. Adjunctive therapies such as intravenous immunoglobulin, corticosteroids, plasmapheresis, and fluoxetine have not been found to improve long-term outcomes. Further research is urgently needed to characterize and optimize management of this emerging, yet poorly understood, condition."

-Division of General Pediatric and Adolescent Medicine, Department of Pediatrics and Adolescent Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN.
-Division of Pediatric Infectious Diseases, Department of Pediatrics and Adolescent Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN.

Acute Heart Failure

Deficiency of type 1 cannabinoid receptors worsens acute heart failure induced by pressure overload in mice

"**Aims:** We investigated the influence of type one cannabinoid receptor (CB1) deficiency on acute heart failure (AHF) and the underlying mechanism. Acute heart failure syndrome is an important clinical problem because of its high morbidity and mortality rates. Activation of CB1 induces vascular dilation and reinforces the properties of morphine, long-standing therapies for AHF syndrome, but the effect of endogenous CB1 activation on AHF is largely unknown.
Conclusion: Endogenous activation of CB1 in mice has cardiac protection in AHF, which is attributable to the inhibition of excessive sympathetic activation."

-Department of Cardiology, and Organ Failure Key Laboratory of Ministry of Education, Nanfang Hospital, Southern Medical University, 1838 Guangzhou avenue north, Guangzhou, China

-Cardiovascular Division of the Department of Medicine, National Cerebral Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka , Japan

-Department of Pathophysiology, Key Laboratory of Shock and Microcirculation Research, Southern Medical University, Guangzhou, China

-IRIBHN Universite´ Libre de Bruxelles, Bruxelles, Belgium

-Molecular Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka, Japan

https://academic.oup.com/eurheartj/article/33/24/3124/2398076

Acute Liver Injury

…"Between 1998 and 2003, acetaminophen was the leading cause of acute liver failure in the US. There are also hundreds of related deaths every year — though keep in mind that millions of people take drugs with acetaminophen, so these more extreme side effects are rare (especially if you're only taking them in small doses occasionally). Still, for the drug's minimal pain-killing benefits, the risks may not be worth it.

"Don't believe that just because something is over-the-counter, it's safe," [Professor Philip] Conaghan added. (He advised people to see their doctor if they're taking any of these painkillers for more than a few days — particularly if they're on other drugs already.)"

https://www.vox.com/2015/8/17/9165189/best-painkiller-tylenol-aspirin-advil

See also Interstitial Nephritis , Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Acute Lung Injury (ALI)

…"The effect of endocannabinoids was studied in the LPS-induced experimental acute lung injury (ALI) model in mice [121]. It is well known that ALI may occur due to sepsis, pneumonia, acid aspiration, toxic inhalation, etc. In their study, Costola-de-Souza et al. showed that treatment with the MAGL inhibitor, JZL184 attenuated the pathological changes of ALI by increasing 2-AG [an endocannabinoid 2-Arachidonoylglycerol] levels in the lungs."…

…"These data suggest that increasing the concentration of endocannabinoids in the airways by the inhibition of primary endocannabinoid degrading enzymes FAAH and MAGL can prevent airway hyperreactivity and airway inflammation."….

-Department of Pharmacology, Faculty of Pharmacy, Hacettepe University

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943521/

Acute Myeloid Leukemia (AML)

"Acute myeloid leukemia (AML) starts in the bone marrow (the soft inner part of certain bones, where new blood cells are made), but most often it quickly moves into the blood, as well. It can sometimes spread to other parts of the body including the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles."

- American Cancer Society
https://www.cancer.org/cancer/acute-myeloid-leukemia/about/what-is-aml.html

A Role for Lipid Mediators in Acute Myeloid Leukemia

"In spite of therapeutic improvements in the treatment of different hematologic malignancies, the prognosis of acute myeloid leukemia (AML) treated solely with conventional induction and consolidation chemotherapy remains poor, especially in association with high risk chromosomal or molecular aberrations. Recent discoveries describe the complex interaction of immune effector cells, as well as the role of the bone marrow microenvironment in the development, maintenance and progression of AML. Lipids, and in particular omega-3 as well as omega-6 polyunsaturated fatty acids (PUFAs) have been shown to play a vital role as signaling molecules of immune processes in numerous benign and malignant conditions. While the majority of research in cancer has been focused on the role of lipid mediators in solid tumors, some data are showing their involvement also in hematologic malignancies. There is a considerable amount of evidence that AML cells are targetable by innate and adaptive immune mechanisms, paving the way for immune therapy approaches in AML. In this article we review the current data showing the lipid mediator and lipidome patterns in AML and their potential links to immune mechanisms."...

"Acute myeloid leukemia (AML) is a complex and biological heterogenous disease. Different mutations lead to alterations in the differentiation of hematopoietic stem cells and are responsible for the accumulation of immature leukemic blast cells in the bone marrow and peripheral blood. AML accounts for approximately 20% of all deaths due to hematologic malignancies, while only comprising 12% of all new cases [1].

The relapse rate after conventional induction chemotherapy is high, particularly in association with adverse chromosomal or molecular aberrations. Therapeutic advances in AML in recent years are mainly attributed to progress in hematopoietic stem cell transplantation techniques

and advances in supportive care."

…"As reviewed before, lipid species and the lipidome are highly abundant and essential components of human cells and tissues [11]. Many of these lipid species (e.g., eicosanoids, sphingolipids, glycerolipids) were shown to be changed in the context of tumor disease and might serve as markers as well as targets for new treatment approaches in malignant disorders. Particularly in the context of the tumor surrounding microenvironment lipid species could be important—and modifiable—targets in oncology [12].

Beside an increased de novo synthesis of fatty acids that is required for membrane synthesis and therefore for cell growth and proliferation, AML cells might have an increased lipid catabolism. Fatty acid oxidation (FAO) has been recognized as a relevant component of the metabolic switch in cancer cells where FAO is used for ATP production in conditions of metabolic stress [13]. Indeed, recent in vitro studies have shown that distinct genetic changes in AML are associated with enhanced dynamics and metabolism of lipid species in AML cells [14].

Data from the late 1970s found altered lipid compositions of AML cells with a decreased total cholesterol and cholesterol-to-phospholipid ratio, and an increased percentage of unsaturated fatty acids when compared to normal mature neutrophils, but these patterns might be shared by normal immature myeloid cells [15].

…"Omega-3-PUFAs were first postulated to act as anti-inflammatory compounds through the competitive inhibition of PGE2 formation and to a certain degree, EPA and DHA do inhibit the formation of AA derived lipid mediators [35]. Studies have shown increased formation of omega-3-PUFA derived prostaglandins (i.e., PGE3) and decreased formation of AA derived mediators (i.e., PGE2) caused by increased intake of dietary omega-3 PUFA [35,36]. Mechanistically, eicosanoids derived from omega-3-PUFA seem to have a lower biological effect than their omega-6-PUFA derived counterparts [37,38]. However, there is also evidence for some distinct functionality, since PGE3 could be shown to have an inhibitory effect on tumor cell growth in vitro [39]. The same is true for the leukotrienes derived from omega-3-PUFA. For example, for leukotriene B5, which is formed through enzymatic conversion by 5-lipoxygenase. Asthmatic subjects receiving omega-3 supplements showed decreased formation of leukotriene B4 (omega-6-PUFA) and increased formation of leukotriene B5 while displaying improved pulmonary function compared to the control group [40]."…

-Department of Medicine B, Ruppin General Hospital, Brandenburg Medical School, Neuruppin, Germany
-Department of Internal Medicine III, University of Munich, Munich, Germany;
-Medical Department, Campus Virchow Klinikum, Charité-Universitätsmedizin Berlin, Berlin, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6567850/

The plasma lipidome in acute myeloid leukemia at diagnosis in relation to clinical disease features

“Early studies established that certain lipids were lower in acute myeloid leukemia (AML) cells than normal leukocytes. Because lipids are now known to play an important role in cell signaling and regulation of homeostasis, and are often perturbed in malignancies, we undertook a comprehensive lipidomic survey of plasma from AML patients at time of diagnosis and also healthy blood donors.”

…”We observed a depletion of plasma total fatty acids and cholesterol, but an increase in certain free fatty acids with the observed decline in sphingolipids, phosphocholines, triglycerides and cholesterol esters probably driven by enhanced fatty acid oxidation in AML cells. Arachidonic acid and precursors were elevated in AML, particularly in patients with high bone marrow (BM) or peripheral blasts and unfavorable prognostic risk. PGF2α was also elevated, in patients with low BM or peripheral blasts and with a favorable prognostic risk. A broad panoply of lipid classes is altered in AML plasma, pointing to disturbances of several lipid metabolic interconversions, in particular in relation to blast cell counts and prognostic risk.”

…“These data indicate potential roles played by lipids in AML heterogeneity and disease outcome.”

-Department of Medical Oncology, Inselspital Bern, Switzerland
-Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital Leipzig, Germany
-Institute of Clinical Chemistry, Inselspital Bern, Switzerland
-Hepatology Research Group, Department of Clinical Research, University of Bern, Switzerland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5357680/

Addison Disease

“Addison disease (or Addison's disease) is adrenocortical insufficiency due to the destruction or dysfunction of the entire adrenal cortex. It affects glucocorticoid and mineralocorticoid function. The onset of disease usually occurs when 90% or more of both adrenal cortices are dysfunctional or destroyed.”
https://emedicine.medscape.com/article/116467-overview

■■■

“Endocannabinoid (eCB) signaling has been identified as a modulator of adaptation to stress, and is integral to basal and stress-induced glucocorticoid regulation.”

-The Hotchkiss Brain Institute and Departments of Cell Biology & Anatomy and Psychiatry, University of Calgary, Calgary AB, Canada-Laboratory of Neuroendocrinology, The Rockefeller University, New York NY USA

-Traumatic Stress Studies Division, Mount Sinai School of Medicine and James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA-Department of Epidemiology, Columbia Mailman School of Public Health, New York, NY, USA

-Neuroscience Research Center and Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee WI, USA

-Direct correspondence to: Matthew N. Hill, Ph.D., Hotchkiss Brain Institute, University of Calgary

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3870889/

Expression and function of endocannabinoid receptors in the human adrenal cortex.

"Endogenous cannabinoids are important signaling molecules in neuroendocrine control of homeostatic and reproductive functions including stress response and energy metabolism. The hypothalamic paraventricular and supraoptic nuclei have been shown to release endocannabinoids, which act as retrograde messengers to modulate the synaptic release of glutamate during stress response. This study endeavors to elucidate possible interaction of the endocannabinoid system with the regulation of adrenocortical function at the adrenal level. Human adrenocortical NCI-H295R cells and normal human adrenal glands were used to study the possible effects of anandamide and cannabinoid receptor 1 (CB1) antagonist SR141716A on aldosterone and cortisol secretion. Our data indicate the expression of CB1 in human adrenal cortex and adrenocortical NCI-H295R cells; CB2 was not expressed. Furthermore, anandamide inhibited basal release and stimulated release of adrenocortical steroids (corticosterone and aldosterone); this effect was reversed by CB1 antagonist (SR141716A). Therefore, the endocannabinoid system at the level of the adrenal, can directly influence adrenocortical steroidogenesis."

-Carl Gustav Carus University Hospital, Department of Medicine III, Dresden, Germany.

https://www.ncbi.nlm.nih.gov/pubmed/19862666

Note: Corticosterone has been shown to upregulate Anandamide (AEA) in animal studies.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951193

Adenocarcinoma

"Adenocarcinoma is cancer that forms in mucus-secreting glands throughout the body. The disease may develop in many different places, but it is most prevalent in the following cancer

types:"…

- **Lung cancer:** Non-small cell lung cancer accounts for 80 percent of lung cancers, and adenocarcinoma is the most common type.
- **Prostate cancer:** Cancer that forms in the prostate gland is typically an adenocarcinoma, which accounts for 99 percent of all prostate cancers.
- **Pancreatic cancer:** Exocrine pancreatic cancer tumors are called adenocarcinomas. They form in the pancreas ducts.
- **Esophageal cancer:** Cancer that forms in the glandular cells of the esophagus is known as adenocarcinoma. This is the most common type of esophageal cancer.
- **Colorectal cancer:** Cancer that develops in the intestinal gland cells that line the inside of the colon and/or rectum is an adenocarcinoma. It makes up 95 percent of colon and rectal cancers.

…"Adenocarcinoma may also develop elsewhere in the body."

- Cancer Treatment Centers of America
https://www.cancercenter.com/adenocarcinoma

Cannabidiol [CBD] as potential anticancer drug

"Cannabinoids are currently used in cancer patients to palliate wasting, emesis and pain that often accompany cancer. A significant advancement in cannabinoid use in cancer treatment came from the discovery of a potential utility of these compounds for targeting and killing cancer cells. In 1975 Munson et al. [17] demonstrated that the administration of Δ9-THC, Δ8-THC and cannabinol inhibited the growth of Lewis lung adenocarcinoma cells in vitro as well as in vivo after oral administration in mice. The interest in anticarcinogenic properties of cannabinoids was even renewed after the discovery of the eCB system and the cloning of the specific cannabinoid receptors. Since then, several cannabinoids have been shown to exert anti-proliferative and pro-apoptotic effects in various cancer types (lung, glioma, thyroid, lymphoma, skin, pancreas, uterus, breast, prostate and colorectal carcinoma) both in vitro and in vivo[18–26]. Moreover, other antitumourigenic mechanisms of cannabinoids are currently emerging, showing their ability to interfere with tumour neovascularization, cancer cell migration, adhesion, invasion and metastasization [27]."

-Department of Pharmacology, Chemotherapy and Toxicology, University of Milan, Via Vanvitelli 32, Milan

-Department of Theoretical and Applied Sciences, Biomedical Division, University of Insubria, Via A. da Giussano 10, Busto Arsizio (VA), Italy

-Professor Daniela Parolaro, Department of Theoretical and Applied Sciences, Biomedical Division, Center of

Neuroscience, University of Insubria, Via A. da Giussano 10, Busto Arsizio (VA), Italy.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3579246/

Adenomatous Polyps

"Adenomatous polyps (adenomas) of the colon and rectum are benign (noncancerous) growths, but may be precursor lesions to colorectal cancer. Polyps greater than one centimeter in diameter are associated with a greater risk of cancer. If polyps are not removed, they continue to grow and can become cancerous."

-AmeriPath
http://www.ameripath.com/adenomatous-polyps

■■■

…"Higher intakes of marine-derived n−3 PUFAs are associated with lower risk of adenomatous polyps in women, and the association may be mediated in part through a reduction in the production of prostaglandin E2. "…

-Divisions of General Internal Medicine (HJM), Public Health and Epidemiology, Vanderbilt Epidemiology Center (MJS, QC, QD, and WZ), Gastroenterology (WES and RMN), and Clinical Pharmacology (GLM)

-Department of Preventive Medicine (WES), Vanderbilt University School of Medicine, Nashville, TN

-Geriatric Research Education and Clinical Care, Department of Veterans Affairs, Tennessee Valley Healthcare System, Nashville, TN

-Vanderbilt Ingram Cancer Center, Nashville, TN

-The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the NIH.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278245/

ADD/ADHD & Learning

Attention Deficit Disorder & Attention Deficit Hyperactivity Disorder

Omega-6 to Omega-3 Fatty Acid Ratio in Patients with ADHD: A Meta-Analysis

…"Children and youth with ADHD have elevated ratios of both blood n6/n3 [omega-6/omega-3]

and AA/EPA fatty acids compared to controls. Thus an elevated n6/n3, and more specifically AA/EPA, ratio may represent the underlying disturbance in essential fatty acid levels in patients with ADHD. These findings have implications for the development of future interventions using essential fatty acids to treat ADHD, and for the use of these ratios as biomarkers for titrating and monitoring ADHD treatment with essential fatty acids."…

-University of Toronto, Department of Psychiatry, Toronto, Ontario
-Centre for Addiction and Mental Health, Social Aetiology of Mental Illness, Toronto, Ontario
-Wellesley Institute, Toronto, Ontario
-Women's College Hospital and Women's College Research Institute, Toronto, Ontario
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879948/

Loss of striatal cannabinoid CB1 receptor function in attention-deficit/hyperactivity disorder mice with point-mutation of the dopamine transporter.

…"Our results point to CB1Rs [cannabinoid receptor 1] as novel molecular players in ADHD, and suggest that therapeutic strategies aimed at interfering with the ECS [the Endocannabinoid system] might prove effective in this disorder."

-Clinica Neurologica, Dipartimento di Neuroscienze, Università Tor Vergata, Via Montpellier, Rome, Italy.
https://www.ncbi.nlm.nih.gov/m/pubmed/22034972/

Association of the Cannabinoid Receptor Gene (CNR1) With ADHD and Post-Traumatic Stress Disorder

…"Second, studies of endogenous cannabinoid (EC) regulation in animal models suggest that it plays a role in some aspects of memory, emotional recognition or processing, and reward, each an area of putative dysregulation in ADHD"…

-Department of Human Genetics, University of California, Los Angeles, California
-Department of Epidemiology and Public Health, Imperial College London, London, United Kingdom
-Clinic of Child Psychiatry, University of Oulu, Oulu, Finland
-Center for Neurobehavioral Genetics, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, California
-Division of Child and Adolescent Psychiatry, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, California
-Wellcome Trust Sanger Institute, Cambridge, United Kingdom
-Institute for Molecular Medicine Finland (FIMM), University of Helsinki and National Public Health Institute, Helsinki, Finland

-Broad Institute, Cambridge, Massachusetts
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2685476/

Omega-3 Fatty Acid and Nutrient Deficits in Adverse Neurodevelopment and Childhood Behaviors

…"Several dietary supplementation trials with omega-3 and omega-6 fatty acids have reported some improvement in ADHD symptoms, typically using either the Parent or Teacher-rated Conners' scales and/or the Clinical Global Impression (CGI) scales as primary outcomes [76, 78, 118–120]."…

…"In humans, DHA insufficiency in utero has been hypothesized to be linked to impaired magnocellular neurite growth associated with dyslexia [67]. Some studies have also reported findings of abnormal omega-3 HUFA levels in the erythrocytes of children and young adults with ADHD [68–75]. In addition, a growing body of clinical research has reported improvements in symptoms of ADHD [76–78], depression [79], learning difficulties and/or dyslexia [80] following supplementation with omega-3/6 fatty acids relative to placebo."…

-Section of Nutritional Neurosciences, Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, 5625 Fishers Lane, Rockville, MD 20892

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4175558/

Adipose Tissue

"Adipose tissue is a specialized connective tissue consisting of lipid-rich cells called adipocytes. As it comprises about 20-25% of total body weight in healthy individuals, the main function of adipose tissue is to store energy in the form of lipids (fat)."…
https://www.kenhub.com/en/library/anatomy/adipose-tissue

■■■

"Adipose tissue was historically regarded as an inert depot for triacylglycerol storage; however, it is now recognised as a major endocrine organ that is central to whole-body metabolic homeostasis."

…"Several observations in this paper have added new knowledge to our understanding, not only of the factors regulating skeletal muscle insulin resistance, but also of the involvement of adipose tissue as a pathogenic organ. **The findings of Eckardt et al. [5] corroborate previous work in mice, which identified the ECS system as an important component of adipose tissue [13], and**

supports the view that dysregulation of the ECS in obesity may contribute to skeletal muscle insulin resistance. It also highlights a previously unappreciated direct role of endocannabinoids in skeletal muscle glucose metabolism, independent of metabolic alterations associated with weight loss or changes in other hormones known to influence nutrient metabolism (e.g. adiponectin). From a clinical viewpoint, the data indicate that peripheral therapeutic targeting of the ECS may prove effective at reducing the development of insulin resistance and type 2 diabetes, independent of central nervous system effects, such as anxiety, depression and nausea, that have been linked to CB1R antagonist/inverse agonist treatment [14, 15]. In this regard, the first approved selective CB1R agonist, rimonabant, was recently suspended by the European Medicines Agency due to the risk of serious psychiatric problems, suggesting specific problems with the target/pathway (i.e. CB1R) or off-target effects of the drug. Caution will be paramount to any future therapeutic strategy involving CB1R."

Department of Physiology, Monash University,Clayton, Australia
https://link.springer.com/article/10.1007/s00125-009-1287-x

The endocannabinoid system in the adipose organ

…"All molecular components of the endocannabinoid system are represented in the adipose organ, where endocannabinoid signals are thought to regulate critical homeostatic processes, including adipogenesis, lipogenesis and thermogenesis. Importantly, obesity was found to be associated with excess endocannabinoid activity in visceral fat depots, and the therapeutic potential of normalizing such activity by blocking CB1 receptors has been the focus of substantial preclinical and clinical research. Results have been mixed thus far, mostly owing to the emergence of psychiatric side effects rooted in the protective functions served by brain endocannabinoids in mood and affect regulation. Further studies about the roles played by the endocannabinoid system in the adipose organ will offer new insights into the pathogenesis of obesity and might help identify new ways to leverage this signaling complex for therapeutic benefit."

-Department of Anatomy and Neurobiology, University of California, Irvine, Irvine, CA, USA.
-Department of Pharmacology, University of California, Irvine, Irvine, CA, USA.
-Department of Biological Chemistry, University of California, Irvine, Irvine, CA, USA.
https://pubmed.ncbi.nlm.nih.gov/33387286

See also Supplements

Age-related Macular Degeneration (Macular Degeneration)

Long-Chain Polyunsaturated Fatty Acids and Age-Related Macular Degeneration

"Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide. Long-chain and very long-chain polyunsaturated fatty acids (LC and VLC-PUFAs) have been linked to AMD pathogenesis through epidemiologic, biochemical, and genetic studies; however, the exact mechanisms of pathogenesis are unknown. Here, we review the scientific and clinical evidence supporting the role of PUFAs in AMD and discuss future directions for elucidating the roles of these fatty acids in AMD pathogenesis."…

"Multiple epidemiologic studies, both retrospective as well as prospective, have suggested that diets high in (n-3)LC-PUFAs are associated with lower rates of age-related macular degeneration, with low dietary intake of (n-3) LC-PUFAs associated with higher risk of developing the disease (reviewed in Chong et al. (2008) and van Leeuwen et al. (2018)). In addition, two large studies demonstrated that high plasma levels of (n-3)LC-PUFAs were correlated with decreased risk of AMD (Christen et al. 2011; Merle et al. 2013). In the Age-Related Eye Disease Study (AREDS), a large prospective study investigating factors of progression to advanced AMD, subjects with the highest self-reported intake of foods rich in (n-3)LC-PUFAS were 30% less likely to develop central GA and 50% less likely to develop AMD than subjects with the lowest self-reported intake (Sangiovanni et al. 2009)."…

-Viterbi Family Department of Ophthalmology, Shiley Eye Institute, University of California, San Diego, La Jolla, CA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7526619/

See also Supplements

Aging

…"Chronic inflammation, of course, is a cause of—or an important contributor to—virtually every major age-related disease, both degenerative and hyperplastic (109–111)."…

-Dr. Judith Campisi Ph.D, Buck Institute for Research on Aging, Lawrence Berkeley National Laboratory, Berkeley;
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC4166529/

Fatty Acid Transporting Proteins: Roles in Brain Development, Aging, and Stroke

…"Aging is a complex process that is accompanied by damage to cellular components, including proteins and critical lipids susceptible to accumulation of damage as a result of oxidation, nitrosylation or inflammation, among other insults. The lack of n-3 [omega-3] polyunsaturated fatty acids (n-3 PUFAs) in the Western diet through lifetime may gradually induce a chronic DHA deficit of lipid membranes in the brain. This may contribute to a chronic pro-inflammatory state in the brain, which is characteristic for brain aging in later life associated with dementia [1]. We and others have suggested that sufficient intake of n-3 PUFAs protects the brain against cerebral ischemia and improves neurological outcomes. In addition to intake via the diet, the cellular uptake of fatty acids is greatly dependent on specialized proteins required for fatty acids transportation. Herein, we will summarize the metabolism of polyunsaturated fatty acid in brain and the function of proteins critical for fatty acids transportation during neurodevelopmental and aging processes."…

-State Key Laboratory of Medical Neurobiology, Institute of Brain Sciences and Collaborative Innovation Center for Brain Science, Fudan University, Shanghai, China

-Pittsburgh Institute of Brain Disorders & Recovery and Department of Neurology University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

-Geriatric Research, Education and Clinical Center Veterans Affairs Pittsburgh Health Care System, Pittsburgh, PA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5650946/

Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

"Chronic inflammation is a pathological condition characterized by continued active inflammation response and tissue destruction. Many of the immune cells including macrophages, neutrophils and eosinophils are involved directly or by production of inflammatory cytokine production in pathology of chronic inflammation. From literatures, it is appear that there is a general concept that chronic inflammation can be a major cause of cancers and express aging processes. Moreover, many studies suggest that chronic inflammation could have serious role in wide variety of age-related diseases including diabetes, cardiovascular and autoimmune diseases. Inflammatory process induces oxidative stress and reduces cellular antioxidant capacity. Overproduced free radicals react with cell membrane fatty acids and proteins impairing their function permanently. In addition, free radicals can lead to mutation and DNA damage that can

be a predisposing factor for cancer and age-related disorders. This article reviews the antioxidant defense systems, free radicals production and their role in cancer and age related diseases and also some of the recent patent relevant to the field. Study of the role of free radicals in human diseases can help the investigators to consider the antioxidants as proper agents in preventive medicine, especially for cancer and aging processes."

-Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
https://pubmed.ncbi.nlm.nih.gov/19149749/

Determinants of fluid intelligence in healthy aging: Omega-3 polyunsaturated fatty acid status and frontoparietal cortex structure

"Introduction: Accumulating evidence indicates that cognitive decline depends not only upon changes in brain health, but critically, also upon nutritional status. Decline in fluid intelligence, one of the most debilitating aspects of cognitive aging, has been linked to omega-3 polyunsaturated fatty acid (PUFA) status; however, it is not known whether this phenomenon results from specific omega-3 PUFAs acting on particular aspects of brain health. Therefore, this study aims to explore whether particular patterns of omega-3 PUFAs influence fluid intelligence by supporting specific neural structures."…

"Results: The mediation analysis revealed that one pattern of omega-3 PUFAs, consisting of alpha-linolenic acid, stearidonic acid, and eicosatrienoic acid, was linked to fluid intelligence, and that total gray matter volume of the left frontoparietal cortex (FPC) fully mediated the relationship between this omega-3 PUFA pattern and fluid intelligence.

Discussion: These data demonstrate that fluid intelligence may be optimally supported by specific omega-3 PUFAs through preservation of FPC gray matter structure in cognitively intact older adults. This report provides novel evidence for the benefits of particular omega-3 PUFA patterns on fluid intelligence and underlying gray matter structure."

-Decision Neuroscience Laboratory , University of Illinois Urbana-Champaign , Urbana , IL, USA.
-Beckman Institute for Advanced Science and Technology, University of Illinois Urbana-Champaign , Urbana , IL, USA.
-Neuroscience Program, University of Illinois Urbana-Champaign , Urbana , IL, USA.
-Department of Psychology , University of Illinois Urbana-Champaign , Urbana , IL, USA.
-Carle Neuroscience Institute, Carle Foundation Hospital , Urbana , IL, USA.
-Department of Internal Medicine , University of Illinois Urbana-Champaign , Urbana , IL, USA.
-Institute for Genomic Biology, University of Illinois Urbana-Champaign , Champaign , IL, USA.
https://pubmed.ncbi.nlm.nih.gov/28492102

…"Omega-3 and omega-6 fatty acids, n-3 PUFAs and n-6 PUFAs, respectively, are termed "essential fatty acids" and are usually obtained from the diet, because they cannot be synthesized by human cells. α-Linolenic acid (ALA) is a n-3 PUFA that is endogenously converted into eicosapentaenoic acid (EPA) and subsequently to docosahexanoic acid (DHA). On the other hand, linoleic acid, a n-6 PUFA, can be progressively converted into arachidonic acid (AA), a precursor for several classes of eicosanoids and pro-inflammatory compounds. In the nervous system, cell membranes contain relatively high concentrations of PUFAs, such as docosahexaenoic acid (DHA) [123,124]. The n-3 PUFAs are known to play a role in nervous system activity, cognitive development, neuroplasticity of nerve membranes, synaptogenesis, and synaptic transmission [125]. On the other hand, n-6 PUFAs (e.g., AA) act as second messengers for pro-apoptotic and inflammatory events. Thus, imbalances in the n-3/n-6 PUFA ratio may result in increased susceptibility to neuronal damage, as observed in neurodegenerative disease [126]. DHA and EPA are mainly found in fish oil (FO) and fatty fish, including salmon, tuna, and trout, whereas ALA is commonly found in vegetable oils such as soya, canola, and linseed oils [127].

Evidence shows that aging and the associated neurodegenerative processes could be influenced by the consumption of EPA and DHA during the lifetime of humans. The dentate gyrus (DG), a sub-region of the hippocampus, is implicated in cognition and mood regulation. The hippocampus represents one of the two areas in the mammalian brain in which adult neurogenesis occurs, with beneficial effects on cognition, mood, and chronic pharmacological treatment. Exposure to DHA and EPA enhances adult hippocampal neurogenesis, which is associated with cognitive and behavioral amelioration, enhanced synaptic plasticity, and the formation of new spines [128]. "…

-Institute of Physical Activity and Sports Science (ICAFE), Cruzeiro do Sul University, Brazil
-Graduation Program in Health Sciences, Cruzeiro do Sul University, Brazil;
-Department of Veterinary Medicine, University Paulista (UNIP), Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3967194/

■■■

"Chronic, low-grade, systemic inflammation is thought to be a major characteristic of aging [so-called "inflammaging" (1)], contributing to age-associated frailty, morbidity, and mortality (2–6). Instances of higher overall inflammatory status, such as those of older individuals or in chronically inflamed disease states, may lead to an increased need for substrates (i.e., protein) to support anti-inflammatory processes. Meeting protein needs in aging populations may therefore be important not just for maintenance of lean mass (7–9), strength (7, 8, 10), and physical function (9, 11, 12), but also for counteracting inflammation, oxidation, and their downstream catabolic effects

[13]. Several studies have observed that proinflammatory cytokines are inversely associated with muscle strength and physical performance [14–18], both of which have been positively associated with at least adequate protein intake [9, 12].

However, higher protein intake is also known to upregulate the IGF/Akt/mTOR cascade, which acts as a key driver of the aging process [19]. Higher protein intake has been associated with higher concentrations of certain circulating inflammatory biomarkers, such as C-reactive protein (CRP) [20, 21], although the dietary source of the protein may be relevant [22–26]. A considerable proportion of dietary protein, notably in most Western populations, comes from animal sources (i.e., dairy, poultry, meat), and some of this protein intake has been shown to be associated with proinflammatory and pro-oxidative states [22, 27–32]. Thus, protein intake may in fact have an overall null effect on inflammation and oxidative stress in aging populations, both providing substrates for anti-inflammatory and antioxidative processes [e.g., cysteine for glutathione synthesis [19]] and supporting anabolism [13], but also inducing a proinflammatory state, potentially depending on its source. "…

…"Dietary protein, particularly from plant sources, may be associated with beneficial changes in the inflammatory burden in aging populations."

-Nutritional Epidemiology, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

-Tufts University Friedman School of Nutrition Science and Policy, Boston, MA.

https://www.ncbi.nlm.nih.gov/pubmed/31037277

Endocannabinoids, exercise, pain, and a path to health with aging

"Physical activity is an important lifestyle factor for growth, development, and sustained health throughout life. In recent years, the benefits of physical activity have drawn more attention to its physiological effects on the body, including well-being. The endocannabinoid system (ECS) has emerged as a focal point to ascertain the mechanisms for how exercise benefits the body and how it reduces or controls pain. The ECS, its ligands [the endocannabinoids (eCB)], receptors (CB1 and CB2), enzymes for the synthesis and degradation of eCB, and the polyunsaturated fatty acids (PUFA) that serve as substrates, comprise a powerful biological organization of multiple controls that affects mood, inflammation, pain, and other neurological aspects of the central nervous system and peripheral nervous system. Recently, investigators have reported increases in circulating levels of eCB after exercise, with some eCB exerting analgesic effects from exercise. The focus of this review is to discuss evidence for the role of eCB and the complexities of the ECS in exercise and pain. Some aspects presented herein are production of eCB and activation of the cannabinoid receptors in the brain following exercise; eCB, pain, and physical activity; oxylipins; and joint pain. Future research on the ECS must include mechanistic approaches to

endocannabinoid signaling and explain the role of dietary PUFA in altering signaling of the receptors that affects pain. Additionally, how other types of exercise, such as Tai Chi, which is reported to improve well-being, should be investigated to ascertain if changes in eCB mediate the mind and body benefits of Tai Chi. As we age, exercise in the form of play has evolved with the exploration of our body from walking to running, recreational, and competitive sports, to midlife physical activity focusing on maintaining fitness and a healthy body weight. Furthermore, exercise has been a target of investigation to explore various hypotheses to explain the mechanisms for cognitive benefits in the young and in older adults. The science of exercise has matured to a level of importance in the life cycle to reduce pain with aging and include new investigations on the ECS to explain its role in well-being and improved quality of life in later years."

-Department of Nutrition, University of California, Davis, CA, USA.
https://pubmed.ncbi.nlm.nih.gov/30290200

Diet, endocannabinoids, and health

"Healthy aging includes freedom from disease, ability to engage in physical activity, and maintenance of cognitive skills for which diet is a major lifestyle factor. Aging, diet, and health are at the forefront of well-being for the growing population of older adults with the caveat of reducing and controlling pain. Obesity and diabetes risk increase in frequency in adults, and exercise is encouraged to control weight, reduce risk of type II diabetes, and maintain muscle mass and mobility. One area of research that appears to integrate many aspects of healthy aging is focused on understanding the endocannabinoid system (ECS) because of its role in systemic energy metabolism, inflammation, pain, and brain biology. Physical activity is important for maintaining health throughout the life cycle. The benefits of exercise facilitate macronutrient use, promote organ health, and augment the maintenance of metabolic activity and physiological functions. One outcome of routine exercise is a generalized well-being, and perhaps, this is linked to the ECS. The purpose of this review is to briefly present the current knowledge of key components of the ECS that contribute to appetite and influence systemic energy metabolism, and dietary factors that alter the responses of ligand binding and activation of cannabinoid receptors and its role in the brain. Herein, the objectives are to (1) explain the role of the ECS in the body, (2) describe the relationship between dietary polyunsaturated fatty acids and macronutrient intake and systemic metabolism, and (3) present areas of promising research where exercise induces endocannabinoid production in the brain to benefit well-being. There are many gaps in the knowledge of how the ECS participates in controlling pain through exercise; however, emerging research will reveal key relationships to understand this system in

the brain and body."

-Department of Nutrition, University of California, Davis, CA, USA.
https://pubmed.ncbi.nlm.nih.gov/31280882/

Omega-3 polyunsaturated fatty acids and human health outcomes

"Current intakes of very long chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are low in most individuals living in Western countries. A good natural source of these fatty acids is seafood, especially oily fish. Fish oil capsules contain these fatty acids too. Very long chain omega-3 fatty acids are readily incorporated from capsules into transport, functional, and storage pools. This incorporation is dose-dependent and follows a kinetic pattern that is characteristic for each pool. At sufficient levels of incorporation, EPA and DHA influence the physical nature of cell membranes and membrane protein-mediated responses, eicosanoid generation, cell signaling and gene expression in many different cell types. Through these mechanisms, EPA and DHA influence cell and tissue physiology, and the way cells and tissues respond to external signals. In most cases, the effects seen are compatible with improvements in disease biomarker profiles or in health-related outcomes. As a result, very long chain omega-3 fatty acids play a role in achieving optimal health and in protection against disease. Long chain omega-3 fatty acids protect against cardiovascular morbidity and mortality, and might be beneficial in rheumatoid arthritis, inflammatory bowel diseases, childhood learning, and behavior, and adult psychiatric and neurodegenerative illnesses. DHA has an important structural role in the eye and brain, and its supply early in life is known to be of vital importance. On the basis of the recognized health improvements brought about by long chain omega-3 fatty acids, recommendations have been made to increase their intake."

-Institute of Human Nutrition, School of Medicine, University of Southampton, MP887 Southampton General Hospital
https://pubmed.ncbi.nlm.nih.gov/19391122/

The endocannabinoid system in normal and pathological brain ageing

"The role of endocannabinoids as inhibitory retrograde transmitters is now widely known and intensively studied. However, endocannabinoids also influence neuronal activity by exerting neuroprotective effects and regulating glial responses. This review centres around this less-studied area, focusing on the cellular and molecular mechanisms underlying the protective effect of the cannabinoid system in brain ageing. The progression of ageing is largely determined by the balance between detrimental, pro-ageing, largely stochastic processes, and the activity of the homeostatic defence system. Experimental evidence suggests that the cannabinoid system is

part of the latter system. Cannabinoids as regulators of mitochondrial activity, as anti-oxidants and as modulators of clearance processes protect neurons on the molecular level. On the cellular level, the cannabinoid system regulates the expression of brain-derived neurotrophic factor and neurogenesis. Neuroinflammatory processes contributing to the progression of normal brain ageing and to the pathogenesis of neurodegenerative diseases are suppressed by cannabinoids, suggesting that they may also influence the ageing process on the system level. In good agreement with the hypothesized beneficial role of cannabinoid system activity against brain ageing, it was shown that animals lacking CB1 receptors show early onset of learning deficits associated with age-related histological and molecular changes. In preclinical models of neurodegenerative disorders, cannabinoids show beneficial effects, but the clinical evidence regarding their efficacy as therapeutic tools is either inconclusive or still missing."….

"Ageing is associated with a decline of motor coordination [1], sensory abilities [2], attention and cognitive performance [3], which together are responsible for the increasing deficits in learning and memory tasks. However, as with all age-related health issues, there is a wide spectrum of potential outcomes: While many senior citizens still enjoy their cognitive abilities at an advanced age, others, especially those who suffer from neurodegenerative disorders such as Alzheimer's disease (AD), may show signs of cognitive impairment early in their life. Thus, a better understanding of the molecular and cellular processes that contribute to, or protect against, cognitive decline, may offer novel routes for therapy and prevention.

The mitotic activity within the central nervous system is low and the newly generated cells are mostly glia cells. Neurogenesis is restricted to the subventricular zone and to the subgranular zone of the hippocampus in mammals. Only a small percentage of the new neurons integrate to the existing neuronal networks, the majority undergo apoptosis and die. Although the brain is mostly a post-mitotic organ, the onset and progression of age-related changes is independent from the chronological age of the neurons but correlates with the lifespan of the species: neurons from 3-year-old mice show signs of accelerated senescence, whereas neurons from the brain of a 3-year-old dog are free from these changes. At present, the reason for this huge interspecies difference, despite identical mechanisms influencing the process of brain ageing, is not fully understood.

The onset and progression of age-related decline in brain functions also differs strongly between the cognitive domains in humans [3] and in animals from primates [4] and rodents [5] to zebrafish [6]. The reason for this large variance is partly the differences in the ability to recruit additional brain areas for task solving, which can partially counterbalance the effect of functional decline [7]. Another factor, which may contribute to the differences in the effect of ageing on cognitive functions, is the large variance in the sensitivity to age-related changes between brain areas and

neuronal types [8,9]. Nevertheless, it is generally assumed that age-related progression in synaptic dysfunction and neuronal plasticity impairment are the direct causes of the alterations in neuronal connectivity [10] and thus functional deficits in ageing [11].

Probably the most consistent change during healthy ageing in the brain structure in humans is the shrinkage in brain volume and the expansion of the ventricular system. The frontal and parietal cortex together with the putamen, thalamus and accumbens are the most affected areas, whereas the volume of the brain stem remains largely unchanged in ageing [12]. Atrophic changes in white matter [13] play a major role in the reduction of brain volume. The white matter, of which the integrity is crucial for the communication between brain areas, contains mostly large myelinated axons. Probably both degeneration and loss of nerve fibres, and deterioration of myelin sheets with age, contribute to the reduction of white matter volume [14,15]. Although it is tempting to speculate that the degeneration of white matter contributes to the development of age-related cognitive deficits, the correlation between these structural and functional changes is weak [16]. In normal healthy ageing, the global number of microglia [17] or neurons [18] does not decrease significantly. However, a significant decline in neuronal number was detected in several brain regions such as the subiculum and hilus regions of the hippocampus [19] and in the entorhinal cortex [20]. These changes correlate well with the severity of declarative memory decline [21]. Although the intensity of adult neurogenesis strongly decreases in ageing, it is improbable that this effect contributes to the reduction of neuronal numbers in the hippocampus [22]. However, because the newly generated neurons participate in pattern separation involving the generation of new neuronal networks [23], this effect can contribute to age-related cognitive deficits. The extent and branching of dendrites is largely preserved during ageing [24] (but see also [25]) with a region-specific pattern [26,27], which suggests that during healthy ageing it is probably functional rather than structural alterations that are responsible for the progression of cognitive ageing.

Although detailed stereological analyses of the ageing brain revealed that the histological structure of the brain is largely preserved, the expression and composition of neurotransmitter receptors, the amount of trophic factor and their receptors characteristically changes in normal ageing and in neurodegenerative disorders [28]. Not surprising therefore that the intracellular signalling systems where the receptor signals converge also undergo characteristic changes during ageing in both neurons and glial cells. Substantial evidence from a variety of species indicates that cAMP response element-binding protein (CREB) is a molecular switch that converts alterations in receptor activity into transcriptional changes leading to long-lasting adaptation [29]. A crucial role of CREB signalling in memory formation was found in both invertebrates and vertebrates [30]. Generally, decreased CREB activity was associated with

learning impairments in healthy aged animals [31,32] and with cognitive deficits in animal models of neurodegenerative disorders [33–35]. Importantly, the level of phosphorylated CREB and the activity-induced increase in CREB phosphorylation is diminished in ageing [36,37], and this itself may influence the ageing process [38,39]. Altered calcium signalling in ageing neurons significantly contributes to diminished CREB activity. It is suggested that the calcium homeostasis is disturbed in ageing, because the amplitude of the calcium-dependent after-hyperpolarising potential is increased in aged neurons [40], which makes them less excitable. The reason for this phenomenon is that the expression of L-type calcium channels increases with age [41], whereas the expression of proteins involved in the termination of calcium signal such as calcium extrusion ATPases [42,43] and calcium-binding proteins [44] is diminished in old neurons. These changes may lead to an enhanced calcium signal after activation and elevated activity of calcium-dependent signalling pathways. Age-dependent alterations in the intracellular signalling system have a huge impact on the transcriptional activity of the cells [30,38,45].

Change in the expression profile during ageing in the brain is a characteristic phenomenon [46] observed from humans [47] and mice [48] to Drosophila [49]. The differences in expression patterns are more prominent between age groups than between sexes, ethnicities or individuals in humans [50]. Generally, among the most affected genes are members of the calcium signalling and the CREB pathway [24], genes playing central roles in synaptic plasticity, stress responses and inflammation [47,51]. The measure of age-dependent changes in gene expression correlated with memory performance [52,53] and could be partially reversed by techniques known to positively influence the process of brain ageing [51,54,55]. It should nevertheless be noted that the detected changes in gene expression could be responsible for the neuronal deficits but they could also be adaptive, helping to maintain the structural integrity of neuronal networks in the ageing environment [56]. In neurodegenerative disorders, an acceleration of expression changes is observed in genes involved in inflammatory and apoptotic processes; thus, there is partially a continuum between age-related and neuropathological expression changes. On the other hand, there is a group of genes where the expression change is specific for the disease and the expression pattern significantly differs from the pattern observed in age-matched healthy controls [57–59]. The reason for the altered gene expression is, besides the changes in the intracellular signalling system, also an alteration of the epigenetic structure. During ageing, there is a characteristic change in chromatin structure owing to histone modifications [60,61], which can profoundly influence the accessibility of genes to transcription factors and thus the cognitive functions [62].“…

4. CANNABINOID SYSTEM MAY CHANGE DURING AGEING IN THE BRAIN

“Because cannabinoid system activity regulates mechanisms underlying normal and pathological

ageing, age-dependent change in the activity of the cannabinoid system might contribute to the process of ageing. Although the results of different groups are sometimes conflicting, a decline in cannabinoid system activity in ageing is probable. Berrendero, in one of his earlier works, found a lower level of CB1 receptor level in rats in a brain-region-specific manner: the reduction was most prominent in the cerebellum and cerebral cortex, whereas it was less pronounced but still significant in the limbic and hypothalamic structures as well as in the hippocampus [222]. A similar decrease in both CB1 receptor binding and mRNA levels was found in most of the basal ganglia in rats during ageing [223]. Also, in isolated rat hippocampal synaptosomes, a reduction in CB1 receptor densities in ageing was described [224]. On the contrary, Liu et al. [225] found no differences in CB1 receptor protein levels between four- and 24-month-old rats in the hippocampus. They found, however, a significant difference in the CB1 receptor levels in the adjacent structures: they were reduced in the postrhinal, whereas elevated in the entorhinal and temporal cortices in the old animals. Wang et al. [226], testing C57BL/6J mice, did not find differences in CB1 densities in the hippocampus, limbic forebrain, amygdala and cerebellum. On the other hand, he reported a significantly reduced coupling between the receptors and Gi proteins in the limbic forebrain during ageing, which could be responsible for a reduced CB1 receptor signalling even when receptor levels are unchanged. In humans, a sex-dependent increase in CB1 receptor binding during ageing in the basal ganglia, lateral temporal cortex and in limbic areas was reported [227]. Whether the level of endogenous cannabinoids changes in ageing is unclear: some studies have reported diminished anandamide levels during ageing in CB1-receptor-deficient mice [228,229], whereas others found no significant differences in the endocannabinoid levels during ageing in different brain regions in WT or CB1-receptor-deficient mice [226]. There are also considerable differences in the endogenous cannabinoid concentrations reported in those earlier studies compared with more recent work (for review, see Buczynski & Parsons [230]). It is now known that multiple factors can influence the endogenous cannabinoid levels, such as post-mortem tissue handling and sample extraction methods, thus contributing to discrepancies between the studies from different groups."…

-Andras Bilkei-Gorzo

-Institute of Molecular Psychiatry, University of Bonn, Bonn 53127, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481530

See also Microglial & Glial Cells

Aging Nervous System

…“Diseases of the aging nervous system, such as Parkinson's disease, Alzheimer's disease, and stroke, are serious global public health crises as there is no cure for them currently. These lucrative markets have thus attracted the interest of a majority of large pharmaceutical companies which have put a tremendous effort into seeking medications to relieve the symptoms. However, despite successful preclinical testing, clinical trials for novel drugs have a poor track record of success.”…

-Grape King Bio Ltd, Zhong-Li Dist., Taoyuan City, Taiwan
-Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei City, Taiwan
-Institute of Food Science and Technology, National Taiwan University, Taipei City, Taiwan
-Department of Food Science, Nutrition and Nutraceutical Biotechnology, Shih Chien University, Taipei City, Taiwan
-Institute of Biotechnology, National Changhua University of Education, Changhua, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987239/

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“The immune system plays important roles in maintaining the homeostasis of tissue and responding to infection and injury.[13-15] Activation of immune cells lead to the release of leukocytes into tissues, but in the brain, this does not occur unless there has been damage or destruction of blood-brain barrier.[16] The term neuroinflammation is used for chronic inflammation of central nervous system (CNS) and defined as a reaction that is caused by infectious diseases, and malicious damage. Two groups of nerve cells inflammatory are involved in the immune response. The first group consists of lymphocytes, monocytes, and macrophages and the second group is microglia and astrocytes in the CNS. Microglia is responsible for the safety and innate response to inflammatory signals and is able to get warning signals. [15,17] Microglial activation is involved in the pathogenesis of several neurodegenerative diseases like Alzheimer’s disease (AD) and Parkinson’s disease (PD). [18-20] “

-Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
-Iranian Centre of Neurological Research, Neuroscience institute, Department of Neurology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
-Headache Department, Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
-Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5937007/

See also, Alzheimer's Disease , Dementia , Lipids , Microglial Cells

Aggressive Behaviour

Long chain n-3 [omega-3] polyunsaturated fatty acids decrease feelings of anger in substance abusers

…"Deficiencies in n-3 [omega-3] PUFAs have been reported in a wide range of psychiatric disorders that have included (but are not limited to) depression, suicidal tendencies and aggressive disorders (Alessandri et al., 2004; Young and Conquer, 2005)." …

-VA New York Harbor Healthcare System – Brooklyn Campus, 800 Poly Place, Brooklyn, NY, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225526/

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"There is mounting evidence that low levels of some polyunsaturated fatty acids (PUFAs) play a role in the pathophysiology of aggressive disorders."…

…"These data suggest that patients' diets prior to their hospitalization were less than optimal and that the diet of the aggressive individuals might have been particularly deficient in n-3 rich nutrients. These data also give additional support to evidence indicating a possible link between an n-3 deficiency and aggression in humans."

-Department of Psychiatry, State University of New York-Health Science Center at Brooklyn, Brooklyn, NY 11209, USA.
https://www.ncbi.nlm.nih.gov/pubmed/12957349

Progress on relationship between omega-3 polyunsaturated fatty acids and violent-aggressive behavior

"The relationship between omega-3 polyunsaturated fatty acids (PUFAs) and violent-aggressive behavior has been payed attention since 1980s. Their correlation was explored by many epidemiological investigations, and the effect of PUFAs on prevention or reduction of violent-aggressive behavior in different groups were also affirmed by some intervention studies. This article summarized the previous studies and reviewed the history of epidemiological or intervention studies on PUFAs and its relationship with violent-aggressive behavior. It also presented the possible influencing factors in these studies and possible mechanisms."…

-Department of Forensic Medicine, Shanghai Medical College, Fudan University, Shanghai, China.
https://pubmed.ncbi.nlm.nih.gov/21425611

Airway & Breathing

Endocannabinoid System in the Airways

"Cannabinoids and the mammalian endocannabinoid system is an important research area of interest and attracted many researchers because of their widespread biological effects. The significant immune-modulatory role of cannabinoids has suggested their therapeutic use in several inflammatory conditions. Airways are prone to environmental irritants and stimulants, and increased inflammation is an important process in most of the respiratory diseases. Therefore, the main strategies for treating airway diseases are suppression of inflammation and producing bronchodilation. The ability of cannabinoids to induce bronchodilation and modify inflammation indicates their importance for airway physiology and pathologies. In this review, the contribution of cannabinoids and the endocannabinoid system in the airways are discussed, and the existing data for their therapeutic use in airway diseases are presented."…

"The studies about the contribution of the endocannabinoid system in the airways indicate the importance of both CB1 and CB2 receptors (Table 1). Among these two receptors, CB1 subtype is more likely to be involved in the functional reactivity of the airways as its stimulation can inhibit the contraction of airway smooth muscle. This effect seems to be mediated by the inhibition of acetylcholine release from cholinergic nerves, rather than a direct effect on the smooth muscle itself. Unlike CB1 receptors, CB2 receptors are likely to be involved in the mechanisms for neurogenic inflammation, probably acting through the sensory nerves (Figure 1). The contribution of both receptors in the immune modulation of airways is well established, as discussed above. The data of the present literature indicate a significant contribution of CB2 receptors in allergic diseases, which can be considered for the treatment of allergic asthma. However, the possible involvement of CB1 receptors should not be excluded, since they are expressed and functional almost in every immune cell. Therefore, appropriate cannabinoid receptor ligands may be rational candidates for the treatment of airway diseases because of their anti-inflammatory and bronchodilatory effects."…

-Department of Pharmacology, Faculty of Pharmacy, Hacettepe University
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943521/

Role of omega-3 fatty acids and their metabolites in asthma and allergic diseases

"Omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are found naturally in fish oil and are commonly thought to be anti-inflammatory nutrients, with protective

effects in inflammatory diseases including asthma and allergies. The mechanisms of these effects remain mostly unknown but are of great interest for their potential therapeutic applications. Large numbers of epidemiological and observational studies investigating the effect of fish intake or omega-3 fatty acid supplementation during pregnancy, lactation, infancy, childhood, and adulthood on asthmatic and allergic outcomes have been conducted. They mostly indicate protective effects and suggest a causal relationship between decreased intake of fish oil in modernized diets and an increasing number of individuals with asthma or other allergic diseases. Specialized pro-resolving mediators (SPM: protectins, resolvins, and maresins) are generated from omega-3 fatty acids such as EPA and DHA via several enzymatic reactions. These mediators counter-regulate airway eosinophilic inflammation and promote the resolution of inflammation in vivo. Several reports have indicated that the biosynthesis of SPM is impaired, especially in severe asthma, which suggests that chronic inflammation in the lung might result from a resolution defect. This article focuses on the beneficial aspects of omega-3 fatty acids and offers recent insights into their bioactive metabolites including resolvins and protectins."

-Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan; -Graduate School of Medical Life Science, Yokohama City University, Kanagawa, Japan.
https://pubmed.ncbi.nlm.nih.gov/25572556

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…"In the lung, anandamide participates in the intrinsic control of airway responsiveness, exerting dual effects (inhibition and initiation of bronchospasm) depending on the state of contraction of the bronchial muscle. Anandamide could be shown to be synthesized in rat lung tissue on calcium ion stimulation [5]. 2-AG has been detected in the rat lung as well [21] with no overt physiological significance. In guinea pigs, high doses of intravenous anandamide did not elicit ronchodilation but reduced airway epithelial injury and pulmonary leukocytosis [34]. Thus cannabinoid actions on bronchial smooth muscle tone might depend on the route of application and the species used."…

-Department of Internal Medicine I/Center of Cardiovascular Medicine, University of Wu¨rzburg, Germany
https://journals.physiology.org/doi/pdf/10.1152/ajpheart.00718.2005

Alcohol

…"In 1987, Glen et al. summarized alcohol effects in PUFAS metabolism. He stated that ethanol consumption leads to an increase in the ratio of linoleic to arachidonic acid in the phospholipids of tissues. Some of the main contributors for this PUFAS altered ratio would be a reduced intake,

absorption, and alteration in fatty acid metabolism [18]. Alcohol also inhibits ∂-6 and ∂-5-desaturases, enzymes associated with the conversion of linoleic acid to gamma linolenic (GLA), and dihomogamma linolenic acids to arachidonic acid [19]. Moreover alcohol has a direct effect on cell membranes composition. A relative increase in n-6 PUFAS in the membranes increases the fluidity resulting in cell damage. Interestingly, it has been reported that this pathological effect could be reduced, at least partially by fatty acid supplementation, especially n-3 PUFAS [18].

Previous studies have evaluated the role of PUFAS in alcoholism. They are linked to the action of neurotransmitters [20], liver damage produced by alcohol [21,22], their effects on tolerance [23] and even as attenuators of the negative effects of chronic alcohol use [24]. Treatment with omega-3 looks promising, but few studies have been published so far. Further studies are needed to identify individuals likely to be benefited by this type of treatment, assess the durability of these effects and to determine dosage and treatment time recommended [25].

There is no literature to date, associating PUFAS as a potential treatment to prevent compulsion for alcohol. This association seems plausible, since the lipid fraction of cell membranes consists of PUFAS, and chronic alcohol use alter the absorption of these acids, modifying its permeability. The aim of this study was to investigate the effects of PUFAS in alcohol-dependent patients, and to evaluate the possible reduction in craving for alcohol."…

-Psychobiology Department, Federal University of São Paulo, Edifício de Ciências Biomédicas, Rua Botucatu 862 - 1° Andar, São Paulo, Brasil

-Laboratory of Physical Activity and Aging of Rio Claro Biosciences Institute - Universidade Paulista Júlio de Mesquita Filho, Rio Claro, São Paulo, Brasil and Centro de Matemática, Computação e Cognição da UFABC, Santo Andrá, São Paulo, Brasil

-Psychobiology Department, Federal University of São Paulo, Edifício de Ciências Biomédicas, Rua Botucatu 862 - 1° Andar, São Paulo, Brasil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3162484/

Genetic impairment of frontocortical endocannabinoid degradation and high alcohol preference.

"Endocannabinoid signaling has recently been implicated in ethanol-seeking behavior. We analyzed the expression of endocannabinoid-related genes in key brain regions of reward and dependence, and compared them between the alcohol-preferring AA (Alko Alcohol) and nonpreferring ANA (Alko Non-Alcohol) rat lines. A decreased expression of fatty acid amidohydrolase (FAAH), the main endocannabinoid-degrading enzyme, was found in prefrontal cortex (PFC) of AA rats, and was accompanied by decreased enzyme activity in this region."…

"Together, this suggests an overactive endocannabinoid transmission in the PFC of AA animals,

and a compensatory downregulation of CB1 signaling. The functional role of impaired FAAH function for alcohol self-administration was validated in two independent ways. The CB1 antagonist SR141716A potently and dose-dependently suppressed self-administration in AA rats when given systemically, or locally into the PFC, but not in the striatum. Conversely, intra-PFC injections of the competitive FAAH inhibitor URB597 increased ethanol self-administration in nonselected Wistar rats. These results show for the first time that impaired FAAH function may confer a phenotype of high voluntary alcohol intake, and point to a FAAH both as a potential susceptibility factor and a therapeutic target."

Laboratory of Clinical and Translational Studies, NIAAA, National Institutes of Health, USA
http://www.ncbi.nlm.nih.gov/pubmed/16482090

Converging action of alcohol consumption and cannabinoid receptor activation on adult hippocampal neurogenesis.

"Alcoholism is characterized by successive periods of abstinence and relapse, resulting from long-lasting changes in various circuits of the central nervous system. Accumulating evidence points to the endocannabinoid system as one of the most relevant biochemical systems mediating alcohol addiction. The endocannabinoid system regulates adult neurogenesis, a form of long-lasting adult plasticity that occurs in a few areas of the brain, including the dentate gyrus. Because exposure to psychotropic drugs regulates adult neurogenesis, it is possible that neurogenesis might be implicated in the pathophysiology, and hence treatment, of neurobiological illnesses related to drugs of abuse."....

..."Furthermore, adult neurogenesis inversely correlated with voluntary consumption of alcohol. These findings suggest that adult hippocampal neurogenesis is a key factor involved in drug abuse and that it may provide a new strategy for the treatment of alcohol addiction and dependence."

Department of Psychobiology, Faculty of Psychology, Campus de Somosaguas, Complutense University of Madrid, Spain.
http://www.ncbi.nlm.nih.gov/pubmed/20047713

Endocannabinoid signaling via cannabinoid receptor 1 is involved in ethanol preference and its age-dependent decline in mice.

"Cannabinoids and ethanol can activate the same reward pathways, which could suggest endocannabinoid involvement in the rewarding effects of ethanol."

... "These findings suggest that endocannabinoids acting at CB1 contribute to ethanol preference,

and decreased coupling of CB1 to G proteins in the limbic forebrain by mechanisms other than altered receptor or G protein levels may be involved in the age-dependent decline in the appetite for both ethanol and food."

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA.

http://www.ncbi.nlm.nih.gov/pubmed/12538878

The role of the cannabinoid system in the pathogenesis and treatment of alcohol dependence

"The lack of satisfactory results of alcohol dependence treatment force us to search for new directions of research. Recent studies concentrate on endocannabinoid transmission. The results show an interplay between the endocannabinoid and dopaminergic signaling in activation of the limbic reward system. The mechanisms leading to development of dependence are very complex and poorly recognized. Endogenous cannabinoids seem to have an important role in the functioning of this system, both directly and indirectly affecting the level of different neurotransmitters. The effect of alcohol on the endocannabinoid system is also complex and involves changes at the molecular level. Experimental studies have demonstrated an important role of the CB1 receptors in the neurochemical mechanism of alcohol consumption and its regulation. SR141716 (rimonabant), a CB1 receptor antagonist, significantly lowers voluntary alcohol intake and motivation for its consumption in various experimental studies. Very encouraging results of preclinical studies were not completely confirmed in the clinical studies. However, further clinical studies are still necessary."

Medical University of Lodz, Poland

http://www.ncbi.nlm.nih.gov/pubmed/21934185

Ethanol self-administration and ethanol conditioned place preference are reduced in mice lacking cannabinoid CB1 receptors.

"Cannabinoids are postulated to play a role in modulating the reinforcing effects of abused drugs, including alcohol."

…"These results demonstrate that the cannabinoid CB1 receptor is an essential component of the molecular pathways underlying the reinforcing effects of alcohol. Thus, medications targeting the CB1 receptors may be beneficial for the treatment of alcoholism."

-Behavioral Pharmacology Lab, Department of Medicine, Brookhaven National Laboratory, Building 490, 30 Bell Avenue, Upton, NY, USA.

http://www.ncbi.nlm.nih.gov/pubmed/16140402

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Manipulation of fatty acid amide hydrolase functional activity alters sensitivity and dependence to ethanol.

..."These findings suggest that an elevation in the AEA [anandamide] content and its action on the limbic CB(1) receptor and MO receptor might contribute to ethanol reinforced behavior. Treatment with drugs that decrease AEA tone might prove useful in reducing excessive ethanol consumption."

Division of Analytical Psychopharmacology, New York State Psychiatric Institute, New York, USA.
http://www.ncbi.nlm.nih.gov/pubmed/17944864

The anandamide transport inhibitor AM404 reduces ethanol self-administration.

"The endocannabinoid system mediates in the pharmacological actions of ethanol and genetic studies link endocannabinoid signaling to alcoholism."...

The European TARGALC Consortium, Hospital Carlos Haya, Spain
http://www.ncbi.nlm.nih.gov/pubmed/17650118

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"These findings suggest that ECS [The Endocannabinoid System] modulation influences both conditioned fear and conditioned alcohol reward behavior."...

Department of Psychological Sciences, Purdue University, USA
http://www.ncbi.nlm.nih.gov/pubmed/20838777

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..."Only in the case of alcohol and nicotine, we observed a common increase in AEA [anandamide] contents in the limbic forebrain. This observation is important considering that this region is a key area for the reinforcing properties of habit-forming drugs, which might support the involvement of endocannabinoid transmission in some specific events of the reward system activated by these drugs."

Department of Biochemistry and Molecular Biology, Faculty of Medicine, University Complutense, University City
http://www.ncbi.nlm.nih.gov/pubmed/12393235

Role of endocannabinoids and cannabinoid CB1 receptors in alcohol-related behaviors

“This review presents the remarkable research during the past several years indicating that some of the pharmacological and behavioral effects of alcohol, including alcohol drinking and alcohol-preferring behavior, are mediated through one of the most abundant neurochemical systems in the central nervous system, the endocannabinoid signaling system. The advances, with the discovery of specific receptors and the existence of naturally occurring cannabis-like substances in the mammalian system and brain, have helped in understanding the neurobiological basis for drugs of abuse, including alcoholism. The cDNA and genomic sequences encoding G-protein-coupled cannabinoid receptors (CB1 and CB2) from several species have now been cloned. This has facilitated discoveries of endogenous ligands (endocannabinoids). To date, two fatty acid derivatives characterized to be arachidonylethanolamide and 2-arachidonylglycerol have been isolated from both nervous and peripheral tissues. Both these compounds have been shown to mimic the pharmacological and behavioral effects of Delta9-tetrahydrocannabinol, the psychoactive component of marijuana. The involvement of the endocannabinoid signaling system in tolerance development to drugs of abuse, including alcohol, were unknown until recently. Studies from our laboratory demonstrated for the first time the downregulation of CB1 receptor function and its signal transduction by chronic alcohol. The observed downregulation of CB1 receptor binding and its signal transduction results from the persistent stimulation of receptors by the endogenous CB1 receptor agonists arachidonylethanolamide and 2-arachidonylglycerol, the synthesis of which is increased by chronic alcohol treatment. The deletion of CB1 receptor has recently been shown to block voluntary alcohol intake in mice, which is consistent with our previous findings where the DBA/2 mice known to avoid alcohol intake had significantly reduced brain CB1 receptor function. These findings suggest a role for the CB1 receptor gene in excessive alcohol drinking behavior and development of alcoholism. Ongoing investigations may lead to the development of potential therapeutic agents to modulate the endocannabinoid signaling system, which will be helpful for the treatment of alcoholism.”

-New York State Psychiatric Institute, New York 10032, USA.
https://pubmed.ncbi.nlm.nih.gov/15542757

Endocannabinoid Signaling in the Central Amygdala and Bed Nucleus of the Stria Terminalis: Implications for the Pathophysiology and Treatment of Alcohol Use Disorder

"High rates of relapse are a chronic and debilitating obstacle to effective treatment of alcohol use disorder (AUD); however, no effective treatments are available to treat symptoms induced by protracted abstinence. In the first part of this two-part review series, we examine the literature supporting the effects of alcohol exposure within the extended amygdala (EA) neural circuitry. In part two, we focus in on a potential way to combat negative affect associated with AUD, by exploring the therapeutic potential of the endogenous cannabinoid (eCB) system. The eCB system is a potent modulator of neural activity in the brain, and its ability to mitigate stress and negative affect has long been an area of interest for developing novel therapeutics. This review details the recent advances in our understanding of eCB signaling in two key regions of the EA, the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST), and their role in regulating negative affect. Despite an established role for EA eCB signaling in reducing negative affect, few studies have examined the potential for eCB-based therapies to treat AUD-associated negative affect. In this review, we present an overview of studies focusing on eCB signaling in EA and cannabinoid modulation on EA synaptic activity. We further discuss studies suggesting dysregulation of eCB signaling in models of AUD and propose that pharmacological augmentation of eCB could be a novel approach to treat aspects of AUD. Lastly, future directions are proposed to advance our understanding of the relationship between AUD-associated negative affect and the EA eCB system that could yield new pharmacotherapies targeting negative affective symptoms associated with AUD."…

-Vanderbilt Center for Addiction Research, Nashville, TN, USA
-Molecular Physiology & Biophysics, the, Nashville, TN, USA
-Vanderbilt Brain Institute, Nashville, TN, USA
-Vanderbilt J.F. Kennedy Center for Research on Human Development, Nashville, TN, USA
-Department of Psychiatry and Behavioral Sciences, Nashville, TN, USA
Co-corresponding Authors:
**These authors contributed equally to this work*
Corresponding Authors: Danny G. Winder, Ph.D., Vanderbilt Center for Addiction Research
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6779484/

Allergies (Allergy)

The expression of cannabinoid receptor 1 is significantly increased in atopic patients

"The human endogenous cannabinoid system (ECS) is a complex signaling network involved in a large number of physiological processes. Recently, 2 articles reported in the Journal of Allergy and Clinical Immunology describe that endocannabinoids and cannabinoid receptor (CB) 1 signaling may play a potent inhibitory role in human mast cell (MC) degranulation and activation in the airway mucosa and skin, suggesting that targeting the ECS in these tissues might well represent a novel strategy for the treatment of allergy. [1,2] In these studies, the pharmacological blockage or gene silencing of CB1 significantly stimulated the degranulation and maturation of MCs from resident progenitors by mechanisms partially depending on the upregulation of stem cell factor production, which was counteracted by the activation of CB1 with specific agonists. Although it is plausible that the ECS may contribute to the regulation of allergic diseases, studies reporting human data are still scarce. Accordingly, we explored the potential effect of the ECS in human allergic diseases by quantifying and comparing the in vivo mRNA expression levels of the main components of the ECS (the receptors CB1 and CB2 and the enzymes fatty acid amide hydrolase [FAAH] and monoacylglycerol lipase [MAGL] that are involved in the hydrolysis and inactivation of endocannabinoids) in tonsils and PBMCs of atopic and healthy subjects."

-Department of Organic Chemistry, School of Chemistry, Complutense University of Madrid, Madrid, Spain.

-Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria.

-Department of Pediatrics, Turku University Hospital, Turku, Finland.

-Department of Otorhinolaryngology, Turku University Hospital, Turku, Finland; Department of Otorhinolaryngology, Satakunta Central Hospital, Pori, Finland.

-Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.

-Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University of Madrid, Madrid, Spain.

https://www.jacionline.org/article/S0091-6749(13)02936-9/abstract

http://bit.do/ecs_allergy

The cannabinoid receptor-2 is involved in allergic inflammation

"These results clearly demonstrate that CB2 [cannabinoid receptors 2] and its endogenous ligands participate not only in the acute, edematous phase of allergic dermatitis, but also in the chronic irreversible acanthosis reaction."

-Pharmaceutical Frontier Research Laboratories, Central Pharmaceutical Research Institute, Japan Tobacco Inc., 1-13-2 Fukuura, Yokohama, Kanagawa 236-0004, Japan.

https://www.ncbi.nlm.nih.gov/m/pubmed/22525379

The role of cannabinoids in inflammatory modulation of allergic respiratory disorders, inflammatory pain and ischemic stroke

"This review is intended to offer updated information on the involvement of cannabinoids in the process of inflammation, focusing on immune/allergic reactions, inflammatory pain and neuroinflammation and discussing the interactions among endocannabinoid metabolism, prostanoids and nitric oxide. Two types of cannabinoid receptors, CB1 and CB2, which belong to the G protein-coupled receptor family, have been identified and are targeted by numerous exogenous and endogenous ligands. The activation of CB2 receptors on mast cells has direct antiinflammatory effects, causing decreased release of pro-inflammatory mediators by these cells. The activation of CB1 receptors on bronchial nerve endings has bronchodilator effects by acting on the airway smooth muscle and may be beneficial in airway hyperreactivity and asthma. Moreover, pharmacologic interference with endocannabinoid metabolism has been demonstrated to result in anti-nociceptive activity, mediated by CB1 and CB2 receptors, in animal models of inflammatory pain. The presence of endocannabinoid machinery in the central nervous system, together with high levels of CB1 expression, suggests that the endocannabinoid system is an important modulator of neuroinflammation and a possible drug target. In selected conditions, the activation of CB1 receptors in cerebral blood vessels can have beneficial antiischemic effects. However, as endocannabinoids can also bind to vanilloid receptors, they may also mediate neurotoxic effects."

See also: National Institute of Health quote below regarding toxicity of endocannabinoids such as THC.

Department of Preclinical and Clinical Pharmacology, University of Florence, Viale G. Pieraccini 6, I- 50139 Florence, Italy.
https://pubmed.ncbi.nlm.nih.gov/22420307/

Arachidonic acid signaling in pathogenesis of allergy: therapeutic implications

"In recent years, significant progress has been made in understanding the involvement of pro-inflammatory lipidic mediators in the pathogenesis of allergic diseases. The most relevant lipidic mediator is arachidonic acid and its metabolites. Arachidonic acid is the precursor for biosynthesis of eicosanoids, potent mediators of inflammation that have been implicated in the pathogenesis of diverse disease processes. Eicosanoids are mainly synthesized by the action of cyclo-oxygenase (prostaglandin endoperoxide synthase) that generates prostaglandins and thromboxane, and 5-lipoxygenase, which leads to the production of leukotrienes. In addition, 12- and 15-lipoxygenase are found in mammalian systems. The activity of these enzymes results in the formation of different hydroxyeicosatetraenoic acids, but their functions in vivo have not

been clearly established in normal or pathological states. Since several arachidonic acid metabolites clearly play an important role in allergic response, a substantial effort has been directed to understanding the cellular and molecular aspects of these pathways and their pharmacological modulation. This review summarizes some of these aspects based on our current knowledge of the involvement of arachidonic metabolism in the pathogenesis of allergic diseases and outlines the potential therapeutic opportunities that can result from the modulation of these metabolites."

-Department of Experimental Pathology, Barcelona Institute for Biomedical Research
https://pubmed.ncbi.nlm.nih.gov/15853735

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..."Studies have shown that endocannabinoids and cannabinoid CB1 receptors may have a significant inhibitory role in human mast cell degranulation and activation in the airway mucosa and skin, suggesting the contribution of the endocannabinoid system in the allergic diseases [59,60]."...

-Department of Pharmacology, Faculty of Pharmacy, Hacettepe University
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943521/

Can Early Omega-3 Fatty Acid Exposure Reduce Risk of Childhood Allergic Disease?

"A causal link between increased intake of omega-6 (n-6) polyunsaturated fatty acids (PUFAs) and increased incidence of allergic disease has been suggested. This is supported by biologically plausible mechanisms, related to the roles of eicosanoid mediators produced from the n-6 PUFA arachidonic acid. Fish and fish oils are sources of long chain omega-3 (n-3) PUFAs. These fatty acids act to oppose the actions of n-6 PUFAs particularly with regard to eicosanoid synthesis. Thus, n-3 PUFAs may protect against allergic sensitisation and allergic manifestations. Epidemiological studies investigating the association between maternal fish intake during pregnancy and allergic outcomes in infants/children of those pregnancies suggest protective associations, but the findings are inconsistent. Fish oil provision to pregnant women is associated with immunologic changes in cord blood. Studies performed to date indicate that provision of fish oil during pregnancy may reduce sensitisation to common food allergens and reduce prevalence and severity of atopic eczema in the first year of life, with a possible persistence until adolescence. A recent study reported that fish oil consumption in pregnancy reduces persistent wheeze and asthma in the offspring at ages 3 to 5 years. Eating oily fish or fish oil

supplementation in pregnancy may be a strategy to prevent infant and childhood allergic disease."

-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK.
-NIHR Southampton Biomeducal Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK
https://pubmed.ncbi.nlm.nih.gov/28754005

The Role of TRP Channels in Allergic Inflammation and its Clinical Relevance

"Allergy refers to an abnormal adaptive immune response to non-infectious environmental substances (allergen) that can induce various diseases such as asthma, atopic dermatitis, and allergic rhinitis. In this allergic inflammation, various immune cells, such as B cells, T cells, and mast cells, are involved and undergo complex interactions that cause a variety of pathophysiological conditions. In immune cells, calcium ions play a crucial role in controlling intracellular Ca2+ signaling pathways. Cations, such as Na+, indirectly modulate the calcium signal generation by regulating cell membrane potential. This intracellular Ca2+ signaling is mediated by various cation channels; among them, the Transient Receptor Potential (TRP) family is present in almost all immune cell types, and each channel has a unique function in regulating Ca2+ signals. In this review, we focus on the role of TRP ion channels in allergic inflammatory responses in T cells and mast cells. In addition, the TRP ion channels, which are attracting attention in clinical practice in relation to allergic diseases, and the current status of the development of therapeutic agents that target TRP channels are discussed."

-Department of Physiology, Dongguk University College of Medicine, Korea.
-Channelopathy Research Center (CRC), Dongguk University College of Medicine, Korea.
-Department of Internal Medicine Graduate School of Medicine, Dongguk University, Korea.
https://pubmed.ncbi.nlm.nih.gov/30474526/

See also Airway & Breathing , TRP Channels (Transient receptor potential channels)

Alopecia (Hair Loss)

"A type of pathological hair loss affecting mostly the scalp; most common forms of alopecia: universalis, areata, androgenetic."

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ 07103, USA

-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck 23538, Germany
-School of Translational Medicine, University of Manchester, Manchester, M13 9PL, UK
-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

Effect of a nutritional supplement on hair loss in women

"A 6-month supplementation with omega 3&6 and antioxidants acts efficiently against hair loss in improving hair density and reducing the telogen percentage and the proportion of miniaturized anagen hair. Objectively measured improvements were confirmed by the subjects' perception of efficacy."

-Laboratoires innéov, R&D, Asnières/Seine, France
https://pubmed.ncbi.nlm.nih.gov/25573272/

Combined Diet and Supplementation Therapy Resolves Alopecia Areata in a Paediatric Patient: A Case Study

"Alopecia areata (AA) is a common autoimmune condition resulting in spot baldness and, rarely, more extensive hair loss. There is an association between both the incidence and the severity of AA and several micronutrients, including vitamin D and zinc. This case reports an eight-year-old male diagnosed with AA and treated with a diet and supplemental regimen based on unrefined foods, rich in vitamins A and D, zinc, and supplemented with a multi-nutrient, zinc sulfate, and fish oil with vitamin D. Complete remission of AA was achieved within five months."

-Clinical Nutrition, The Holistic Performance Institute, Auckland, NZL
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7721078/

Alopecia Areata

Hair growth disorders: aiming to increase or decrease ECS tone

"The novel concept that human HFs [hair follicles] are both targets and sources of endocannabinoids, which, via CB1 establish an autocrine–paracrine system for negatively regulating hair growth, invites careful investigation of the growth-inhibitory effects of CB1 agonists in the putative management of unwanted hair growth such as hirsutism. Likewise, future exploitation of CB1-antagonist-based adjuvant treatment options in the clinical

management of alopecia areata and effluvium is also of potential interest."

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ, USA
-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck, Germany
-School of Translational Medicine, University of Manchester, Manchester, UK
-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

"Alopecia areata is a common autoimmune disorder that often results in unpredictable hair loss. It affects roughly 6.8 million people in the United States."

https://www.medicalnewstoday.com/articles/70956.php

Role of Arachidonic Acid in Promoting Hair Growth

"Arachidonic acid (AA) is an omega-6 polyunsaturated fatty acid present in all mammalian cell membranes, and involved in the regulation of many cellular processes, including cell survival, angiogenesis, and mitogenesis. The dermal papilla, composed of specialized fibroblasts located in the bulb of the hair follicle, contributes to the control of hair growth and the hair cycle."…

"AA was found to enhance the viability of hDPCs [human dermal papilla cells] and promote the expression of several factors responsible for hair growth, including fibroblast growth factor-7 (FGF-7) and FGF-10."…

"This study concludes that AA plays a role in promoting hair growth by increasing the expression of growth factors in hDPCs and enhancing follicle proliferation and survival."

-Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea.
-Institute of Human-Environment Interface Biology, Seoul National University Medical Research Center, Seoul, Korea.; Laboratory of Cutaneous Aging and Hair Research, Biomedical Research Institute, Seoul National University Hospital, Seoul, Korea.
-Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea.; Institute of Human-Environment Interface Biology, Seoul National University Medical Research Center, Seoul, Korea.; Laboratory of Cutaneous Aging and Hair Research, Biomedical Research Institute, Seoul National University Hospital, Seoul, Korea.
https://pubmed.ncbi.nlm.nih.gov/26848219/

Effect of a nutritional supplement on hair loss in women

"A 6-month supplementation with omega 3&6 and antioxidants acts efficiently against hair loss in improving hair density and reducing the telogen percentage and the proportion of miniaturized anagen hair. Objectively measured improvements were confirmed by the subjects'

perception of efficacy."

-Laboratoires innéov, R&D, Asnières/Seine, France.
https://pubmed.ncbi.nlm.nih.gov/25573272/

"A nutritional supplement withomega-3 and omega-6 essential fatty acids and antioxidants may improve hair density in women. "

- Health Library / Beth Israel Lahey Health, Winchester Hospital
https://www.winchesterhospital.org/health-library/article?id=21376

See also Prostaglandins , Omega Ratio

alpha-linolenic acid (ALA)

Fatty acids and fish

"So why is it important, from a health standpoint, for humans to eat fatty acid-rich foods? There are two essential fatty acids: the omega-3 fatty acid alpha-linolenic acid (ALA) and the omega-6 counterpart linoleic acid (LA); our body needs both of them for good health, but we don't synthesize them ourselves. Hence, we must obtain them through our diet. ALA is found in many leafy vegetables, nuts, and fish; LA is present in all major plant and vegetable oils. So what is the big difference between these essential fatty acids? Omega-6 fatty acid LA is converted into Prostaglandin E1 (PGE1), while omega-3 fatty acid ALA is converted into Prostaglandin E3 (PGE3). PGE1 and PGE3 can be referred to as "good" prostaglandins, since both are anti-inflammatory. Omega-6 arachidonic acid, found in dairy products, meat, and breast milk, is converted into Prostaglandin E2 (PGE2), which promotes immune inflammation through the differentiation and proliferation of specific types of lymphocytes (respectively Th1 and Th17 cells) . The functions of the three prostaglandins of the E-series, although different, all reflect a balance between effects upon interaction with activating and inhibiting proteins within cells.

The human body converts ALA to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two other essential omega-3 fatty acids that promote the "good" PGE3 pathway. This conversion, however, is not efficient and will only happen if certain enzymes are present and active. Therefore it is essential for people who consume little ALA to also get EPA and DHA in their diet.

The best source of these two omega-3 fatty acids is fatty fish.

Omega-3 fatty acids are significant structural components of the phospholipid membranes that surround cells in tissues throughout the human body, and are especially rich in the retina, brain, and spermatozoa; their presence is necessary to maintain optimal health. Omega-3 fatty acids may also reduce the risks of heart and vascular diseases through a complex cascade of reactions. Recent findings, however, put this correlation under debate, suggesting these reactions are more likely to be mediated by the full range of nutrients present in fish. Interestingly, in contrast to omega-6 fatty acids, omega-3 fatty acids do not decrease the concentrations of HDL (known as "good cholesterol"). Until the early 1900s, the consumption of omega-3 and omega-6 was more or less equal, but today we consume 10 times more omega-6 than omega-3. It is therefore also important not to forget about the direct impact of LA-rich (omega-6) diets, which can reduce ALA's (omega-3) health benefits and make ALA's conversion to EPA and DHA less efficient.

In both human consumption and the aquaculture industry, fish oil is a key source of omega-3. Its use has become controversial since it is extracted unsustainably from world oceans, yielding around one million tons of fish oil annually worldwide. Fish, however, do not themselves produce EPA and DHA; these fats make up half the weight of certain species of phytoplankton and become increasingly concentrated in marine organisms higher on the food chain. These phytoplankton, which are single-cell photosynthesizing algae, are easy to farm and may therefore play an important role in future, more sustainable directions for production of omega-3 supplements."…

-Harvard University Blog
https://sitn.hms.harvard.edu/flash/2013/issue133b

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…"ALA is metabolized to EPA, currently thought to occur predominately in liver cells, by sequential desaturation and elongation: delta-6desaturase, chain elongation and delta-5desaturase."…

-Centre for Occupational and Health Psychology, School of Psychology, Cardiff University
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257695

Alzheimer's Disease

"Amyloidogenesis is the process in which amyloid beta (Aβ) peptide aggregation results in plaque formation in central nervous system (CNS) are associated with many neurological diseases such

as Alzheimer's disease. "…

-University School of Biotechnology, Guru Gobind Singh Indraprastha University, Dwarka, India
-Department of Zoology, Jai Narain Vyas University, Jodhpur, India
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6664621/

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"Affecting more than 46.8 million people worldwide, dementia is an illness with no known cure or treatment. This number is expected to double every 20 years (Alzheimer's Disease International, 2015). AD pathology is characterized by a progressive decrease in neurons, axons, and dendrites in the brain, with progressive impairment in cognitive functioning (Sperling et al., 2011). Most theories targeting AD have focused on the role of β-amyloid deposition and accumulation in the brain, and subsequent clinically observable neurodegeneration (Hardy and Selkoe, 2002). Although the exact role of β-amyloid (Aβ) in the pathogenesis of AD is still debated, Aβ is widely believed to be a neurotoxin, inducing oxidative stress and accumulating as extracellular deposits (plaque) in the brain (Masters et al., 2013)."…

-Robert Stempel College of Public Health and Social Work, School of Social Work, Florida International University, Miami, FL, USA
-Simmons College School of Social Work, Boston, MA, USA
-Oral Health Policy and Epidemiology, Harvard School of Dental Medicine, Boston, MA, USA
-Department of Social and Behavioral Sciences, Harvard T. H. Chan School of Public Health, Boston, MA, USA
-Department of Epidemiology, University of Washington, Seattle, WA, USA
-National Alzheimer's Coordinating Center, University of Washington, Seattle, WA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5711617/

Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis

"The defining features of Alzheimer disease (AD) include conspicuous changes in both brain histology and behavior. The AD brain is characterized microscopically by the combined presence of 2 classes of abnormal structures, extracellular amyloid plaques and intraneuronal neurofibrillary tangles, both of which comprise highly insoluble, densely packed filaments. The soluble building blocks of these structures are amyloid-β (Aβ) peptides for plaques and tau for tangles. Amyloid-β peptides are proteolytic fragments of the transmembrane amyloid precursor protein, whereas tau is a brain-specific, axon-enriched microtubule-associated protein. The behavioral symptoms of AD correlate with the accumulation of plaques and tangles, and they are a direct consequence of the damage and destruction of synapses that mediate memory and cognition. Synapse loss can be caused by the failure of live neurons to maintain functional axons and dendrites or by neuron death. During the past dozen years, a steadily accumulating body of

evidence has indicated that soluble forms of Aβ and tau work together, independently of their accumulation into plaques and tangles, to drive healthy neurons into the diseased state and that hallmark toxic properties of Aβ require tau. For instance, acute neuron death, delayed neuron death following ectopic cell cycle reentry, and synaptic dysfunction are triggered by soluble, extracellular Aβ species and depend on soluble, cytoplasmic tau. Therefore, Aβ is upstream of tau in AD pathogenesis and triggers the conversion of tau from a normal to a toxic state, but there is also evidence that toxic tau enhances Aβ toxicity via a feedback loop. Because soluble toxic aggregates of both Aβ and tau can self-propagate and spread throughout the brain by prionlike mechanisms, successful therapeutic intervention for AD would benefit from detecting these species before plaques, tangles, and cognitive impairment become evident and from interfering with the destructive biochemical pathways that they initiate."

-Departments of Biology and Cell Biology, University of Virginia, Charlottesville.
https://pubmed.ncbi.nlm.nih.gov/24493463/

Dietary Docosahexaenoic Acid and Docosapentaenoic Acid Ameliorate Amyloid-β and Tau Pathology via a Mechanism Involving Presenilin 1 Levels

…"One environmental factor that is increasingly being recognized as contributing to brain aging is diet, which has evolved markedly over modern history. Here we show that dietary supplementation with docosahexaenoic acid (DHA), an n-3 polyunsaturated fatty acid, in the 3xTg-AD mouse model of AD reduced the intraneuronal accumulation of both amyloid-β (Aβ) and tau. In contrast, combining DHA with n-6 fatty acids, either arachidonic acid or docosapentaenoic acid (DPAn-6), diminished the efficacy of DHA over a 12 month period."…

-Department of Neurobiology and Behavior, University of California, Irvine, California, and
-Martek Biosciences Corporation, Columbia, Maryland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6672302/

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Inflammation drives tau damage in Alzheimer's

"Scientists have found an inflammation mechanism that appears to play a key role in the formation of the toxic tau proteins that characterize Alzheimer's and other brain diseases."

- Catharine Paddock, Ph.D.
- Medical News Today
https://www.medicalnewstoday.com/articles/327107

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…“Deficiency in DHA [Docosahexaenoic acid / omega-3] has also been strongly correlated with neurodegenerative diseases common in the elderly population, particularly Alzheimer’s disease (Freemantle et al. 2006)”…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

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...“AD [Alzheimer's Disease] pathology is characterized at the neuronal level, by synaptic loss and cell death of selected neuronal populations (Echeverria and Cuello (2002)). There are approximately 17 million people affected by the disease world wide, and it is estimated that by 2050 there will be approximately 25 million affected in the United States. There are no effective therapeutic agents for this disease, new drugs and potential cures are being intensely investigated. According to many studies the aggregated form of Aβ and not the monomeric form of the peptide is toxic. One of the strategies being investigated as a potential cure for AD is the search for molecules that are able to stop Aβ aggregation. Thus, it is important to be able to detect Aβ peptide in animal tissue.”...

-Department of Veterans Affairs Funded Patent,
-University of Florida.
http://www.google.com/patents/US20100104504

The therapeutic potential of the phytocannabinoid cannabidiol [CBD] for Alzheimer's disease.

“Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by progressive loss of cognition. Over 35 million individuals currently have AD worldwide. Unfortunately, current therapies are limited to very modest symptomatic relief. The brains of AD patients are characterized by the deposition of amyloid-β and hyperphosphorylated forms of tau protein. AD brains also show neurodegeneration and high levels of oxidative stress and inflammation. The phytocannabinoid cannabidiol (CBD) possesses neuroprotective, antioxidant and anti-inflammatory properties and reduces amyloid-β production and tau hyperphosphorylation in vitro. CBD has also been shown to be effective in vivo making the phytocannabinoid an interesting candidate for novel therapeutic interventions in AD, especially as it lacks psychoactive or cognition-impairing properties. CBD treatment would be in line with preventative, multimodal drug strategies targeting a combination of pathological symptoms,

which might be ideal for AD therapy. Thus, this review will present a brief introduction to AD biology and current treatment options before outlining comprehensively CBD biology and pharmacology, followed by in-vitro and in-vivo evidence for the therapeutic potential of CBD. We will also discuss the role of the endocannabinioid system in AD before commenting on the potential future of CBD for AD therapy (including safety aspects)."

-School of Medicine, Western Sydney University, Campbelltown
-Neuroscience Research Australia (NeuRA), Randwick c
-Illawarra Health and Medical Research Institute
-School of Biological Sciences, University of Wollongong, Wollongong
-Victor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia.
https://www.ncbi.nlm.nih.gov/pubmed/27471947

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"Alzheimer's disease (AD) is characterized by multiple cognitive deficits including memory and sensorimotor gating impairments as a result of neuronal and synaptic loss. The endocannabinoid system plays an important role in these deficits but little is known about its influence on the molecular mechanism regarding phosphorylated tau (p-tau) protein accumulation – one of the hallmarks of AD –, and on the density of synaptic proteins. Thus, the aim of this study was to investigate the preventive effects of anandamide (N-arachidonoylethanolamine, AEA) on multiple cognitive deficits…"

…"This study showed, for the first time, that the administration of an endocannabinoid can prevent AD-like effects induced by STZ [injection of streptozotocin], boosting further investigations about the modulation of endocannabinoid levels as a therapeutic approach for AD."

…"AEA [anandamide] (and all the endocannabinoid system) is recognized to influence the progress of AD, by regulating neurogenesis, cognitive and neuroinflammatory processes during senescence (Koppel and Davies, 2008; Marchalant et al., 2012; Bedse et al., 2014). Decreased levels of AEA have been found in the brain of AD transgenic mice and patients with AD, and were correlated with the cognitive deficits of the subjects (Jung et al., 2012; Maroof et al., 2014). Interestingly, the increase in AEA levels in vitro was reported to reduce tau phosphorylation through the inhibition of the activity of protein kinases (Lin et al., 2016).

In the course of AD, changes occur in the enzymatic pathways of endocannabinoids synthesis (Mulder et al., 2011) and degradation (Pascual et al., 2014) as well as in the density of cannabinoid receptor type 1 receptors (CB1R) (Farkas et al., 2012). The decreased density of CB1R, which is mostly located in synapses (Bouskila et al., 2012), is accompanied by a lower density of different synaptic markers (Canas et al., 2014), also observed in AD patients (Shimohama et al., 1997), in accordance with the hypothesis that AD

begins as a synaptic dysfunction [Selkoe, 2002]."

-Center for Mathematics, Computing and Cognition, Universidade Federal do ABC, São Bernardo do Campo, Brazil

-Center for Natural and Human Sciences, Universidade Federal do ABC, São Bernardo do Campo, Brazil

-Faculty of Medicine, University of Coimbra, Coimbra, Portugal

-Center for Neuroscience and Cell Biology (CNC), University of Coimbra, Coimbra, Portugal

-Edited by: Fabricio A. Pamplona, Entourage Phytolab, Brazil

-Reviewed by: Salim Yalcin Inan, Meram Faculty of Medicine, Turkey; Mychael V. Lourenco, Universidade Federal do Rio de Janeiro, Brazil; Vincenzo Micale, Università di Catania, Italy; Grasielle Clotildes Kincheski, Universidade Federal do Rio de Janeiro, Brazil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6176656

Omega-3 polyunsaturated fatty acids promote amyloid-β clearance from the brain through mediating the function of the glymphatic system

"Impairment of amyloid-β (Aβ) clearance leads to Aβ accumulation in the brain during the development of Alzheimer's disease (AD). Strategies that can restore or improve the clearance function hold great promise in delaying or preventing the onset of AD. Here, we show that n-3 polyunsaturated fatty acids (PUFAs), by use of fat-1 transgenic mice and oral administration of fish oil, significantly promote interstitial Aβ clearance from the brain and resist Aβ injury. Such beneficial effects were abolished in Aqp4-knockout mice, suggesting that the AQP4-dependent glymphatic system is actively involved in the promoting the effects of n-3 PUFAs on the clearance of extracellular Aβ. Imaging on clarified brain tissues clearly displayed that n-3 PUFAs markedly inhibit the activation of astrocytes and protect the AQP4 polarization in the affected brain region after Aβ injection. The results of the present study prove a novel mechanism by which n-3 PUFAs exert protective roles in reducing Aβ accumulation via mediating the glymphatic system function."…

"Omega-3 polyunsaturated fatty acids promote amyloid-β clearance from the brain through mediating the function of the glymphatic system."

-State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China.

-Department of Neurology, Second Clinical Medical College, Guangdong Medical University, Dongguan, China.

-Department of Neurology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; and.

-Laboratory for Lipid Medicine and Technology, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA.

-State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China;

https://pubmed.ncbi.nlm.nih.gov/27789520/

The endocannabinoid system as a target for the treatment of neurodegenerative disease

…"Alzheimer's disease (AD), a disease with major impact on memory systems, has therefore been investigated for evidence of dysfunction of the endocannabinoid system resulting from, or contributing to, disease pathophysiology. AD is the most common neurodegenerative disorder, with a prevalence of approximately 10% in humans over 80 years old (Ferri et al., 2005). There is both genetic and idiopathic aetiology for the disease, which is characterized by gross atrophy of cholinergic neurons projecting to the cerebral cortex and hippocampus, and also of glutamatergic neurons of those regions (Whitehouse et al., 1982; Greenamyre et al., 1985; Wenk, 2003). Neurodegeneration appears to follow the extracellular deposition of β-amyloid protein in 'plaques' and/or the formation of intracellular 'tangles' of hyperphosphorylated tau protein (see Minati et al. 2009 for a recent review).

There is much debate regarding which, if either, of these proteins is central to the neurodegenerative process (reviewed in Mudher and Lovestone, 2002). While anti-β-amyloid vaccination of humans (Hock et al., 2003; Nicoll et al., 2003; Gilman et al., 2005) and transgenic animals (Schenk et al., 1999; Dodart et al., 2002) has led to various degrees of cognitive or histological improvement, a Phase III trial currently underway may further implicate or absolve β-amyloid plaques in the impairment of cognitive function. Already there is much compelling evidence for β-amyloid cascade/neuroinflammation hypothesis, which proposes that misfolded β-amyloid is both injurious to neurons and also invokes a microglial response which, while perhaps evolved to phagocytically clear plaques, is itself neurotoxic (Haga et al., 1989; Itagaki et al., 1989; Hardy and Higgins, 1992; Streit et al., 2005; Hickman et al., 2008). The finding that CB2 is expressed on the microglia clustered around β-amyloid plaques therefore suggests that endocannabinoids may have the ability to modulate the effector cells of AD (Benito et al., 2003)."

Cannabinoid agents as therapeutics in AD

…"Synthetic Δ9-THC (dronabinol) has been shown to alleviate behavioural disturbances and weight loss, and night-time agitation symptoms in human studies of Alzheimer's and severe dementia respectively (Volicer et al., 1997; Walther et al., 2006). As yet however, cannabinoid neuroprotection studies have only been conducted in animals. In BAP rats, the AMT inhibitor VDM11 was able to attenuate hippocampal neuron damage through the elevation of AEA levels alone, while in BAP mice neuronal rescue was associated with elevations in both AEA and 2-AG levels (van der Stelt et al., 2006). Pharmacological dissection suggests that these endocannabinoids may mediate neuroprotection through activation of CB1, and inhibit the inflammatory microglial response through activation of CB2 (Ramirez et al., 2005). CB2 agonists have been shown to inhibit TNF-α and nitric oxide production by microglia/macrophages, as well as stimulating their phagocytosis of β-amyloid peptide (Ehrhart et al.,

2005; Tolon et al., 2009). In a study by Esposito et al. a CB2 antagonist was able to attenuate markers of astrogliosis (Esposito et al., 2007a). Interestingly, the same group showed similar anti-inflammatory effects in another in vivo AD model following administration of cannabidiol, which does not bind to CB2 (Esposito et al., 2007b).

The unifying hypothesis encompassing most of these studies is that pathologic changes in endocannabinoid levels and CB2 expression are induced by the inflammatory environment which occurs in AD. Activation of CB2 by up-regulated endocannabinoids goes some way towards halting microglial activation; however, this innate compensation is insufficient to prevent the subsequent inflammatory damage to neurons, which may also suffer from a loss of protection due to the down-regulation of CB1. On the basis of the pre-clinical efficacy already demonstrated, cannabinoid stimulave therapeutic benefit by augmenting the brain's innate response."

-Centre for Brain Research and Department of Pharmacology, University of Auckland, Auckland, New Zealand
-Department of Anatomy and Cell Biology, Centre foators may hr Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931550/

Role of docosahexaenoic acid in the modulation of glial cells in Alzheimer's disease

"Docosahexaenoic acid (DHA) is an omega-3 (ω-3) long-chain polyunsaturated fatty acid (LCPUFA) relevant for brain function. It has largely been explored as a potential candidate to treat Alzheimer's disease (AD). Clinical evidence favors a role for DHA in the improvement of cognition in very early stages of the AD. In response to stress or damage, DHA generates oxygenated derivatives called docosanoids that can activate the peroxisome proliferator-activated receptor γ (PPARγ). In conjunction with activated retinoid X receptors (RXR), PPARγ modulates inflammation, cell survival, and lipid metabolism. As an early event in AD, inflammation is associated with an excess of amyloid β peptide (Aβ) that contributes to neural insult. Glial cells are recognized to be actively involved during AD, and their dysfunction is associated with the early appearance of this pathology. These cells give support to neurons, remove amyloid β peptides from the brain, and modulate inflammation. Since DHA can modulate glial cell activity, the present work reviews the evidence about this modulation as well as the effect of docosanoids on neuroinflammation and in some AD models. The evidence supports PPARγ as a preferred target for gene modulation. The effective use of DHA and/or its derivatives in a subgroup of people at risk of developing AD is discussed."

Conclusions

”DHA is a natural compound that can easily be obtained from animal sources, especially cold-water fish. DHA can easily cross the BBB, especially in the form of the DHA-LPC, and therefore, it is suitable as a therapeutic agent for neurological disorders. DHA, free or bound in to PLs, is incorporated into cellular membranes, where it is released and transformed into docosanoids (oxygenated derivatives) to exert its function within the cells via RXR and PPARγ. Although DHA has been associated with protection, based on the modification of cellular membrane fluidity, increasing data suggest that DHA’s action can be attributable to a signaling cascade in which docosanoids exert their action by regulating gene expression of anti-inflammatory and other protective pathways. The neurodegenerative disease of Alzheimer has a complex etiology in which the deposition of Aβ plays an important role. Inflammation is an early event in AD that contributes to increased neuronal damage, especially due to the dysfunction of glial cells. This dysfunction leads to the lack of clearance of Aβ, which further increases the over-activation of glial cells. Overall, a harmful environment is created, withdrawing support to neurons and favoring plaque formation.

In animal models and in vitro, DHA and its derivatives have proven to regulate gene expression of inflammatory mediators, as well as enzymes involved in lipid metabolism and Aβ processing. Activation of PPARγ has been shown to mediate some of the effects promoted by DHA and its derivatives in neurons and glial cells. Therefore, based on the current evidence, DHA or its derivatives can help to prevent or retard inflammatory aspects of the pathology of AD. This aspect of the disease has been considered to be an important player in the determination of the outcome of AD. On the other hand, patients carrying the APOE ε4 allele show disrupted metabolism of DHA. Further evaluation of this trait is needed. New longitudinal studies considering early symptoms of cognitive deterioration associated to AD, including MCI, DHA metabolism in APOE ε4 participants, and inflammatory status, might help to conclude whether people at risk of developing AD can potentially be treated with DHA.”

-Departamento de Biología, Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 México, DF México

-Laboratorio de Farmacología, Subdirección de Investigación Básica, Instituto Nacional de Cancerología (INCan), Av. San Fernando #22, Tlalpan 14080, Apartado Postal 22026 México, DF México

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4787218/

Protection against Alzheimer's Disease

…“There has been growing evidence which suggested that Alzheimer's disease progression becomes a runaway chain reaction after a certain point. In the presence of amyloid-β plaques, secondary injuries such as inflammation, excitotoxicity, and apoptosis may trigger the deposition

of hyperphosphorylated tau proteins [40]. Once the process starts, the tau tangles are unabated even after the removal of amyloid-β plaques. Moreover, studies in transgenic amyloid precursor protein (APP) mice have shown that therapies are most effective when administered before plaque formation [41, 42]. Therefore, amyloid-β has become an ideal therapeutic target for primary prevention.

In one study, APPswe/PS1dE9 transgenic mice were utilized to evaluate the therapeutic effect of H. erinaceus mycelia [from lion's main mushroom] containing 19 mg/g erinacine A on Alzheimer's disease. After 30 days of oral administration to 5-month-old transgenic mice, these mycelia were able to attenuate cerebral Aβ plaque burden, prevent recruitment and activation of plaque-associated microglia and astrocytes, promote the expression of IDE, increase the NGF-to-NGF precursor (proNGF) ratio, and enhance the proliferation of neuron progenitors and the number of newly born neurons in the dentate gyrus region [43]. Additionally, improvements in the impairment of other multiple brain regions were also shown when APP/PS1 transgenic mice treated with H. erinaceus mycelia could recover behavioral deficits after 81 days of administration. Collectively, these findings raise the possibility that prevention with erinacine A-enriched H. erinaceus mycelia could be an effective therapeutic strategy for managing Alzheimer's disease."

-Grape King Bio Ltd, Zhong-Li Dist., Taoyuan City, Taiwan
-Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei City, Taiwan
-Institute of Food Science and Technology, National Taiwan University, Taipei City, Taiwan
-Department of Food Science, Nutrition and Nutraceutical Biotechnology, Shih Chien University, Taipei City, Taiwan
-Institute of Biotechnology, National Changhua University of Education, Changhua, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987239/

Cannabinoid Receptor 2 Signaling in Neurodegenerative Disorders: From Pathogenesis to a Promising Therapeutic Target

"Support for the involvement of the CB2 receptors in AD [Alzheimer's Disease] pathology is provided by a number of preclinical and human studies. In particular, post-mortem brains from patients with AD have shown that CB2 receptors are upregulated in cells that are associated with Aβ-enriched neuritic plaques (Benito et al., 2003; Ramírez et al., 2005; Grünblatt et al., 2009; Halleskog et al., 2011; Mulder et al., 2011; Solas et al., 2013). Apart from human studies, transgenic models of AD have also revealed overexpression of CB2 receptors in brain areas affected by AD-pathology (Horti et al., 2010). Increased CB2 mRNA in peripheral blood has been suggested as a peripheral biomarker for the early diagnosis of AD (Grünblatt et al., 2009). Moreover, an increase in CB2 receptors was also observed in rats and C6 astroglioma cells pre-treated with Aβ42 (Esposito et al., 2007).

…"AD [Alzheimer's Disease] is the most common form of dementia in the elderly, clinically characterised by memory dysfunction, loss of lexical access, spatial and temporal disorientation, and impaired judgement [10]. The pathogenesis of AD is extremely complex, with genetic factors, education, and lifestyle all playing crucial roles in disease onset. However, a poor understanding of the pathogenesis of AD means that there are no curative treatments yet available. **Recently, much interest has been shown in the role of diet in both the pathogenesis and prevention of this disease. The role of n-6 PUFA and oxidised eicosanoid derivatives of n-6 PUFA have recently been reviewed as contributing to β-amyloid deposition, a hallmark of AD onset and progression** [142, 143]. AA [arachidonic acid / omega-6] is distributed in several different cell types in both the grey and white matter in the brain [10]. The role AA plays in oxidative stress and lipid peroxidation has already been discussed in relation to NAFLD; however, oxidative stress and production of ROS has also been suggested to play a role in AD, thus suggesting a role of AA and lipid oxidation products (eicosanoids) in the onset and progression of the disease [144, 145]. Furthermore, the enhanced consumption of n-6 PUFA leads to an excessive production of the proinflammatory cytokines derived from AA through COX and LOX enzymatic activity which lead to brain damage [146, 147]. As an example, a study using transgenic mice with memory impairment and β-amyloid deposition, fed a diet poor in n-3 PUFA but rich in n-6 PUFA, showed that they were found to have a significant decrease in the postsynaptic receptor complex in the brain which regulates memory and learning and a net potentiation of programmed cell death [148]. In contrast, n-3 PUFA may play a role in the prevention of AD. Studies have shown that DHA provides support to learning and memory events in animal models of AD and protection against the disease [149–151]. Another recent epidemiological study indicated a relationship between higher fish consumption and improved cognitive function in later life [152]. Both DHA and EPA have been shown to competitively counteract the production of proinflammatory eicosanoids derived from n-6 PUFA in the brain of AD patients [153]. The neuroprotective role of EPA has been demonstrated since EPA competes with AA for incorporation into cell membrane phospholipids and for oxidation by the COX enzyme, thus exerting anti-inflammatory actions. The resulting production of anti-inflammatory PGE3 might result in decreased levels of proinflammatory PGE2 [154]. The balance between the n-6:n-3 PUFA ratio may therefore play a crucial role in the onset of AD. A recent study showed that a lower n-6:n-3 PUFA ratio was associated with a lower incidence of dementia, especially in depressed patients [155]. Furthermore, we have previously demonstrated in patients with major depression, increases in plasma AA and IL-6 associated with inflammation [156]. Therefore, a dietary pattern consisting of lower n-6 PUFA and higher n-3 PUFA or a more balanced n-6:n-3 PUFA ratio may be therapeutic in the pathogenesis of AD."…

-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland

-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

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All these effects may be counteracted by the activation of CB2 receptors, and mechanistic insights of the beneficial effects provided by CB2 receptor stimulation in AD has been provided (Ehrhart et al., 2005; Ramírez et al., 2005; Sheng et al., 2005; Chen et al., 2010; Fakhfouri et al., 2012; Martin-Moreno et al., 2012) (Table (Table1).1). In particular, the CB2 agonist, JWH-015, significantly attenuated CD40-mediated inhibition of microglial phagocytosis of Aβ42 by interfering with the Janus kinase/Signal transducer and activator of transcription 1 (JAK/STAT1) pathway (Benveniste et al., 2004; Ehrhart et al., 2005). Interestingly, CP55940 (CB1/CB2 full agonist) and JWH-015 treatment significantly reduced the interferon-gamma- (IFN-γ)-induced CD40 expression in microglial cells (Ehrhart et al., 2005)."

…"Ramírez and colleagues demonstrated the effects of CB receptor agonists on microglial activation (Ramírez et al., 2005). Authors studied in vitro the effects of WIN55,212-2, the mixed CB1/CB2 agonist devoid of antioxidant properties (Howlett et al., 2002; Marsicano et al., 2002), HU-210 and JWH-133, respectively CB1 and CB2 selective agonist, in Aβ-induced microglial cells (Ramírez et al., 2005). As expected, Aβ peptide activated microglial cells and this was associated with increased mitochondrial activity, TNF-α release, cellular morphological changes and secretion of pro-inflammatory cytokines. Cannabinoid treatments prevented the enhancement of TNF-α release and counteracted Aβ-mediated activation of microglia (Ramírez et al., 2005)."

-Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy
-Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy
-Laboratory of Virology, The Regina Elena National Cancer Institute, IRCCS, Rome, Italy
-Edited by: Marialessandra Contino, University of Bari Aldo Moro, Italy
-Reviewed by: Luigi Bubacco, University of Padua, Italy; Kevin Donald Broad, UCL Institute for Women's Health, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5288380/

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"Alzheimer's disease (AD) is the most common progressive neurodegenerative disease. The annual incidence of AD is currently estimated at 4.6 million cases, and as the general population ages, the worldwide prevalence is expected to increase to more than 80 million cases by the year 2040 (Ferri et al. 2005). Currently, the treatment options for AD only ameliorate the symptoms and do not inhibit the natural progression of AD. Strong evidence has shown that amyloid beta (Aβ) plaques and tau-associated neurofibrillary tangles (NFTs) "clog" the brain and prevent neuronal communication in patients with AD, causing further brain dysfunction (Braak and Braak 1991a, b).

Many studies have found that both Aβ and tau drive the pathogenesis of AD by modulating glycogen synthase kinase 3 (GSK3) activity (Querfurth and LaFerla 2010). Accumulating evidence has demonstrated that GSK3β plays a role in tau hyperphosphorylation and the associated memory impairment in AD (Dolan and Johnson 2010). In addition, the oxidative stress, inflammation, and neuroinflammation associated with AD are also mediated by GSK3β activation (Zhang et al. 2015; D'Angelo et al. 2016). Evidence also shows that GSK-3β is a potential link between diabetes mellitus (DM) and AD (Zhang et al. 2018), and DM might accelerate the progression of AD (Guo et al. 2016). According to the announcement by Jackson laboratory at February 2014, male 3xTg-AD mice may not exhibit the phenotypic traits originally described by donating investigator. Therefore, hyperglycemia was applied to accelerate the phenotypes of 3xTg-AD mice at 6 months old in the study.

Extensive evidence has shown that the endocannabinoid system is an important regulator of synaptic function (Hill et al. 2010; Campolongo et al. 2011). Animal studies have also demonstrated that the endocannabinoid system modulates recognition memory by selectively affecting encoding within the hippocampus (Barna et al. 2007). N-arachidonoylphenolamine (AM404), a paracetamol lipid metabolite, acts as a modulator of the endocannabinoid system and is endowed with pleiotropic activities including activating transient receptor potential vanilloid receptor 1 (TRPV1), inhibiting fatty acid amide hydrolase (FAAH)-mediated hydrolysis of N-arachidonoyl ethanolamide (anandamide; AEA), and inhibiting the synthesis of cyclooxygenase (COX)-1, COX-2, and prostaglandin (Hogestatt et al. 2005). Several studies have also shown that AM404 has a role in the extinction of fear memories in rats (Bitencourt et al. 2008), produces anxiolytic and antidepressant-like effects in rats and mice (Patel and Hillard 2006; Adamczyk et al. 2008), and is neuroprotective in ischemic gerbils (Zani et al. 2007) and rats with Parkinson's disease (Garcia-Arencibia et al. 2007). "

…"In this study, AM404 at 0.5 μM exerted neuroprotective effects on primary murine hippocampal neuron cultures by inhibiting tau toxicity. In addition, chronic administration of AM404 at low dose (0.25 mg/kg; i.p.) improved spatial cognition and attenuated pathological features, which might be in part by the Akt/GSK3β pathway in hyperglycemic 3×Tg-AD mice. Therefore, we suggest that chronic systemic administration of AM404 at low dose could be a potential therapeutic for AD, which might be through Akt/GSK3β pathway, not dependent by a direct GSK3β inhibitor, or receptor of CB1 and TRVP1."

-Department of Nursing, Mackay Junior College of Medicine, Nursing and Management, Taipei, Taiwan
-Department of Life Science, National Taiwan Normal University, Taipei, Taiwan
-Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6469654/

“Several mechanisms suggest that omega-3 PUFA supplementation may improve the cognitive performance of individuals with Alzheimer's disease and other types of dementia. In particular, the antioxidative and anti-inflammatory properties of these PUFA may help protect neurons, promote synaptic plasticity, and limit cellular death. The PUFA composition of the diet appears to influence blood cholesterol, which may play a role in the pathology of Alzheimer's disease. However, the current evidence from clinical trials is not supportive of omega-3 supplementation in the treatment of Alzheimer’s disease in humans. A 2016 Cochrane review identified three randomized, placebo-controlled trials in patients with Alzheimer's disease of mild-to-moderate severity [201]. These trials compared daily supplementation with DHA (between 675 mg and 1,700 mg) and EPA (between 600 mg and 975 mg) to a placebo for 12 months [202, 203] or 18 months [204]. Of note, the study by Quinn et al. [204] also included 4 mg/day of vitamin E (used as preservative — see also Nutrient interactions) in the intervention arm, and the study by Freund-Levi et al. [202] included DHA (900-1,100 mg/day) but no EPA. The pooled analysis of these trials showed no beneficial effect of omega-3 supplementation on measures of global and specific cognitive functions, measures of functional outcomes, and measures of dementia severity [201]. There was no difference between intervention and placebo arms regarding the occurrence of adverse effects [201].”

- Oregon State University
https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids#neuropsychiatric-disorders-treatment

Note: See also Omega-3 Supplements they have been found to raise triacylglycerol [aka triglycerides] . Omega-3s should be acquired from diet.

…“Increased levels of triglycerides at midlife predict brain Aβ and tau pathology 20 years later in cognitively healthy individuals. Certain lipoprotein subfractions may also be risk factors for Aβ pathology. These findings further support an involvement of lipids in the very early stages of AD development.”…

-Clinical Memory Research Unit (K.N., A.-M.G., E.S., O.H.) and Clinical Research Centre (O.M.), Department of Clinical Sciences Malmö, Lund University

- Memory Clinic (K.N., A.-M.G., E.S., O.H.), Skåne University Hospital, Malmö; Psychiatry (D.L.) and Diagnostic Radiology (D.v.W.), Department of Clinical Sciences Lund, Lund University;

-Department of Psychiatry and Neurochemistry (K.B., H.Z.), Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg;

-Clinical Neurochemistry Laboratory (K.B., H.Z.), Sahlgrenska University Hospital, Mölndal, Sweden; and Department of Molecular Neuroscience (H.Z.), UCL Institute of Neurology, Queen Square, London, UK.

Therapeutic Implications of the Prostaglandin Pathway in Alzheimer's Disease

"An important pathologic hallmark of Alzheimer's disease (AD) is neuroinflammation, a process characterized in AD by disproportionate activation of cells (microglia and astrocytes, primarily) of the non-specific innate immune system within the CNS. While inflammation itself is not intrinsically detrimental, a delicate balance of pro- and anti-inflammatory signals must be maintained to ensure that long-term exaggerated responses do not damage the brain over time. Non-steroidal anti-inflammatory drugs (NSAIDs) represent a broad class of powerful therapeutics that temper inflammation by inhibiting cyclooxygenase-mediated signaling pathways including prostaglandins, which are the principal mediators of CNS neuroinflammation. While historically used to treat discrete or systemic inflammatory conditions, epidemiologic evidence suggests that protracted NSAID use may delay AD onset, as well as decrease disease severity and rate of progression. Unfortunately, clinical trials with NSAIDs have thus far yielded disappointing results, including premature discontinuation of a large-scale prevention trial due to unexpected cardiovascular side effects. Here we review the literature and make the argument that more targeted exploitation of downstream prostaglandin signaling pathways may offer significant therapeutic benefits for AD while minimizing adverse side effects. Directed strategies such as these may ultimately help to delay the deleterious consequences of brain aging and might someday lead to new therapies for AD and other chronic neurodegenerative diseases."

-University of Washington Harborview Medical Center, Department of Pathology
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3972296/

Free fatty acids stimulate the polymerization of tau and amyloid beta peptides. In vitro evidence for a common effector of pathogenesis in Alzheimer's disease.

"Alzheimer's disease is a degenerative disorder of the central nervous system, characterized by the concomitant deposition of extracellular filaments composed of beta-amyloid peptides and intracellular filaments composed of the microtubule-associated protein tau. We have discovered that free fatty acids (FFAs) stimulate the assembly of both amyloid and tau filaments in vitro. The minimal concentration of arachidonic acid [omega-6] observed to stimulate tau assembly ranged from 10 to 20 mumol/L, depending on the source of the purified tau. Tau preparations that do not exhibit spontaneous assembly were among those induced to polymerize by arachidonic acid. All long-chain FFAs tested enhanced assembly to some extent, although greater stimulation was usually associated with unsaturated forms. Utilizing fluorescence spectroscopy, unsaturated

FFAs were also demonstrated to induce beta-amyloid assembly. The minimal concentration of oleic or linoleic acid observed to stimulate the assembly of amyloid was 40 mumol/L. The filamentous nature of these thioflavin-binding amyloid polymers was verified by electron microscopy. These data define a new set of tools for examining the polymerization of amyloid and tau proteins and suggest that cortical elevations of FFAs may constitute a unifying stimulatory event driving the formation of two of the obvious pathogenetic lesions in Alzheimer's disease."

-Department of Cell Biology, University of Alabama at Birmingham, USA.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1858305

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…"FAs are the basic building blocks of more complex lipids. Triglyceride (TG) is the storage form of FAs and degrades via β-oxidation while releasing energy for ATP production [4]. The major categories of FAs are saturated, trans, monounsaturated and polyunsaturated FAs. FAs can be classified as saturated versus unsaturated based on the number of double bonds. There are no double bonds in SFAs which tend to be solid at room temperature, whereas unsaturated ones contain at least one (monounsaturated, MUFA), or two or more (polyunsaturated, PUFA) double bonds. FA compositions of natural foods are inherently variable; there are higher SFAs in meat and dairy products, while fruits and vegetables contain predominantly unsaturated FAs. Trans FAs are made either by the ruminal and intestinal bacterial metabolism or the hydrogenation of multiple unsaturated FAs from vegetable oils; they are hypercholesterolemic and are linked to an adverse outcome with high risk of cardiovascular diseases [24]. SFAs are considered the most harmful of all FAs, being capable to accelerate the development of atherosclerosis in the setting of insulin resistance and inflammation [14]. The brain is highly enriched in LCPUFAs-DHA (22:6n-3) and AA (20:4n-6). In the brain, PUFAs are mostly incorporated into phospholipids of neural membranes to influence membranous fluidity, signal transduction, gene transcription, and protect against neuronal apoptosis and death [25]. PUFAs act as precursors for biosynthesis of the lipid mediators which dominate the inflammatory response. N-6 FAs are precursors of eicosanoids including prostaglandins, thromboxanes, leukotrienes, lipoxins, resolvins, and eoxins. Therefore, the dietary n-3/n-6 PUFA ratio can influence the FA composition of membranous phospholipids, which are metabolized to lipid mediators which may have detrimental (pro-inflammatory effects of AA derivatives), beneficial (anti-inflammatory, neuroprotective and antioxidant effects of DHA metabolites) or neuromodulatory effects (AA-derived endocannabinoids) [26]. Alterations in the FA composition of erythrocyte also occurs in early stage of AD, prior to cognitive impairment. Compared to those with low neocortical β-amyloid load, individuals with higher β-amyloid load had elevated plasma AA and lower docosapentaenoic acid

(DPA) [27]"....

-Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Taiwan
-Department of Pediatrics, E-DA Hospital, Taiwan
-Department of Orthopedics, E-DA Hospital, Taiwan
-Research Center of Clinical Medicine, National Cheng Kung University Hospital, College of Medicine,
-National Cheng Kung University, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7073164

Transgenic tomatoes expressing human beta-amyloid for use as a vaccine against Alzheimer's disease

"Human β-amyloid (Aβ) is believed to be one of the main components of Alzheimer's disease, so reduction of Aβ is considered a key therapeutic target. Using Agrobacterium-mediated nuclear transformation, we generated transgenic tomatoes for Aβ with tandem repeats. Integration of the human Aβ gene into the tomato genome and its transcription were detected by PCR and Northern blot, respectively. Expression of the Aβ protein was confirmed by western blot and ELISA, and then the transgenic tomato line expressing the highest protein level was selected for vaccination. Mice immunized orally with total soluble extracts from the transgenic tomato plants elicited an immune response after receiving a booster. The results indicate that tomato plants may provide a useful system for the production of human Aβ antigen."....

-Plant Genomics Research Center, KRIBB, 111 Gwahangno, Yuseong-gu, Daejeon, Korea
-Digital Biotech Inc., R&D, 1227, SinGil Dong, AnSan City, KyungGiDo, Korea
-Department of Biological Science, College of Natural Sciences, Wonkwang University, Iksan, Chonbuk, Korea
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2522325

Crosstalk between the M1 muscarinic acetylcholine receptor and the endocannabinoid system: A relevance for Alzheimer's disease?

"Alzheimer's disease (AD) is a neurodegenerative disorder which accounts for 60–70% of the 50 million worldwide cases of dementia and is characterised by cognitive impairments, many of which have long been associated with dysfunction of the cholinergic system. Although the M1 muscarinic acetylcholine receptor (mAChR) is considered a promising drug target for AD, ligands targeting this receptor have so far been unsuccessful in clinical trials. As modulatory receptors to cholinergic transmission, the endocannabinoid system may be a promising drug target to allow fine tuning of the cholinergic system. Furthermore, disease-related changes have been found in the endocannabinoid system during AD progression and indeed targeting the endocannabinoid system at specific disease stages alleviates cognitive symptoms in numerous mouse models of

AD. Here we review the role of the endocannabinoid system in AD, and its crosstalk with mAChRs as a potential drug target for cholinergic dysfunction.

Introduction

50 million people worldwide currently live with dementia and, with an increasingly ageing population, this figure is expected to rise to >150 million worldwide by 2050, becoming the second leading cause of morbidity in the developed world after cancer [1]. The current estimated financial cost of dementia in the United Kingdom is £26.3 billion per year. Although the National Health Service and social services cover approximately £14.6 billion of this, some £17.4 billion – two thirds of the total cost – is covered by patients and their families [2]. Of the 50 million worldwide cases of dementia, 60–70% of these are cases of Alzheimer's disease (AD).

AD is predominantly associated with memory loss, but symptoms also include agitation, psychosis, depression, apathy, disinhibition, anxiety and sleep disorders [3]. The pathological hallmarks of Alzheimer's disease are brain atrophy and neuroinflammation, which are thought to be largely provoked by the deposition of amyloid-beta (Aβ) peptide into neuritic plaques and neurofibrillary tangles of tau protein [4,5] although the role of these is still not entirely understood. However, the cholinergic system has long been implicated in the pathophysiology of AD, as a plethora of cholinergic pathways serving roles in conscious awareness, attention and working memory have been consistently found to be damaged in the brains of those with advanced AD [6,7]. Furthermore, cholinergic transmission is reduced in several key brain regions in AD including the hippocampus, which is associated with memory formation [8,9]. This has resulted in the development of the 'cholinergic hypothesis', which postulates that a loss of cholinergic function in the central nervous system (CNS) significantly contributes to the cognitive decline associated with AD [10] and, as such, represents a druggable target for AD. Consequently, current AD treatment strategies focus on improving acetylcholine (ACh) availability. Indeed, currently available drugs for AD – acetylcholinesterase (AChE) inhibitors – alleviate symptoms by increasing ACh availability in the synaptic cleft of affected brain regions. By augmenting synaptic ACh concentration, AD symptoms can be relieved and the rate of cognitive decline can be slowed. Although improving ACh availability clearly shows improvements in AD symptoms, AChE inhibitors are nonselective in nature, which renders a myriad of dose-related adverse effects – such as gastrointestinal disturbances and bronchoconstriction [8]. Furthermore, only 30–40% of patients are responsive to AChE inhibitors [11]. Therefore, the clinical usefulness of AChE inhibitors is limited."… - See Also Lion's Mane (Hericium erinaceus)

-Centre for Translational Pharmacology, Institute of Molecular Cell and Systems Biology, Davidson Building, University of Glasgow, Glasgow, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184673

Acetylcholine receptors and tau phosphorylation

“Alzheimer's disease (AD) is characterized by the presence, in the brain of the patients, of two aberrant structures: intracellular neurofibrillary tangles (NFTs), containing an abnormal hyperphosphorylated form of tau protein, and extracellular senile plaques (SPs), mainly composed by fibrillar amyloid beta peptide. Another feature of AD is the neurodegeneration and dysfunction of basal forebrain cholinergic system. A possible connection among those AD characteristics could occur. Thus, the purpose of this short review is to summarize the involvement of nicotinic [acetylcholine receptor] (nAChR) and muscarinic [acetylcholine receptor] (mAChR) receptors on tau phosphorylation, in a direct way, or through the previous interaction of some of these receptors with amyloid beta. Several studies have demonstrated that nAChR activation results in a significantly increase of tau phosphorylation, whereas mAChR activation, may prevent tau phosphorylation.”

-Centro de Biología Molecular Severo Ochoa, Universidad Autónoma de Madrid, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/16900665

Accumulation of human full-length tau induces degradation of nicotinic acetylcholine receptor α4 via activating calpain-2

“Cholinergic impairments and tau accumulation are hallmark pathologies in sporadic Alzheimer’s disease (AD), however, the intrinsic link between tau accumulation and cholinergic deficits is missing. Here, we found that overexpression of human wild-type full-length tau (termed hTau) induced a significant reduction of α4 subunit of nicotinic acetylcholine receptors (nAChRs) with an increased cleavage of the receptor producing a ~55kDa fragment in primary hippocampal neurons and in the rat brains, meanwhile, the α4 nAChR currents decreased. Further studies demonstrated that calpains, including calpain-1 and calpain-2, were remarkably activated with no change of caspase-3, while simultaneous suppression of calpain-2 by selective calpain-2 inhibitor but not calpain-1 attenuated the hTau-induced degradation of α4 nAChR. Finally, we demonstrated that hTau accumulation increased the basal intracellular calcium level in primary hippocampal neurons. We conclude that the hTau accumulation inhibits nAChRs α4 by activating calpain-2. To our best knowledge, this is the first evidence showing that the intracellular accumulation of tau causes cholinergic impairments.

Alzheimer’s disease (AD) is the most common neurodegenerative disease in the elderly. Pathologically, it is marked by the extracellular accumulation of plaques composed of β-amyloid peptide1 and intracellular neurofibrillary tangles that mainly contain the hyperphosphorylated tau proteins2. A massive loss of cholinergic neurons and nicotinic acetylcholine receptors (nAChRs) has been found in early stage of the disease onset3. The nAChRs interacts directly with

β-amyloid and the cholinergic dysfunction in AD mouse model can be reversed by an anti-Aβ antibody4. Currently, the relationship of tau abnormality and cholinergic dysfunction/degeneration in the pathogenesis of AD is not understood."

-Department of Pathophysiology, School of Basic Medicine and the Collaborative Innovation Center for Brain Science, Key Laboratory of Ministry of Education of China for Neurological Disorders, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

-Department of Physiology and Neurobiology, Henan province Key Laboratory of Brain Research, Xinxiang Medical University, Xinxiang, China

-Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4899694

The Potential of Small Molecules in Preventing Tau Oligomer Formation and Toxicity

"The accumulation of pathological protein deposits, amyloids, in neurodegenerative disease represents a formidable challenge for drug development. With no effective treatment in sight, and recent findings suggesting that protein aggregates are diverse, dynamic, and capable of spreading, it is crucial that researchers find safe and successful therapeutic approaches that target the most toxic amyloid species. The pathological aggregation of microtubule-associated protein tau has been identified as a critical factor in the progression of Alzheimer's disease and other neurodegenerative disorders. More evidence continues to come to light to suggest that soluble, intermediate tau aggregates—tau oligomers—are the most toxic species in disease and may be responsible for the spread of pathology, rather than neurofibrillary tangles, the primary tauopathy hallmark, suggesting that oligomeric tau may be the best therapeutic target. Here we discuss the potential of small molecules in preventing amyloid and tau oligomer toxicity and future directions."…

-Mitchell Center for Neurodegenerative Diseases, University of Texas Medical Branch, Galveston, USA

-Departments of Neurology, Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, USA

https://www.sciencedirect.com/science/article/pii/B9780128036907000065

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"Free radical activity and phospholipid membrane degeneration have been associated with neurodegenerative disorders. With aging, neural membrane fluidity is generally compromised due to an increase in cholesterol, reduced activity level of desaturase enzymes, impaired phospholipid metabolism and increased oxidative stress [20]. Such derangements may be associated with dementia and Alzheimer's Disease (AD), e.g., autopsied brains of patients who

suffered AD showed significantly higher saturated fat and lower PUFA content, particularly DHA, in the hippocampus and frontal lobes compared to aged controls [157], which is consistent with reports of decreased hippocampus size and function in AD patients [20].

Prospective cohort/population studies have indicated that higher fish consumption is associated with reduced risk of dementia/AD [158,159,160,161,162,163,164,165]. A single case report of an elderly dementia patient noted clinical improvement over several months of increased fish consumption, which led the author to hypothesise that n-3 PUFA contributed to his improved functioning, although it could have been attributed to numerous other factors associated with admittance to a nursing home [166]. Investigation of n-3 PUFA status in AD patients did find significantly reduced EPA and DHA levels compared to controls, particularly DHA levels which were consistently less than half those in the control group [167]."

-Nutritional Physiology Research Centre, Sansom Institute for Health Research, University of South Australia
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257637/

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…"It is well known that the inflammatory response plays an important role in AD[139,140] and other tauopathies,[141,142] and that a chronic inflammatory state, including diabetes mellitus, hypertension and periodontitis, is a risk factor for AD.[143] Aβ deposition is considered to be an important inducer of the chronic inflammatory response.[144]"…

-Clinical Research Centre, Chiba East National Hospital, Chiba, Chiba, Japan
-Department of Neurology, Chiba East National Hospital, Chiba, Chiba, Japan
-Center for Neurodegenerative Disease Research, Institute on Aging, Department of Pathology
-Laboratory Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3912572/

Alzheimer's & Dementia: Translational Research & Clinical Interventions

…"The link between nutrition and the risk of developing Alzheimer's disease (AD) has been recognized for several decades. Specific dietary patterns have been associated with increased risk of developing AD, whereas others are linked to protection. Dietary patterns such as the Mediterranean diet that is characterized by high intakes of legumes, fruits, fish, unsaturated fats, and high in antioxidants offer protection [1]. Conversely, diets high in saturated fats, high trans-fat, and low antioxidants levels have been linked to an increased risk for developing AD [2]. In addition, diet-related disorders such as obesity, hypertension, hypercholesterolemia, and diabetes have consistently been shown to be associated with AD [3], [4], [5].

Since understanding the pivotal importance of B-vitamins for neuronal functioning and cognition,

at the beginning of the 20th century [6], [7], [8], several nutrients, including antioxidants, choline, and omega-3 fatty acids, have been suggested to influence cerebral functioning (reviewed in Bourre [9] and in Smith and Blumenthal [10]). It is no surprise, therefore, that these nutrients have been postulated to play roles in the pathophysiological processes in AD. For example, antioxidants reduce reactive oxygen species–induced damage and stabilize membranes; the fatty acid docosahexaenoic acid (DHA) affects abnormal membrane–located protein processing (amyloid-b, tau); and DHA, choline, and uridine modulate neuronal membrane formation (reviewed in van Wijk et al. [11]). Neuronal membrane function has been shown to be dependent on its phospholipid composition, and alterations could lead to membrane instability and synaptic loss and, in that way, contribute to AD pathology [12]. Recent evidence suggests that a multinutrient intervention which enhances phospholipid formation comprising DHA, eicosapentaenoic acid (EPA), uridine monophosphate, choline, folate, vitamin B6, vitamin B12, vitamin C, vitamin E, selenium, and phospholipids modulated functional connectivity measures (assessed by electroencephalography) in AD, indicative of preserved synaptic function [13], [14]. These data suggest that adequate supply of specific nutrients may preserve synaptic function, prevent neurodegeneration, and eventually neuronal loss, while previous work showed that people with AD have lower systemic availability of several nutrients that may limit optimal brain function [15]. Publications on brain nutrients in AD compared with non-AD suggest differences in brain nutrient levels as well, but the available evidence is not fully consistent and systematic reviews are lacking.”..

-Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, The Netherlands
-Gerontopole and UMR INSERM 1027 University Paul Sabatier, Toulouse University Hospital, Toulouse, France
https://www.sciencedirect.com/science/article/pii/S2352873717300409

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“Cognitive decline in the elderly, particularly Alzheimer's disease (AD), is a major socio-economic and healthcare concern. We review here the literature on one specific aspect of diet affecting AD, that of the omega3 fatty acids, particularly the brain's principle omega3 fatty acid - docosahexaenoic acid (DHA). DHA has deservedly received wide attention as a nutrient supporting both optimal brain development and for cardiovascular health. Our aim here is to critically assess the quality of the present literature as well as the potential of omega3 fatty acids to treat or delay the onset of AD. We start with a brief description of cognitive decline in the elderly, followed by an overview of well recognized biological functions of DHA. We then turn to epidemiological studies, which are largely supportive of protective effects of fish and DHA against risk of AD. However, biological studies, including blood and brain DHA analyses need careful interpretation and further investigation, without which the success of clinical trials with DHA may continue to struggle. We draw attention to some of the methodological issues that

need resolution as well as an emerging mechanism that may explain how DHA could be linked to protecting brain function in the elderly."

-Department of Medicine and Research Center on Aging, Université de Sherbrooke, QC, Canada.
https://pubmed.ncbi.nlm.nih.gov/19362576

The omega-6/omega-3 ratio and dementia or cognitive decline: a systematic review on human studies and biological evidence

"It has been suggested that the intake of certain fatty acids may influence the risk of dementia. However, current reviews have focused only on the therapeutic effects of omega-3 fatty acids, mostly as supplements. To date, the evidence for the relevance of the omega-6/omega-3 ratio has been neglected. Therefore, we searched the databases Alois, Medline, Biosis, Embase, Cochrane Central Register of Controlled Trials, and The Cochrane Database of Systematic Reviews for "essential fatty acids" and "dementia" and aimed to conduct a comprehensive review across study types. All studies that reported on the association between the n-6/n-3 ratio and dementia or cognitive decline were selected. In the 13 animal studies we examined, the dietary n-6/n-3 ratio was shown to affect brain composition, Alzheimer's disease pathology, and behavior. Our review of the 14 studies in humans that fulfilled the selection criteria (7 prospective studies, 3 cross-sectional studies, 1 controlled trial, 3 case-control studies) provided evidence, albeit limited, supporting an association between the n-6/n-3 ratio, cognitive decline, and incidence of dementia. This review supports growing evidence of a positive association between the dietary n-6/n-3 ratio and the risk of Alzheimer's disease."

-Institute of Transcultural Health Studies, European University Viadrina, Frankfurt (Oder), Germany.
https://pubmed.ncbi.nlm.nih.gov/23451843

Essential fatty acids preparation (SR-3) improves Alzheimer's patients quality of life

"In a number of previous reports we showed the salutary effects on rats of SR-3, a compound comprising a 1:4 ratio of n-3 and n-6 fatty acids. **Improvements were noted in learning tasks, thermoregulation, recovery from neurotoxins, and seizure protection.** Because we were impressed that these effects are related to changes in membrane fluidity and neuronal functioning and because Alzheimer's Disease is also associated with lipid defects, we undertook a short term (4 week) double blind study with 100 Alzheimer patients (60 received SR-3 and 40 in a placebo control). The results indicated improvements in mood, cooperation, appetite, sleep, ability to navigate in the home, and short term memory. Overall improvement was reported for

49 patients, and in no case did a guardian report adverse effects to the compound. While not uniform or permanent, and while no mode of action for SR-3 can be precisely identified at this time, the promising results in quality of life for the patient and caregiver warrant further clinical trials and continued basic research into the neuropsychological substrate of the disease and its response to SR-3."

-Department of Psychology Bar-Ilan University, Ramat Gan, Israel.
https://pubmed.ncbi.nlm.nih.gov/9003975

ω-3 Fatty Acids in the Prevention of Cognitive Decline in Humans

…"The brain is highly enriched in lipids. Thus, it is reasonable to assume that the composition of fatty acids in the brain has relevance for brain functions, including cognition and neuropsychiatric development. The content of DHA (22:6n–3) in the human brain generally increases with age over the first 2 decades and then levels off (1). In 1991 it was reported (2) that DHA as well as arachidonic acid (ARA7; 20:4n–6) and its elongation product, adrenic acid (22:4n–6), were all greatly decreased in various phosphoglyceride fractions [e.g., phosphatidylcholine (PC) and phosphatidylethanolamine (PE)] in 4 areas of the brain with Alzheimer's disease (AD) and in the frontal cortex (2). Whether such changes are causal or consequential effects with regard to cognitive function cannot be determined from observational studies. However, these observations clearly indicate interesting possible relations between FAs and cognition and dementia disorders."…

-Clinical Nutrition and Metabolism, Uppsala University, and Department of Geriatric Medicine, Uppsala University Hospital, Sweden

-Nutritional Lipids, DSM Nutritional Products, Columbia, MD; and

-Department of Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

-Presented at the symposium "Nutritional Prevention of Cognitive Decline" held 25 April 2012 at the American Society of Nutrition Scientific Sessions and Annual Meeting at Experimental Biology 2012 in San Diego, CA. The symposium was sponsored by the American Society for Nutrition, Nutrition Epidemiology RIS, and a grant from the Office of Dietary Supplements at NIH.

-A summary of the symposium "Nutritional Prevention of Cognitive Decline" was published in the September 2012 issue of Advances in Nutrition.

- Author disclosures: T. Cederholm and J. Palmblad, no conflicts of interest. N. Salem is employed by a company that produces and sells essential fatty acids, including the n–3 fatty acids EPA and DHA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3823515

Brain-Gut-Microbiota Axis in Alzheimer's Disease

"Disturbances along the brain-gut-microbiota axis may significantly contribute to the

pathogenesis of neurodegenerative disorders. Alzheimer's disease (AD) is the most frequent cause of dementia characterized by a progressive decline in cognitive function associated with the formation of amyloid beta (Aβ) plaques and neurofibrillary tangles. Alterations in the gut microbiota composition induce increased permeability of the gut barrier and immune activation leading to systemic inflammation, which in turn may impair the blood-brain barrier and promote neuroinflammation, neural injury, and ultimately neurodegeneration. Recently, Aβ has also been recognized as an antimicrobial peptide participating in the innate immune response. However, in the dysregulated state, Aβ may reveal harmful properties. Importantly, bacterial amyloids through molecular mimicry may elicit cross-seeding of misfolding and induce microglial priming. The Aβ seeding and propagation may occur at different levels of the brain-gut-microbiota axis. The potential mechanisms of amyloid spreading include neuron-to-neuron or distal neuron spreading, direct blood-brain barrier crossing or via other cells as astrocytes, fibroblasts, microglia, and immune system cells. A growing body of experimental and clinical data confirms a key role of gut dysbiosis and gut microbiota-host interactions in neurodegeneration. The convergence of gut-derived inflammatory response together with aging and poor diet in the elderly contribute to the pathogenesis of AD. Modification of the gut microbiota composition by food-based therapy or by probiotic supplementation may create new preventive and therapeutic options in AD."

-Department of Gastroenterology and Hepatology, Wroclaw Medical University, Poland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6326209/

See also

Allicin , Civilizational Diseases , Lipids , Microglial & Glial Cells , Prostaglandins

Allergic Rhinitis

"Allergic rhinitis is an inflammatory nasal disorder in which a range of different cells participates."…

-IIR Research Division, Mail Point 810, Southampton General Hospital, Tremona Road, Southampton, Hampshire, United Kingdom.
https://pubmed.ncbi.nlm.nih.gov/15746881

TRPV1-mediated itch in seasonal allergic rhinitis

"Background: Patients with allergic rhinitis may be abnormally sensitive to stimulation of the ion channel transient receptor potential vanilloid-1 (TRPV1)."…

"Conclusion: Patients with allergic rhinitis feature an increased itch response to TRPV1 stimulation at seasonal allergen exposure. We suggest that this reflects part of the hyperresponsiveness that characterizes on-going allergic rhinitis. Intervention with the TRPV1-signalling pathway may offer potential treatments of this condition."

-Department of Clinical Chemistry and Pharmacology, Lund University Hospital, Lund, Sweden.
https://pubmed.ncbi.nlm.nih.gov/19220220

Allergic sensitisation and allergic rhinitis are associated with n-3 [omega-3] polyunsaturated fatty acids in the diet and in red blood cell membranes

…"In this cross-sectional study among adults, a high content of n-3 fatty acids in RBC membranes (EPA) or in the diet (ALA) is associated with a decreased risk of allergic sensitisation and allergic rhinitis."

-Unit of Human Nutrition and Cancer Prevention, Technical University of Munich, Munich, Germany.
https://pubmed.ncbi.nlm.nih.gov/16015268

Allicin

"A pungent oily liquid with antibacterial properties, present in garlic."

- Oxford / Google

Cannabinoid Ligands Targeting TRP Channels

"Many endogenous and exogeneous compounds activate receptors found in the TRP [Transient receptor potential channels] superfamily. Natural, pungent compounds like capsaicin and allicin, from chili peppers and garlic respectively, can activate and gate specific TRP channels. In addition to these pungent compounds, the six TRP channels that make up the ionotropic cannabinoid receptors can also be modulated by endogenous, phytogenic, and synthetic cannabinoids."….

-Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, NC
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340993/

Anti-Aggregation Property of Allicin by In Vitro and Molecular Docking Studies

"Amyloidogenesis is the process in which amyloid beta (Aβ) peptide aggregation results in plaque formation in central nervous system (CNS) are associated with many neurological diseases such as Alzheimer's disease. The peptide aggregation initiated from peptide monomers results in formation of dimers, tetramers, fibrils, and protofibrils. The ability of allicin, a lipid-soluble volatile organosulfur biological compound, present in freshly crushed garlic (Allium sativum L.) to inhibit fibril formation by the Aβ peptide in vitro was investigated in the present study. Inhibition of fibrillogenesis was measured by a Thioflavin T (ThT) fluorescence assay and visualized by transmission electron microscopy (TEM). The molecular interaction between allicin and Aβ peptide was also demonstrated by in silico studies. The results show that allicin strongly inhibited Aβ fibrils by 97% at 300μM, compared with control (Aβ only) ($P<.001$). These results were further validated by visual of fibril formation by transmission microscopy and molecular interaction of amyloid peptide with allicin by molecular docking. Aβ forms favourable hydrophobic interaction with Ile32, Met35, Val36, and Val39, and oxygen of allicin forms hydrogen bond with the amino acid residue Lys28. Allicin anti-amyloidogenic property suggests that this naturally occurring compound may have potential to ameliorate and prevent Alzheimer's disease."

…"In conclusion, allicin demonstrated significant anti-amyloidogenic potential by inhibiting Aβ fibril formation under in vitro condition, this study is giving a significant lead that allicin has a potential to be used as anti-aggregation compound that might have disease-modifying effects in AD. Furthermore, animal studies and pharmacokinetic studies are required to validate the anti-amyloidogenic potential in vivo models."

-University School of Biotechnology, Guru Gobind Singh Indraprastha University, Dwarka, India
-Department of Zoology, Jai Narain Vyas University, Jodhpur, India
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6664621/

See also TRP Channels (Transient receptor potential channels) & Garlic

AM404

…"AM404, an active metabolite of acetaminophen, is an uptake inhibitor that can be used to investigate physiological effects of anandamide."

-Department of Psychiatry; The Taylor Family Institute for Innovative Psychiatric Research, Washington University

School of Medicine, St. Louis, MO, United States
https://www.sciencedirect.com/topics/neuroscience/am404

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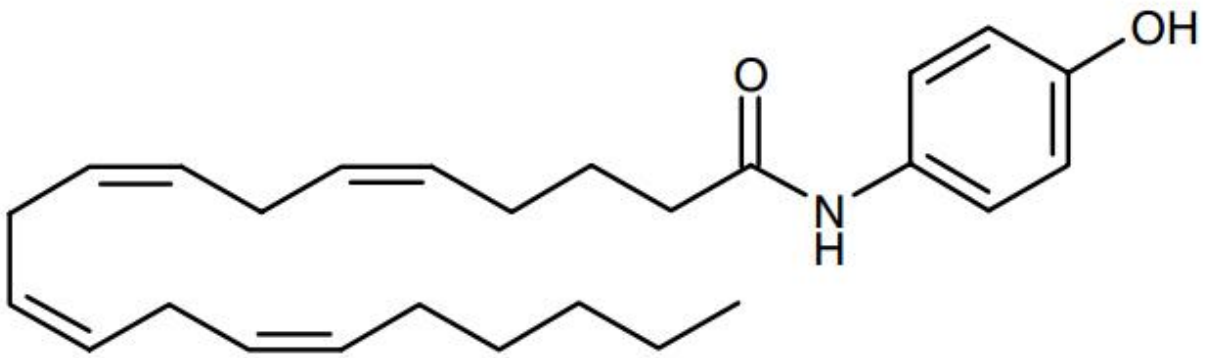
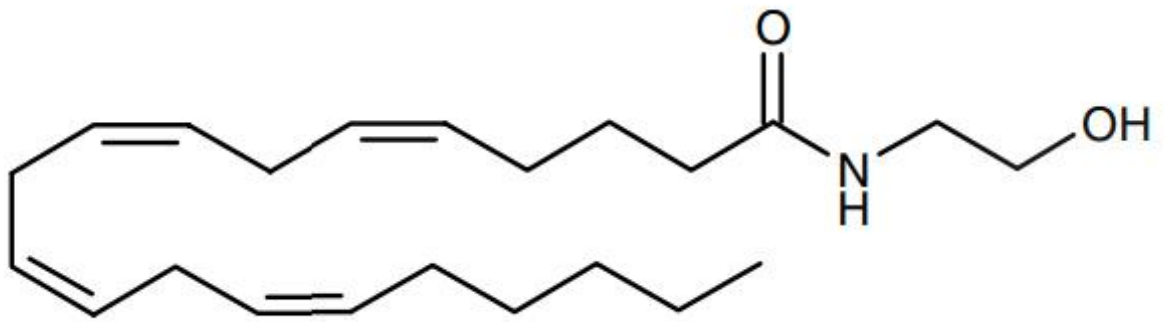
…"N-arachidonoylphenolamine (AM404), a paracetamol lipid metabolite, acts as a modulator of the endocannabinoid system and is endowed with pleiotropic activities including activating transient receptor potential vanilloid receptor 1 (TRPV1), inhibiting fatty acid amide hydrolase (FAAH)-mediated hydrolysis of N-arachidonoyl ethanolamide (anandamide; AEA), and inhibiting the synthesis of cyclooxygenase (COX)-1, COX-2, and prostaglandins (Hogestatt et al. 2005)."..

-Department of Nursing, Mackay Junior College of Medicine, Nursing and Management, Taipei, Taiwan
-Department of Life Science, National Taiwan Normal University, Taipei, Taiwan
-Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6469654/

AM404



Anandamide



See also Prostaglandins

AMP-Activated Protein Kinase (AMPK)

AMPK in Health and Disease

"The function and survival of all organisms is dependent on the dynamic control of energy metabolism, when energy demand is matched to energy supply. The AMP-activated protein kinase (AMPK) alphabetagamma heterotrimer has emerged as an important integrator of signals that control energy balance through the regulation of multiple biochemical pathways in all eukaryotes. In this review, we begin with the discovery of the AMPK family and discuss the recent structural studies that have revealed the molecular basis for AMP binding to the enzyme's gamma subunit. AMPK's regulation involves autoinhibitory features and phosphorylation of both the catalytic alpha subunit and the beta-targeting subunit. We review the role of AMPK at the cellular level through examination of its many substrates and discuss how it controls cellular energy balance. We look at how AMPK integrates stress responses such as exercise as well as nutrient and hormonal signals to control food intake, energy expenditure, and substrate utilization at the whole body level. Lastly, we review the possible role of AMPK in multiple common diseases and the role of the new age of drugs targeting AMPK signaling."

-Protein Chemistry and Metabolism, St. Vincent's Institute of Medical Research, University of Melbourne, Fitzroy, Victoria, Australia.

https://www.ncbi.nlm.nih.gov/pubmed/19584320/

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…"A number of publications showed evidence that cannabinoids contribute to AMPK activation and thereby exert central and peripheral metabolic and cardiac effects.[21–23] In contrast, other publications revealed reduced AMPK activity after activation of the endocannabinoid system24 or AMPK as upstream effector of the endocannabinoid system.[25] "…

-Pharmazentrum frankfurt/ZAFES, Institut für Klinische Pharmakologie, Klinikum der Goethe-Universität Frankfurt, Frankfurt am Main, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5426584

The Endocannabinoid System (ECS) has shown to be involved in up/down regulation of many if

not all systems in the body.

See also: Kidney Disease

Amyotrophic Lateral Sclerosis (ALS)

The endocannabinoid system in amyotrophic lateral sclerosis

"Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative condition characterised by the selective loss of motor neurons from the spinal cord, brainstem and motor cortex. Although the pathogenic mechanisms that underlie ALS are not yet fully understood, there is significant evidence that several neurotoxic mechanisms including excitotoxicity, inflammation and oxidative stress, all contribute to disease pathogenesis. Furthermore, recent results have established that although primarily a motor neuron specific disorder, ALS is not cell-autonomous and non-neuronal cells including astroglia and microglia play a critical role in mechanism of disease. Currently the only licensed therapy available for the treatment of ALS is the anti-glutamatergic agent Riluzole, which has limited therapeutic effects. However, there is increasing evidence that cannabinoids and manipulation of the endocannabinoid system may have therapeutic value in ALS, in addition to other neurodegenerative conditions. Cannabinoids exert anti-glutamatergic and anti-inflammatory actions through activation of the CB(1) and CB(2) receptors, respectively. Activation of CB(1) receptors may therefore inhibit glutamate release from presynaptic nerve terminals and reduce the postsynaptic calcium influx in response to glutamate receptor stimulation. Meanwhile, CB(2) receptors may influence inflammation, whereby receptor activation reduces microglial activation, resulting in a decrease in microglial secretion of neurotoxic mediators. Finally, cannabinoid agents may also exert anti-oxidant actions by a receptor-independent mechanism. Therefore the ability of cannabinoids to target multiple neurotoxic pathways in different cell populations may increase their therapeutic potential in the treatment of ALS. Recent studies investigating this potential in models of ALS, in particular those that focus on strategies that activate CB(2) receptors, are discussed in this review."

-Molecular NeuroPathobiology, Cancer Research UK, London, UK
https://pubmed.ncbi.nlm.nih.gov/18781981/

The CB2 cannabinoid agonist AM-1241 prolongs survival in a transgenic mouse model of amyotrophic lateral sclerosis when initiated at symptom onset

"Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive motor neuron loss, paralysis and death within 2-5 years of diagnosis. Currently, no effective pharmacological agents exist for the treatment of this devastating disease. Neuroinflammation may accelerate the progression of ALS. Cannabinoids produce anti-inflammatory actions via cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), and delay the progression of neuroinflammatory diseases. Additionally, CB2 receptors, which normally exist primarily in the periphery, are dramatically up-regulated in inflamed neural tissues associated with CNS disorders. In G93A-SOD1 mutant mice, the most well-characterized animal model of ALS, endogenous cannabinoids are elevated in spinal cords of symptomatic mice. Furthermore, treatment with non-selective cannabinoid partial agonists prior to, or upon, symptom appearance minimally delays disease onset and prolongs survival through undefined mechanisms. We demonstrate that mRNA, receptor binding and function of CB2, but not CB1, receptors are dramatically and selectively up-regulated in spinal cords of G93A-SOD1 mice in a temporal pattern paralleling disease progression. More importantly, daily injections of the selective CB2 agonist AM-1241, initiated at symptom onset, increase the survival interval after disease onset by 56%. Therefore, CB2 agonists may slow motor neuron degeneration and preserve motor function, and represent a novel therapeutic modality for treatment of ALS."

-Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, USA.
https://pubmed.ncbi.nlm.nih.gov/17241118/

Anandamide (AEA)

"The previous sections have shown a rather complex AEA [anandamide] metabolism, storage and trafficking, strongly suggesting that for every cell it is important to properly synthesize, degrade and transport this eCB."…

-Department of Medicine, Campus Bio-Medico University of Rome, Rome, Italy
-European Center for Brain Research, IRCCS Santa Lucia Foundation, Rome, Italy
-Edited by: Ildikó Ràcz, University Hospital Bonn, Germany
-Reviewed by: John J. Woodward, Medical University of South Carolina, United States
-Meliha Karsak, University Medical Center Hamburg-Eppendorf, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5447297/

“Anandamide exerts neuroprotective and immunosuppressive properties that are mediated by cannabinoid receptor-dependent and -independent pathways."…

-Departments of Pharmacology (N.T.S., V.J.W., P.F.H.)
-Molecular and Integrative Physiology (N.T.S.), University of Michigan Medical School, Ann Arbor, Michigan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835397/

■■■

…“ECBs [Endocannabinoids], like anandamide, are different from classical neurotransmitters in the sense that they are not stored in and released from nerve vesicles, but rather released on demand from the nerve cell membrane during inflammation.[18] “…

-Departments of Urology, William Beaumont Hospital, MI 48073
-University of Pittsburgh
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2878434/

■■■

“The endocannabinoid system plays an important role in numerous physiological processes including mood, appetite, and pain sensation. A critical compound in maintaining cannabinoid tone is the endocannabinoid anandamide (AEA).”…

- Departments of Pharmacology, University of Michigan School of Medicine, Ann Arbor, Michigan, USA.
https://pubmed.ncbi.nlm.nih.gov/20702771/

■■■

“The existence of specific receptors in mammalian cells that recognize a plant-derived substance rekindled the question raised two decades earlier, after brain receptors for morphine had been first described, i.e., is there an endogenous ligand? A positive answer was provided in 1992 by the report by Devane et al. describing the isolation from porcine brain of the lipid arachidonoyl ethanolamide, named anandamide, which bound to the brain cannabinoid receptor with reasonably high affinity and mimicked the behavioral actions of THC when injected into rodents (Devane et al., 1992). Three years later a second endocannabinoid, 2-arachidonoylglycerol (2-AG), was discovered independently by Mechoulam et al. (1995) and Sugiura et al. (1995). Since then, a number of related endogenous lipids with endocannabinoid-like activity have been reported (Fig. 1c), but follow-up studies about biosynthesis, cellular transport, metabolism, and biological function have focused on anandamide and 2-AG, with much less information available about the other compounds with endocannabinoid-like properties. The biochemical aspects of endocannabinoids have been recently reviewed by Bisogno et al. (2005).”

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2241751/

■■■

..."These results demonstrate that anandamide has biological and behavioral effects in awake rodents, some of which are similar to the reported actions of THC"

-Section on Behavioral Neuropharmacology, National Institute of Mental Health, Bethesda, MD, USA

http://www.ncbi.nlm.nih.gov/pubmed/7906042

■■■

"Anandamide is the newly discovered endogenous cannabinoid ligand that binds to brain cannabinoid receptors and shares most, but not all, of the pharmacological properties of delta 9-THC."....

-Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, USA.

https://www.ncbi.nlm.nih.gov/pubmed/9495885

■■■

"Both THC and anandamide can increase serum levels of ACTH and corticosterone in animals. Those hormones are involved in regulating many responses in the body, including those to inflammation. The possible link between experimental cannabinoid -induced analgesia and reported antiinflammatory effects of cannabinoids is important for potential therapeutic uses of cannabinoid drugs"

-The National Academy of Sciences -Marijuana and Medicine (page 68)

https://www.nap.edu/catalog/6376/marijuana-and-medicine-assessing-the-science-base

Note: Corticosterone has been shown to upregulate Anandamide (AEA) in animal studies.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951193

Intracellular trafficking of anandamide: new concepts for signaling

"Endocannabinoids are key mediators of many aspects of human health and disease. The biological activity of anandamide, a prominent member of this group, depends on the metabolic control exerted by biosynthetic, catabolic and oxidative pathways working together. Cellular uptake and intracellular trafficking of anandamide are crucial steps in the process. Whereas the

identity of anandamide transmembrane carriers remains undetermined, recent insights have been gained related to its intracellular stores (adiposomes) and intracellular binding proteins, particularly fatty acid binding proteins, albumin and heat shock protein 70. On this basis, we propose a reconsideration of the dogma that endocannabinoids are exclusively synthesized and released 'on demand', and suggest that their metabolic control is complemented by intracellular trafficking and storage in specific reservoirs."

-Department of Biomedical Sciences, University of Teramo, Piazza Aldo Moro 45, 64100 Teramo, Italy.
https://pubmed.ncbi.nlm.nih.gov/20570522

Exogenous delta^9-tetrahydrocannabinol [THC] influences circulating endogenous cannabinoids in humans

…"We show that administration of a single oral dose of 20 mg THC to 30 healthy volunteers resulted in higher circulating concentrations of anandamide, 2-AG, palmitoyl ethanolamide, and oleoylethanolamide at 2 and 3 hours after administration as compared with placebo."..."Thus, administration of THC to human volunteers influenced the concentrations of circulating endocannabinoids,"....

-Institute of Clinical Pharmacology, Goethe-University, Frankfurt am Main, Germany.
https://www.ncbi.nlm.nih.gov/pubmed/23899642

Antineoplastic activity of cannabinoids.

"Lewis lung adenocarcinoma growth was retarded by the oral administration of delta9-tetrahydrocannabinol (delta9-THC), delta8-tetrahydrocannabinol (delta8-THC), and cannabinol (CBN), but not cannabidiol (CBD). Animals treated for 10 consecutive days with delta9-THC, beginning the day after tumor implantation, demonstrated a dose-dependent action of retarded tumor growth. Mice treated for 20 consecutive days with delta8-THC and CBN had reduced primary tumor size. CBD showed no inhibitory effect on tumor growth at 14, 21, or 28 days. Delta9-THC, delta8-THC, and CBN increased the mean survival time (36% at 100 mg/kg, 25% at 200 mg/kg, and 27% at 50 mg/kg, respectively), whereas CBD did not. Delta9-THC administered orally daily until death in doses of 50, 100, or 200 mg/kg did not increase the life-spans of (C57BL/6 times DBA/2)F1 (BDF1) mice hosting the L1210 murine leukemia. However, delta9-THC administered daily for 10 days significantly inhibited Friend leukemia virus-induced splenomegaly by 71% at 200 mg/kg as compared to 90.2% for actinomycin D. Experiments with bone marrow and isolated Lewis lung cells incubated in vitro with delta9-THC and delta8-THC showed a dose-dependent (10(-4)-10(-7)) inhibition (80-20%, respectively) of tritiated thymidine and 14C-

uridine uptake into these cells. CBD was active only in high concentrations (10(-4)).”

-Journal of National Cancer Institute (1975)
https://www.ncbi.nlm.nih.gov/pubmed/1159836

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…“The endogenous ligands arachidonyl ethanolamide (anandamide) and 2-arachidonyl glycerol (2-AG) mimic most of the biological effects of Δ^9-tetrahydrocannabinol [THC], the main active ingredient of the marijuana plant Cannabis sativa [10, 26].”…

-Department of Internal Medicine I/Center of Cardiovascular Medicine, University of Wu¨rzburg, Germany
https://journals.physiology.org/doi/pdf/10.1152/ajpheart.00718.2005

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“The objective of this review is to point out some important facts that we don’t know about endogenous cannabinoids — lipid-derived signaling molecules that activate CB1 cannabinoid receptors and play key roles in motivation, emotion and energy balance. The first endocannabinoid substance to be discovered, anandamide, was isolated from brain tissue in 1992. Research has shown that this molecule is a bona fide brain neurotransmitter involved in the regulation of stress responses and pain, but the molecular mechanisms that govern its formation and the neural pathways in which it is employed are still unknown. There is a general consensus that enzyme-mediated cleavage, catalyzed by fatty acid amide hydrolase (FAAH), terminates the biological actions of anandamide, but there are many reasons to believe that other as-yet-unidentified proteins are also involved in this process. “…

- Daniele Piomelli PhD, Departments of Anatomy and Neurobiology, Pharmacology and Biological Chemistry University of California
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3855347

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…”Epidemiological evidence suggests that a diet rich in the ω-3 fatty acids (ω-3 FAs) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) promotes beneficial cardiovascular [1], neurological [2], and anti-inflammatory [3] health effects. The biochemical mechanisms facilitating these beneficial effects are yet to be fully elucidated. Mounting evidence suggests that these actions are mediated through both oxidative and nonoxidative routes of metabolism that convert ω-3 FAs into bioactive lipid metabolites.

One of the nonoxidative pathways involves the conversion of the ω-3 FAs DHA and EPA into docosahexaenoyl ethanolamide (DHEA) and eicosapentaenoyl ethanolamide (EPEA) (Fig. 1)

through the N-acyl ethanolamine synthesis pathway similar to the conversion of arachidonic acid (AA) into arachidonoyl ethanolamine (AEA, anandamide) [4, 5]. The endocannabinoids AEA, DHEA, and EPEA exert effects similar to those of Δ9-tetrahydrocannabinol (THC), the active ingredient of Cannabis sativa. Endocannabinoids play important physiological roles that are exerted primarily through the activation of cannabinoid receptor-1 (CB1) and -2 (CB2) [6, 7]. CB1 is found predominantly in the CNS, and CB2 is found in both peripheral and CNS immune cells [8]."…

-Department of Comparative Biosciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Medical Scholars Program, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Biochemistry, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Materials Science and Engineering, University of Illinois at Urbana–Champaign, Champaign, IL,
-Department of Pharmacology, University of Michigan, Ann Arbor, MI;
-Division of Nutritional Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-College of Veterinary Medicine, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Animal Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Bioengineering, University of Illinois at Urbana–Champaign, Champaign IL;
-Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI;
-Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana–Champaign, Champaign, IL,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5544256

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"Endocannabinoids are bioactive lipids, that comprise amides, esters and ethers of long chain polyunsaturated fatty acids. Anandamide (N-arachidonoylethanolamine; AEA) and 2-arachidonoylglycerol (2-AG) are the best studied endocannabinoids, and act as agonists of cannabinoid receptors. Thus, AEA and 2-AG mimic several pharmacological effects of the exogenous cannabinoid delta9-tetrahydrocannabinol, the psychoactive principle of hashish and marijuana."…

-Department of Biomedical Sciences, University of Teramo, Teramo, Italy.
https://pubmed.ncbi.nlm.nih.gov/17274532

New insights into endocannabinoid degradation and its therapeutic potential

"Endocannabinoids are amides, esters and ethers of long chain polyunsaturated fatty acids, which act as new lipidic mediators. Anandamide (N-arachidonoylethanolamine; AEA) and 2-arachidonoylglycerol (2-AG) are the main endogenous agonists of cannabinoid receptors, able to mimic several pharmacological effects of (-)-Delta9-tetrahydrocannabinol (THC), the active principle of Cannabis sativa preparations like hashish and marijuana. The activity of AEA and 2-AG at their receptors is limited by cellular uptake through an anandamide membrane transporter

(AMT), followed by intracellular degradation. A fatty acid amide hydrolase (FAAH) is the main AEA hydrolase, whereas a monoacylglycerol lipase (MAGL) is critical in degrading 2-AG. Here, we will review growing evidence that demonstrates that these hydrolases are pivotal regulators of the endogenous levels of AEA and 2-AG in vivo, overall suggesting that specific inhibitors of AMT, FAAH or MAGL may serve as attractive therapeutic targets for the treatment of human disorders. Recently, the N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD), which synthesizes AEA from N-arachidonoylphosphatidylethanolamine (NArPE), and the diacylglycerol lipase (DAGL), which generates 2-AG from diacylglycerol (DAG) substrates, have been characterized. The role of these synthetic routes in maintaining the endocannabinoid tone in vivo will be discussed. Finally, the effects of inhibitors of endocannabinoid degradation in animal models of human disease will be reviewed, with an emphasis on their ongoing applications in anxiety, cancer and neurodegenerative disorders."

-Department of Biomedical Sciences, University of Teramo, Teramo, Italy.
https://pubmed.ncbi.nlm.nih.gov/16515464

The endocannabinoid system, anandamide and the regulation of mammalian cell apoptosis

"Endocannabinoids are a new class of lipid mediators, which include amides, esters and ethers of long-chain polyunsaturated fatty acids. Anandamide (N-arachidonoylethanolamine; AEA) and 2-arachidonoylglycerol (2-AG) are the main endogenous agonists of cannabinoid receptors able to mimic several pharmacological effects of Delta-9-tetrahydrocannabinol, the active principle of Cannabis sativa preparations like hashish and marijuana. The pathways leading to the synthesis and release of AEA and 2-AG from neuronal and non-neuronal cells are still rather uncertain. Instead, it is known that the activity of AEA is limited by cellular uptake through a specific membrane transporter, followed by intracellular degradation by a fatty acid amide hydrolase. Together with AEA and congeners these proteins form the 'endocannabinoid system'. Here, the involvement of AEA in apoptosis and the underlying signal transduction pathways will be reviewed, along with the metabolic routes and the molecular targets of this endocannabinoid. Also, recent findings on the apoptotic potential of AEA for neuronal cell differentiation and brain development will be discussed."

-Department of Biomedical Sciences, University of Teramo, Teramo, Italy.
https://pubmed.ncbi.nlm.nih.gov/12934069

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…"We have shown that anandamide acts as substrate for prostamide production and that

stimulation with cytokines mainly induces prostamide output rather than prostaglandin output [12]. Because all presently available antisera to prostaglandins e.g. prostaglandin E2 (PGE2) recognize prostamides, when a substrate is targeted to the site of inflammation, a prostamide may be secreted rather than a prostaglandin (Fig 1). Hence, the overall response to treatment depends on the properties of the prostaglandin or prostamide formed; these substances have widely divergent contractile activities. Furthermore, this induces variation across studies and affects the reproducibility of diagnostic results. In particular, studies of cytokine effects on prostaglandin biosynthesis, which is a critical step in intrauterine infection-induced preterm labor, may have dramatically different results and may fail to reveal key information about specific cytokines. We have now used the gold standard method of mass spectrometry to identify unequivocally products of endocannabinoid and eicosanoid biosynthetic pathways that are formed upon exposure to inflammatory stimuli of human choriodecidua."

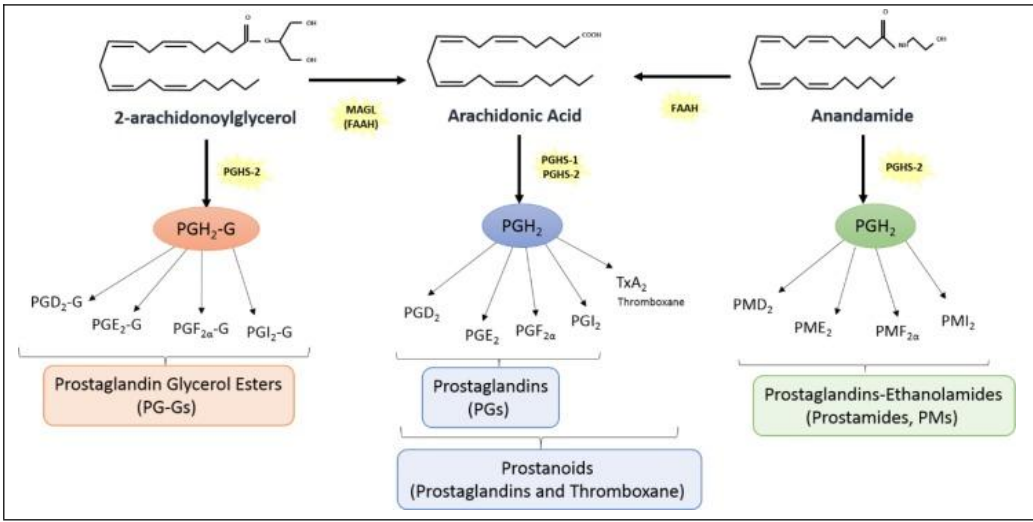

Fig 1

Endocannabinoid pathway.

Endocannabinoid pathway giving rise to prostaglandins glycerol esters, prostaglandins and prostamides.

-University of Queensland Centre for Clinical Research, Centre for Clinical Diagnostics, University of Queensland, Royal Brisbane

-Women's Hospital, Queensland, Brisbane, Australia

-University of Southampton School of Medicine, UNITED KINGDOM

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740432

See also Lung Cancer

Anandamide (AEA) & 2-AG (2-Arachidonoyl-glycerol)

Regulation of inflammation by cannabinoids, the endocannabinoids 2-arachidonoyl-glycerol and arachidonoyl-ethanolamide, and their metabolites

"2-Arachidonoyl-glycerol (2-AG) and arachidonyl-ethanolamide (AEA) are endocannabinoids that have been implicated in many physiologic disorders, including obesity, metabolic syndromes, hepatic diseases, pain, neurologic disorders, and inflammation. Their immunomodulatory effects are numerous and are not always mediated by cannabinoid receptors, reflecting the presence of an arachidonic acid (AA) molecule in their structure, the latter being the precursor of numerous bioactive lipids that are pro- or anti-inflammatory. 2-AG and AEA can thus serve as a source of AA but can also be metabolized by most eicosanoid biosynthetic enzymes, yielding additional lipids. In this regard, enhancing endocannabinoid levels by using endocannabinoid hydrolysis inhibitors is likely to augment the levels of these lipids that could regulate inflammatory cell functions. This review summarizes the metabolic pathways involved in the biosynthesis and metabolism of AEA and 2-AG, as well as the biologic effects of the 2-AG and AEA lipidomes in the regulation of inflammation."

-Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), Département de Médecine, Faculté de Médecine, Université Laval, Québec City, QC, Canada.
https://pubmed.ncbi.nlm.nih.gov/25877930

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…"The eCB signaling is terminated via a two-step process involving an active uptake of eCB by a membrane transporter, which remains to be characterized, and a subsequent intracellular hydrolysis (Beltramo et al., 1997; Hillard et al., 1997). Anandamide is metabolized by fatty acid amid hydrolase (FAAH) (Cravatt et al., 1996), whereas 2-AG is metabolized by monoglyceride lipase (MGL) (Goparaju et al., 1999). 2-AG can also be hydrolyzed by the recently described serine hydrolase α-β-hydrolase domain 6 (ABHD6) (Marrs et al., 2010), which is expressed in the brain. Genetic deletion of ABHD6 has been shown to increase the accumulation and efficacy of 2-AG in the brain (Marrs et al., 2010). In addition to these catabolic enzymes, both anandamide and 2-AG can be metabolized by cyclooxygenase type 2 (COX 2) into prostaglandins (Kozak et al., 2000)."…

-Research Institute on Addictions, University at Buffalo, State University of New York, Buffalo, New York
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110547/

Endocannabinoids and their oxygenation by cyclo-oxygenases, lipoxygenases and other oxygenases

“The naturally occurring mammalian endocannabinoids possess biological attributes that extend beyond interaction with cannabinoid receptors. These extended biological properties are the result of oxidative metabolism of the principal mammalian endocannabinoids arachidonoyl ethanolamide (anandamide; A-EA) and 2-arachidonoylglycerol (2-AG). Both endocannabinoids are oxidized by cyclo-oxygenase-2 (COX-2), but not by COX-1, to a series of prostaglandin derivatives (PGs) with quite different biological properties from those of the parent substrates. PG ethanolamides (prostamides, PG-EAs) and PG glyceryl esters (PG-Gs) are not only pharmacologically distinct from their parent endocannabinoids, they are distinct from the corresponding acidic PGs, and are differentiated from each other. Ethanolamides and glyceryl esters of the major prostanoids PGD2, PGE2, PGF2α, and PGI2 are formed by the various PG synthases, and thromboxane ethanolamides and glyceryl esters are not similarly produced. COX-2 is also of interest by virtue of its corollary central role in modulating endocannabinoid tone, providing a new therapeutic approach for treating pain and anxiety. Other major oxidative conversion pathways are provided for both A-EA and 2-AG by several lipoxygenases (LOXs), resulting in the formation of numerous hydroxyl metabolites. These do not necessarily represent inactivation pathways for endocannabinoids but may mimic or modulate the endocannabinoids or even display alternative pharmacology. Similarly, A-EA and 2-AG may be oxidized by P450 enzymes. Again a very diverse number of metabolites are formed, with either cannabinoid-like biological properties or an introduction of disparate pharmacology. The biological activity of epoxy and hydroxyl derivatives of the endocannabinoids remains to be fully elucidated. This review attempts to consolidate and compare the findings obtained to date in an increasingly important research area. This article is part of a Special Issue entitled "Oxygenated metabolism of PUFA: analysis and biological relevance".”

-Manchester Pharmacy School, Faculty of Medical and Human Sciences, Stopford Building, Oxford Road, The University of Manchester, UK.

-Manchester Pharmacy School, Faculty of Medical and Human Sciences, Stopford Building, Oxford Road, The University of Manchester, UK.

-Dept of Biological Sciences, Allergan, Inc., Irvine, USA.

https://pubmed.ncbi.nlm.nih.gov/25543004/

See also Cyclooxygenase (COX)

Anger Issues

"Anger worsens in some patients during interferon-alpha (IFN-α) therapy. Elevated anger has also been associated with lower long-chain omega-3 (LCn-3) fatty acid levels. We examined whether fatty acids could influence vulnerability to anger during IFN-α exposure."…

"LCn-3 fatty acid status may influence anger development during exposure to elevated inflammatory cytokines, and may interact with genetic risk for increased brain TNF-α. LCn-3 supplements may be one strategy for minimizing this adverse side effect of IFN-α."..

IFN-α based therapies are often clinically employed for treating chronic hepatitis C (HCV) [32, 36], where depression occurs in about patients [37–41]. One risk factor for depression may be lower levels of long-chain omega-3 (LC-n-3) polyunsaturated fatty acids [42, 43]. Specifically, depression risk has been associated with the ratio of the omega-6 fatty acid arachidonic acid (AA; 20:4n-6) to two LCn-3 fatty acids, eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) – congruent with a range of other findings where the AA/EPA+DHA ratio correlates with depression [44–48], though not in all studies [49].

There are also multiple lines of evidence to support the hypothesis that vulnerability to anger is influenced by AA/EPA+DHA. Homicide rates amongst countries correlate with lower seafood intake [50]; low dietary intake of LCn-3 correlates with increased hostility in young urban adults [51]; lower levels of LCn -3 correlates with elevated hostility in drug-free schizophrenia subjects [52]; and trans fatty acids, which are associated with lower LCn -3 levels, correlate with increased irritability and aggression in adults [53]. Lower LCn -3 levels are associated with aggression, [54] with poor affective regulation and impulse control [55], and with increased rejection of unfair offers in a neuro-economic task [56]. Rodent models implicate low LCn -3 levels in increased aggression, particular in settings of increased stress [57, 58]; and even aggression in German Shepherd dogs is associated with low DHA levels [59].

In further support for a causal role, supplementation of LCn -3 fatty acids may reverse increased anger and aggression. LCn -3 supplementation decreased anger in substance users [60], where increased plasma DHA levels correlated with lower anger [61]. Similarly, EPA supplementation reduced aggression in patients with borderline personality [62]. LCn -3 supplements have likewise improved irritability in patients with bipolar disorder [63], hyperactive behaviors in autistic children [64], aggression in female Japanese school children [65], aggressive incidents in prisoners [66], and aggression in settings of high stress [67]. There are only a few counter examples. For instance, while DHA supplementation could prevent increase stress-induced aggression, there was no benefit for aggression in non-stressful situations [68]. Another study observed that EPA reduced suicidality but had no benefit for hostility [69].

It is plausible that these anti-irritability/anger/hostility/aggression effects of EPA and DHA may be related to their anti-inflammatory properties. They, as well as their lipoxygenase and cyclo-oxygenase metabolites (known as “resolvins” and “protectins”), can influence cytokine synthesis [70] and resolve inflammation [71, 72]. As one example, DHA can be converted to ‘neuroprotectin,’ which has potent inflammatory resolving activities in the brain [73]. At least one receptor for D-series resolvins exists in the brain, formyl peptide receptor 2 (FPR2) [74]. Conversely, AA is a substrate for the synthesis of prostacyclins, thromboxanes, and prostaglandins such as PGE2, which stimulate the synthesis of inflammatory cytokines [75, 76]. Consistent with these observations, elevated AA/EPA+DHA ratios are associated with greater lipopolysaccharide-induced elevations in IL-6 [77], whileLCn-3 fatty acids can reverse inflammatory cytokine-induced behaviors [78].

Thus our primary hypothesis, guided by this literature, was that pre-treatment measures of AA/EPA+DHA would prospectively and specifically predict subsequent vulnerability to inflammatory cytokine-associated anger in human patients treated with IFN-α. Also, DHA and/or its D-series resolvins can diminish TNF-α production by macrophages [79, 80], and experimental LCn-3 fatty acid deficiency is associated with elevated TNF-α levels in rat plasma [81]. Because we have previously found that a promoter polymorphism in the gene encoding for TNF-α is associated with risk for labile anger [35], we additionally explored whether there might be an interaction with AA/EPA+DHA.”…

-Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA

-Inflammation Research Foundation, Marblehead, Massachusetts

-Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3817416/

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See Supplements for related research quotes.

See also Intermittent explosive disorder (IED)

Angioedema (Hives)

Life Threatening Idiopathic Recurrent Angioedema Responding to Cannabis

"We present a case of a 27-year-old man with recurrent episodes of angioedema since he was 19, who responded well to treatment with medical grade cannabis. Initially, he responded to steroids and antihistamines, but several attempts to withdraw treatment resulted in recurrence. In the last few months before prescribing cannabis, the frequency and severity of the attacks worsened and included several presyncope events, associated with scrotal and neck swelling. No predisposing factors were identified, and extensive workup was negative. The patient reported that he was periodically using cannabis socially and that during these periods he was free of attacks. Recent data suggest that cannabis derivatives are involved in the control of mast cell activation. Consequently, we decided to try a course of inhaled cannabis as modulators of immune cell functions. The use of inhaled cannabis resulted in a complete response, and he has been free of symptoms for 2 years. An attempt to withhold the inhaled cannabis led to a recurrent attack within a week, and resuming cannabis maintained the remission, suggesting a cause and effect relationship."

-General Intensive Care Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba, Israel

-Infection Control and Hospital Epidemiology Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba, Israel

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4519555/

Ankylosing Spondylitis

Supplementation of omega-3 fatty acids in patients with ankylosing spondylitis

“To study the effect of supplementation with omega-3 fatty acids on disease variables and drug consumption in patients with ankylosing spondylitis (AS).”

”Eighteen patients completed the study, nine patients from each group. The patients inw the high-dose group exhibited a significant decrease in disease activity according to the Bath Ankylosing Disease Activity Index (BASDAI; p = 0.038), which was not seen in the low-dose group. Significant differences were not found on drug consumption or in functional capacity in either of the groups. No significant differences were found when comparing the results between the high- and low-dose groups.”

“Omega-3 fatty acids in adequate doses may have the capacity to decrease the disease activity

of AS. However, larger and better controlled studies are needed before any further conclusions can be made on the extent of this capacity."

-Department of Medical Rehabilitation, Gällivare Hospital, Sweden.

https://www.ncbi.nlm.nih.gov/pubmed/17062435

Antidepressants

Untapped Potential Of Antidepressants For Cancer

…"Antidepressants work by affecting levels of chemicals known as prostaglandins. These are ephemeral, infinitesimal signallers self-regulating every cell in the body, including those serving mood and immunity. When first discovered they were perceived as a master switch, but are now believed to regulate every component of cellular microanatomy and physiology, including those of the organelles, cytoskeleton, proteins, enzymes, nucleic acids and mitochondria.

Prostaglandins are responsible, paradoxically, for both cell function and dysfunction. Excessive prostaglandin synthesis depresses immune function and may induce cancer."…

-ecancermedicalscience

https://www.sciencedaily.com/releases/2008/09/080911142620.htm

Note: See also Prostaglandins - medications that reduce prostaglandins can have long term consequences.

Antiphospholipid Syndrome

"Endothelial cells are thought to play a central role in the pathogenesis of antiphospholipid syndrome (APS). Omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation has been shown to improve endothelial function in a number of diseases; thus, it could be of high clinical relevance in APS. "

…."In conclusion, 16weeks of n-3 PUFA supplementation improved endothelial function in patients with well-controlled PAPS. These results support a role of n-3 PUFA supplementation as an adjuvant therapy in APS. "

-Applied Physiology and Nutrition Research Group, Laboratory of Assessment and Conditioning in Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil

-Heart Institute (InCor), Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil

-School of Applied Sciences, Universidade Estadual de Campinas (UNICAMP), Limeira, Brazil
-Edited by: Niccolo Terrando, Duke University, United States
-Reviewed by: Jesmond Dalli, Queen Mary University of London, United Kingdom; Joan Clària, Hospital Clínic de Barcelona, Spain
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5840153/

Antitumorigenic

"The endocannabinoid system is comprised of cannabinoid receptors (CB1 and CB2), their endogenous ligands (endocannabinoids), and proteins responsible for their metabolism participate in many different functions indispensable to homeostatic regulation in several tissues, exerting also antitumorigenic effects."…

-First Department of Pathology, Medical School, University of Athens, Athens, Greece
-Department of Food Science and Nutrition, University of the Aegean, Myrina, Lemnos, Greece
-Department of Radiotherapy, School of Health Sciences, Faculty of Medicine, University of Thessaly
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619873/

Antitumorigenic effects of cannabinoids beyond apoptosis.

"According to the World Health Organization, the cases of death caused by cancer will have been doubled until the year 2030. By 2010, cancer is expected to be the number one cause of death. Therefore, it is necessary to explore novel approaches for the treatment of cancer. Over past years, the antitumorigenic effects of cannabinoids have emerged as an exciting field in cancer research. Apart from their proapoptotic and antiproliferative action, recent research has shown that cannabinoids may likewise affect tumor cell angiogenesis, migration, invasion, adhesion, and metastasization. This review will summarize the data concerning the influence of cannabinoids on these locomotive processes beyond modulation of cancer cell apoptosis and proliferation. The findings discussed here provide a new perspective on the antitumorigenic potential of cannabinoids."

-Institute of Toxicology and Pharmacology, University of Rostock, Rostock, Germany.
https://www.ncbi.nlm.nih.gov/pubmed/19889794/

Antitumorigenic Properties of Omega-3 Endocannabinoid Epoxides.

"Accumulating studies have linked inflammation to tumor progression. Dietary omega-3 fatty acids, such as docosahexaenoic acid (DHA), have been shown to suppress tumor growth through

their conversion to epoxide metabolites."….

Journal of Medical Chemistry 2018, Roy J, Watson JE, Hong IS, Fan TM, Das A.
https://www.ncbi.nlm.nih.gov/pubmed/29856219

Garlic: its anticarcinogenic and antitumorigenic properties.

"Overall, several investigations indicate that garlic and its organic allyl sulfur components inhibit the cancer process. Furthermore, these studies reveal that the benefits of garlic are not limited to a specific species, a particular tissue, or a specific carcinogen. Finally, odor is not a prerequisite for the protection provided by garlic against the initiation of chemical carcinogenesis. Although the water-soluble compound S-allyl cysteine is effective in reducing the risk of chemically induced tumors in experimental animals, it has no effect on established tumors. However, oil-soluble compounds such as diallyl disulfide are effective in reducing the proliferation of neoplasms. Although the evidence supports the benefits of garlic, additional evidence is needed to determine the quantity needed by humans to minimize cancer risk."

-Nutrition Department, Pennsylvania State University, University Park 16802, USA.
https://www.ncbi.nlm.nih.gov/pubmed/9110580

See also Garlic

Anticoagulant

Anticoagulant effects of a Cannabis extract in an obese rat model.

"Blood coagulation studies were conducted to determine the possible anti-/prothrombotic effect of an organic cannabis extract and the three major cannabinoids, THC, CBD and CBN. The in vitro effect of the cannabis extract on thrombin activity produced an IC50 value of 9.89 mg/ml, compared to THC at 1.79 mg/ml. It was also found that the extract, THC and CBN showed considerable inhibition of thrombin-induced clot formation in vitro with IC50 values of 600, 87 and 83 microg/ml for the extract, THC and CBN respectively. In an in vivo model used to determine clotting times of lean and obese rats treated with a cannabis extract, 50% clotting times were found to be 1.5 and 2 fold greater than their respective control groups, supporting the results obtained in the in vitro model. **The study thus shows that Cannabis sativa and the cannabinoids, THC and CBN, display anticoagulant activity and may be useful in the treatment of diseases such as type 2 diabetes in which a hypercoagulable state exists.**"

Department of Biochemistry and Microbiology, Nelson Mandela Metropolitan University, PO Box 77000, Port Elizabeth 6031, South Africa
https://www.ncbi.nlm.nih.gov/pubmed/16644197

Antimicrobial resistance

Effectiveness of omega-3 polyunsaturated fatty acids against microbial pathogens

"LNA and its derivatives (EPA and DHA) are omega-3 FAs that have been widely studied for their beneficial effects on human health, mainly the brain, eye, cardiovascular system, and general human growth. However, their utilization as antimicrobial agents has not been widely appreciated perhaps because of little understanding on antimicrobial mechanism. Nonetheless, the efficacy of these agents on microbial cell membranes and their antioxidant properties have been shown to inhibit the growth of microorganisms and thereby promote human health and animal health. Hence, omega-3 FAs can be considered as potential alternative or adjunctive therapeutic agents because of their antimicrobial and immunomodulatory properties. Moreover, the escalating levels of resistance may be minimized because they have been reported to have little effect on evolving antimicrobial resistance (Desbois and Smith, 2010), and are also safe for human use. Since the development of antimicrobial resistance outruns antimicrobial drug development, it is worthwhile to consider omega-3 FAs in the list of potential antimicrobial agents. However, more clinical studies are required to support this hypothesis."

-Department of Microbiology, College of Basic Medical Sciences, Dalian Medical University, Dalian 116044, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5964344/

Antioxidants

Cannabinoids protect cells from oxidative cell death: a receptor-independent mechanism.

…"Direct measurement of oxidative stress revealed that cannabinoids prevented serum-deprived cell death by antioxidation. The antioxidative property of cannabinoids was confirmed by their ability to antagonize oxidative stress and consequent cell death induced by the retinoid

anhydroretinol. Therefore, cannabinoids act as antioxidants to modulate cell survival and growth of B lymphocytes and fibroblasts."

Department of Pharmacology, Joan & Sanford I. Weill Medical College of Cornell University, New York, NY, USA.
https://www.ncbi.nlm.nih.gov/pubmed/10869379

Antioxidant properties of the vasoactive endocannabinoid, 2-arachidonoyl glycerol (2-AG).

"Reactive oxygen species (ROS) were shown to play a role in altering blood-brain barrier (BBB) permeability and formation of brain edema induced by trauma and/or ischemia. 2-arachidonoyl glycerol (2-AG), a novel, potent vasodilatory and cytoprotective endocannabinoid has been implicated to act as an antioxidative agent. This study examines: 1) the possible 2-AG modulation of BBB injury and edema formation induced by closed head injury (CHI); and 2) comparable effects between 2-AG and 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (TPL), a known antioxidant nitroxide on endothelial Ca2+ and cytoskeletal responses to H2O2 (ROS). 2-AG treatment reduced the CHI-induced increase in BBB permeability and brain edema. The endothelial H2O2-stimulated Ca2+ mobilization and cytoskeleton (vimentin) rearrangement was modified by either 2-AG or TPL. **These findings provide evidence of 2-AG antioxidant activity and are consistent with the involvement of ROS in the pathomechanism of CHI-induced BBB injury and brain edema.**"

-Resuscitative Medicine Department, Naval Medical Research Center, Forest Glen, MD, USA.
https://www.ncbi.nlm.nih.gov/pubmed/14753451

Identification of six phenylpropanoids from garlic skin as major antioxidants.

"The extract of garlic skins (peels) showed strong antioxidant activity, and some responsible constituents were isolated and identified. Garlic (Allium sativum L.) has been used as an herbal medicine, but there is no report on the health benefits of the skin or peel."…
"Also, the antioxidant activities of these compounds were determined."

-Healthcare Research Institute, Wakunaga Pharmaceutical Company, Ltd., 1624 Shimokotachi, Kodacho, Takatagun, Hiroshima
https://www.ncbi.nlm.nih.gov/pubmed/14640577

Two cinnamoyloctopamine antioxidants from garlic skin attenuates oxidative stress and liver pathology in rats with non-alcoholic steatohepatitis

"Hepatic oxidative stress plays a key role in the development of non-alcoholic steatohepatitis (NASH), therefore, treatment approaches that address the antioxidant is helpful in the therapy of patients with NASH. N-trans-coumaroyloctopamine (1) and N-trans-feruloyloctopamine (2) were identified as the primary antioxidant constituents of garlic skin with high antioxidant activities. The aim of this study was to elucidate the protective effect and mechanism of the antioxidants on NASH in rats. The results provide morphological and molecular biological evidences for the protective role of the antioxidant 2 in ameliorating oxidative stress and hepatic apoptosis in experimental NASH for the first time. Mechanism study indicated that the antioxidant 2 significantly reduced the expression of COX-2 mRNA and protein by western blot, RT-PCR and immunohistochemical techniques."

-School of Pharmaceutics, Lanzhou University, People's Republic of China

-Institute of Microbiology, School of Life Sciences, Lanzhou University, 222 Tian Shui South Road, Lanzhou 730000, People's Republic of China

https://www.sciencedirect.com/science/article/abs/pii/S0944711314003948

Anxiety

Omega-3 Supplementation Lowers Inflammation and Anxiety in Medical Students: A Randomized Controlled Trial

…"Students who received n-3 [omega-3] PUFAs showed a 14% decrease in stimulated IL-6 [interleukin-6] production and a 20% reduction in anxiety symptoms compared to controls. Additional analyses that used changes in the plasma n-6:n-3 ratio as a continuous measure enhanced the magnitude of the effects seen by group assignment; in addition to anxiety, these analyses demonstrated significant effects for both stimulated TNF-α and IL-6 production by PBMCs, as well as a borderline effect for serum TNF-α levels. Individuals can differ in absorption and metabolism of the n-3 PUFA supplements, as well as in adherence, and these analyses helped to clarify the intervention's impact.

The differences in inflammation are particularly striking because our medical students had higher levels of n-3 and lower n-6 than anticipated, based on population data (Simopoulos, 2002). Indeed, their average dietary n-6:n-3 ratio at baseline was 10.82, substantially lower than the typical North American dietary ratios of 15:1 to 17:1 (Simopoulos, 2002). Despite this fact, we nonetheless saw significant decrements in inflammation related to changes in their plasma n-6:n-3 ratios in

response to the n-3 PUFA supplements."…

-Institute for Behavioral Medicine Research, Ohio State University College of Medicine, USA
-Department of Psychiatry, Ohio State University College of Medicine, USA
-Department of Human Nutrition, Ohio State University
-Division of Biostatistics, College of Public Health, Ohio State University
-Department of Internal Medicine, Ohio State University College of Medicine, USA
-Department of Molecular Virology, Immunology, and Medical Genetics, Ohio State University College of Medicine, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191260

Cannabinoid-related agents in the treatment of anxiety disorders: current knowledge and future perspectives

"As outlined above, clinical evidence strongly suggests that acute administration of low doses of CB1 receptor agonists results in anxiolytic effects, while excessive activation of these targets elicits opposite outcomes, following a reverse U-shaped dose-response pattern. Hence, a primary strategy to harness the anxiolytic properties of cannabinoids could consist in the employment of partial, low-affinity CB1 agonists, which may ensure a relatively high therapeutic index and the stabilization of the activation of this target within a range associated with mood enhancement and/or anxiolysis. "

-Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3691841/

Cannabidiol as a Potential Treatment for Anxiety Disorders

"Cannabidiol (CBD), a Cannabis sativa constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations."….

"Preclinical evidence conclusively demonstrates CBD's efficacy in reducing anxiety behaviors relevant to multiple disorders, including PTSD, GAD, PD, OCD, and SAD, with a notable lack of anxiogenic effects. CBD's anxiolytic actions appear to depend upon CB1Rs and 5-HT1ARs in several brain regions; however, investigation of additional receptor actions may reveal further mechanisms. Human experimental findings support preclinical findings, and also suggest a lack of anxiogenic effects, minimal sedative effects, and an excellent safety profile. Current preclinical and human findings mostly involve acute CBD dosing in healthy subjects, so further studies are required to establish whether chronic dosing of CBD has similar effects in relevant clinical populations. Overall, this review emphasizes the potential value and need for further study of CBD in the treatment of anxiety disorders."

-New York University School of Medicine, New York, NY USA
-Instituto de Neurociencias de Alicante, Universidad Miguel Hernández and Consejo Superior de Investigaciones Científicas, Alicante, Spain
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604171/

The Endocannabinoid System (ECS) In regulation of Anxiety

"With respect to functionality, there is a surprisingly consistent body of literature implicating AEA [anandamide an endocannabinoid] signaling in humans in the regulation of anxiety and amygdala activity. For example, in both healthy and psychiatric populations, lower levels of circulating AEA have been found to correlate with higher anxiety.(Dlugos et al, 2012; Hill et al, 2008c)"

Referenced by:
- Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
- Mathison Centre for Mental Health Research and Education, University of Calgary
- Department of Molecular Physiology and Biophysics and Psychiatry, Vanderbilt Brain Institute, Vanderbilt-Kennedy Center for Research on Human Development, Vanderbilt University Medical Center,
- Department of Physiology and Pharmacology, University of Calgary
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4677118/
bit.do/ecsanxiety

■■■

"The endocannabinoid anandamide exerts neurobehavioral, cardiovascular, and immune-regulatory effects through cannabinoid receptors (CB). Fatty acid amide hydrolase (FAAH) is an enzyme responsible for the in vivo degradation of anandamide. Recent experimental studies have suggested that targeting the endocannabinergic system by FAAH inhibitors is a promising novel approach for the treatment of **anxiety**, inflammation, and hypertension. "

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

-The Skaggs Institute for Chemical Biology and Department of Cell Biology, The Scripps Research Institute, La Jolla, California

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225481/

Association of Use of Omega-3 Polyunsaturated Fatty Acids With Changes in Severity of Anxiety Symptoms

"The anxiolytic effect of omega-3 PUFAs was significantly better than that of controls only in subgroups with a higher dosage (at least 2000 mg/d) and not in subgroups with a lower dosage (<2000 mg/d)."

…"Omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential nutrients that have potential preventive and therapeutic effects on psychiatric disorders, such as anxiety and depression,[7-15] as well as comorbid depression and anxiety in physically ill patients,[16-19] patients with coronary heart disease,[20,21] and pregnant women.[22,23] Preclinical data support the effectiveness of omega-3 PUFAs as treatment for anxiety disorders. Song et al[24,25] found that an EPA-rich diet could reduce the development of anxiety-like behaviors in rats as well as normalize dopamine levels in the ventral striatum. In addition, Yamada et al[26] showed that a high dietary omega-3 to omega-6 PUFA ratio reduced contextual fear behaviors in mice and that these effects were abolished by a cannabinoid CB1 receptor antagonist."

-Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan

-Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan

-College of Medicine, China Medical University, Taichung, Taiwan

-WinShine Clinics in Specialty of Psychiatry, Kaohsiung City, Taiwan

-Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

-Chang Gung University College of Medicine, Kaohsiung, Taiwan

-Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

-Division of Health Care Research, Center for Public Health Sciences, National Cancer Center Japan, Tokyo, Japan

-Department of Psychiatry, Tri-Service General Hospital, Taipei, Taiwan

-School of Medicine, National Defense Medical Center, Taipei, Taiwan

-Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

-Prospect Clinic for Otorhinolaryngology & Neurology, Kaohsiung, Taiwan

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2702216

Anandamide hydrolysis: a new target for anti-anxiety drugs?

…"Anandamide is released in selected regions of the brain and is deactivated through a two-step

process consisting of transport into cells followed by intracellular hydrolysis. Pharmacological blockade of the enzyme fatty acid amide hydrolase (FAAH), which is responsible for intracellular anandamide degradation, produces anxiolytic-like effects in rats without causing the wide spectrum of behavioral responses typical of direct-acting cannabinoid agonists. These findings suggest that anandamide contributes to the regulation of emotion and anxiety, and that FAAH might be the target for a novel class of anxiolytic drugs."

-Department of Psychiatry, University of California, Irvine, CA, USA.
https://www.ncbi.nlm.nih.gov/pubmed/14604824

The endocannabinoid system as a target for novel anxiolytic drugs.

"The endocannabinoid (eCB) system has attracted attention for its role in various behavioral and brain functions, and as a therapeutic target in neuropsychiatric disease states, including anxiety disorders and other conditions resulting from dysfunctional responses to stress. In this mini-review, we highlight components of the eCB system that offer potential 'druggable' targets for new anxiolytic medications, emphasizing some of the less well-discussed options. We discuss how selectively amplifying eCBs recruitment by interfering with eCB-degradation, via fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), has been linked to reductions in anxiety-like behaviors in rodents and variation in human anxiety symptoms. We also discuss a non-canonical route to regulate eCB degradation that involves interfering with cyclooxygenase-2 (COX-2). Next, we discuss approaches to targeting eCB receptor-signaling in ways that do not involve the cannabinoid receptor subtype 1 (CB1R); by targeting the CB2R subtype and the transient receptor potential vanilloid type 1 (TRPV1). Finally, we review evidence that cannabidiol (CBD), while representing a less specific pharmacological approach, may be another way to modulate eCBs and interacting neurotransmitter systems to alleviate anxiety. Taken together, these various approaches provide a range of plausible paths to developing novel compounds that could prove useful for treating trauma-related and anxiety disorders."…

-Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, USA
-Vanderbilt Brain Institute, Vanderbilt University, Nashville, USA
-Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, USA
-Vanderbilt Kennedy Center for Human Development, Vanderbilt University Medical Center, Nashville, USA.
-Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
-Mathison Centre for Mental Health Research and Education, University of Calgary, Calgary, AB, Canada
-Departments of Cell Biology and Anatomy and Psychiatry, University of Calgary, Calgary, AB, Canada.
-Department of Anatomy and Neurobiology and Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA.
-Max Planck Institute of Psychiatry, Department of Stress Neurobiology & Neurogenetics, Munich, Germany.
-Laboratory of Behavioral and Genomic Neuroscience, National Institute on Alcohol Abuse and Alcoholism, National

Institutes of Health, Bethesda, MD, USA.
https://www.ncbi.nlm.nih.gov/pubmed/28434588/

Facilitation of endocannabinoid effects in the ventral hippocampus modulates anxiety-like behaviors depending on previous stress experience

"Although several pieces of evidence indicate that the endocannabinoid system modulates anxiety-like behaviors and stress adaptation, few studies have investigated the brain sites of these effects. The ventral hippocampus (VHC) has been related to anxiety behaviors and has a high expression of cannabinoid-1 (CB1) receptors. Moreover, endocannabinoid signaling in the hippocampus is proposed to regulate stress adaptation. In the present study we investigated the role of previous stressful experience on the effects of AM404, an anandamide uptake inhibitor, microinjected into the VHC of rats submitted to the elevated plus maze (EPM), a widely used animal model of anxiety. Stressed animals were forced restrained for two h 24 h before the test. AM404 (5-50 pmol) microinjection promoted an anxiogenic-like effect in non-stressed rats but decreased anxiety in stressed animals. AM251 (0.01 to 1000 pmol), a CB1 receptor antagonist, failed to change behavior in the EPM over a wide dose range but prevented the effects of AM404. Anxiolytic-like effects of AM404 (5 pmol) intra-VHC injection were also observed in the Vogel conflict test (VCT), another model of anxiety that involves previous exposure to stressful situations (48 h of water deprivation). **These results suggest that facilitation of endocannabinoid system neurotransmission in the ventral hippocampus modulates anxiety-like behaviors and that this effect depends on previous stress experience.**"

-Department of Pharmacology, School of Medicine of Ribeirão Preto, University of Sao Paulo
https://pubmed.ncbi.nlm.nih.gov/20167262/

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…"CB1 [cannabinoid receptor 1] is a G-protein coupled receptor (Matsuda et al., 1990). Activation of CB1 receptors inhibits adenylate cyclase, resulting in decreases in intracellular calcium, and activates inwardly K+ channels (Howlett et al., 2002), reduces neurotransmitter release (Vaughan, Connor, Bagley, & Christie, 2000), and finally mediates anxiolytic-like effect (Rubino et al., 2007). Therefore, pharmacological substances that enhance endogenous cannabinoid signaling demonstrate anxiolytic-like actions (Bortolato et al., 2006; Kathuria et al., 2003).

Recent studies suggest the involvement of vanilloid receptors in the expression of anxiety-like behavior and the anxiolytic properties of cannabinoid agonists in mice and rats (Kasckow, Mulchahey, &

Thomas, 2004; Patel and Hillard, 2006; Roohbakhsh, Moghaddam, Massoudi, & Zarrindast, 2007; Rubino et al., 2007). Blockade of TRPV1 resulted in anxiolytic-like behavior in TRPV1 receptor-deficient mice, (Marsch et al., 2007) and rats treated with a TRPV1 antagonist into the medial prefrontal cortex showed a similar effect (Aguiar et al., 2009). Moreover, blockade of TRPV1 channels induces anxiolytic-like effects (Aguiar et al., 2009; Fogaça et al., 2012). TRPV1 promotes cellular depolarization and increases neuronal firing rate (Xing and Li, 2007). TRPV1 is a calcium permeable ligand-gated cation channel that is expressed in various peripheral non-neuronal tissues and throughout the central nervous system (Montell et al., 2002). Activation of TRPV1 channels can stimulate calcium influx, facilitate the release of neurotransmitters (Musella et al., 2009, Starowicz et al., 2007) and may facilitate anxiogenic behavior (Marsch et al., 2007).”..

-Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran.
-Department of Biology, Hamadan Branch, Islamic Azad University, Hamadan, Iran.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440922/

See also Ginger , TRP Channels (Transient receptor potential channels)

See also Mental Health

Aortic Aneurysm

“Our study provides evidence for differential regulation and activation of the endocannabinoid system in human aortic aneurysms. “…

-Department of Cardiac Surgery, University Clinical Centre Bonn, Sigmund-Freud Street 25, 53105 Bonn, Germany
-Institute of Molecular Psychiatry, Life & Brain Center, Sigmund-Freud Street 25, 53105 Bonn, Germany
-Institute of Physiological Chemistry, University Medical Centre of the Johannes Gutenberg University Mainz, Duesbergweg 6, Mainz, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619808/

Aphthous stomatitis

Also called Canker Sores

“Aphthous stomatitis is an illness that causes small ulcers to appear in the mouth, usually inside the lips, on the cheeks, or on the tongue. Aphthous ulcers are also known as "canker sores."

- Children’s Hospital of Philadelphia

https://www.chop.edu/conditions-diseases/aphthous-stomatitis

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Introduction

"Aphthous stomatitis is a common ailment, idiopathic in nature, with recurrent painful aphthous ulcers (commonly termed "canker sores") on the non-keratinized oral mucous membranes.[1][2][3]"

Etiology

"The cause of aphthous stomatitis is idiopathic and multifactorial, but likely involves activation of the cell-mediated immune system. Aphthous ulcers are not caused by acute infections and are therefore not contagious. Aphthous stomatitis may be triggered by local trauma, emotional or physiologic stress, allergy or sensitivity (such as to sodium lauryl sulfate present in toothpaste and oral hygiene products, foods such as cinnamon, cheese, citrus, figs or pineapple), toxin exposure (nitrates in drinking water), menstruation, or alterations in the oral microbiome. Malabsorption, enteropathy, or celiac disease may be present. As many as 20% of cases are related to hematinic deficiencies (iron, folate, vitamin B6 and B12), although other deficiencies such as vitamin D, zinc, or thiamine may also be present. Aphthous ulcers are more prevalent in nonsmokers and smokers who quit and less common in individuals with good oral hygiene practices.[4][5][6]"

Epidemiology

"Aphthous stomatitis affects approximately 20% of the general population. It is slightly more common in girls and women as well as among affluent socioeconomic classes and countries. Race does not appear to be a factor in the disease. Age of onset may be during childhood, but more commonly in the second and third decade of life, becoming less common with advancing age. Aphthous stomatitis can be a manifestation of Behcet syndrome, systemic lupus erythematosus, reactive arthritis, or inflammatory bowel disease (especially Crohn disease). These disorders may be excluded based on systemic signs and symptoms. [7][8]"

-Michael C. Plewa, Calcutta School of Tropical Medicine
https://www.ncbi.nlm.nih.gov/books/NBK431059

Efficacy of Omega-3 in Treatment of Recurrent Aphthous Stomatitis: A Randomised, Double-blind, Placebo-controlled Study

…"The recurrence of ulcers in the omega-3 group showed a significant decrease in the fifth and sixth months compared with the placebo group ($P < 0.05$). The current study indicated that omega-3 consumption decreased the symptoms of recurrent aphthous stomatitis."

-*Tahereh Nosratzehi, Azadeh Akar*

-*The Chinese Journal of Dental Research (2016)*

https://pubmed.ncbi.nlm.nih.gov/27622219

Arachidonic Acid (Omega-6)

Arachidonic Acid is abbreviated as AA or ARA [20:4]

arachidonic acid [AA / ARA] - is an unsaturated, essential fatty acid. It is found in animal and human fat as well as in the liver, brain, and glandular organs, and is a constituent of animal phosphatides. It is formed by the synthesis from dietary linoleic acid and is a precursor in the biosynthesis of prostaglandins, thromboxanes, and leukotrienes.

- *U.S National Library of Medicine / ChemID Plus*

https://pubchem.ncbi.nlm.nih.gov/compound/Arachidonic-acid

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"The endocannabinoid system (ECS) is an ancient panorgan eicosanoid signalling network in which arachidonic acid (AA) derived lipids act in concert with particular receptors and enzymes resulting in the complex modulation of numerous central and peripheral physiological and pathophysiological processes (Pertwee, 2005, 2009; Di Marzo, 2008a; Pacher and Mechoulam, 2011; DiPatrizio and Piomelli, 2015)."...

"In inflamed tissue, COX-2 catalyses the oxygenation of both AA and ECs, leading to an additional control of tissue EC concentration during inflammation (Hermanson et al., 2014). Finally, there is an as yet unidentified facilitated EC cellular reuptake mechanism in certain neuronal cell types and immune cells that can be selectively inhibited and may thus present another level of biological regulation (Nicolussi and Gertsch, 2015). CB1 receptors are involved in the control of behaviour (e.g. motivation, reward, memory processing and habituation to stress) and are thus expressed widely in the CNS where they act as major neuronal circuit breakers, generating a negative retrograde feedback at both glutamatergic and GABAergic synapses in the CNS (Freund et al., 2003; Kano, 2014). CB1 receptors are not only among the most frequent GPCR species in the brain, but functional CB1 receptors are also expressed peripherally and overall probably evolved under the selection pressure of fundamental physiological stress stimuli (Bowles et al., 2015; Morena et al., 2016). These include physical activity, famine, the fight or flight response, traumata and microbial infections."....

- *Jürg Gertsch*
- *Institute of Biochemistry and Molecular Medicine, NCCR TransCure, University of Bern, Bühlstrasse 28, 3012, Bern, Switzerland*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5429335/

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…"Polyunsaturated fatty acids (PUFAs) play fundamental roles in many cellular and multicellular processes, including inflammation, immunity, and neurotransmission. They must be obtained through diet, and a proper balance between omega-6 (ω-6) PUFAs and ω-3 PUFAs is essential. The typical Western diet contains a surfeit of ω-6s and a deficiency of ω-3s [130].

Arachidonic acid (AA) is the archetypical ω-6, with 20 carbons and four double bonds (20:4ω-6). Some of its metabolites cause chronic diseases seen in Western populations: prostaglandins cause pain and swelling, and leukotrienes cause bronchoconstriction and asthma. The inflammatory metabolites of AA are countered by dietary ω-3s. The two best-known ω-3s are eicosapentaenoic acid (EPA, 20:5ω-3) and docosahexaenoic acid (DHA, 22:6ω-3)."…

- GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom,
- Department of Family Medicine, University of Vermont, Burlington, Vermont, USA,
- Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei, Pozzuoli, Napoli, Italy,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951193/

Omega-6 fatty acids and inflammation.

"Inflammation is a normal process that is part of host defence and tissue healing. However, excessive or unresolved inflammation can lead to uncontrolled tissue damage, pathology and disease. In humans on a Western diet, the omega-6 polyunsaturated fatty acid arachidonic acid (ARA) makes a significant contribution to the fatty acids present in the membrane phospholipids of cells involved in inflammation. ARA is a precursor to a number of potent pro-inflammatory mediators including well described prostaglandins and leukotrienes, which has led to the development of anti-inflammatory pharmaceuticals that target the ARA pathway to successfully control inflammation. Hence, it is commonly believed that increasing dietary intake of the omega-6 fatty acids ARA or its precursor linoleic acid (LA) will increase inflammation. However, studies in healthy human adults have found that increased intake of ARA or LA does not increase the concentrations of many inflammatory markers. Epidemiological studies have even suggested that ARA and LA may be linked to reduced inflammation. Contrastingly, there is also evidence that a high omega-6 fatty acid diet inhibits the anti-inflammatory and inflammation-resolving effect of the omega-3 fatty acids. Thus, the interaction of omega-3 and omega-6 fatty acids and their lipid mediators in the context of inflammation is complex and still not properly

understood."

-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, IDS Building, MP887 Southampton General Hospital, Tremona Road, Southampton, United Kingdom.

-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, IDS Building, MP887 Southampton General Hospital, Tremona Road, Southampton, United Kingdom

-National Institute for Health Research Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust

-University of Southampton, Southampton, United Kingdom.

https://www.ncbi.nlm.nih.gov/pubmed/29610056

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"Similarly, arthritis, Crohn's disease, ulcerative colitis and lupus erythematosis are autoimmune diseases characterized by a high level of IL-1 and the proinflammatory leukotriene LTB(4) produced by omega-6 fatty acids."....

-The Center for Genetics, Nutrition and Health, Washington, DC, USA.

https://www.ncbi.nlm.nih.gov/pubmed/12480795

■■■

..."A diet rich in n-6 PUFAs (e.g., AA) has been linked to the development and persistence of various diseases (Shek et al., 2012)."...

-Department of Veterinary Pathobiology, University of Missouri, Columbia, MO, USA

-Edited by: Tanja Petnicki-Ocwieja, Tufts University School of Medicine and Tufts Medical Center, USA

-Reviewed by: Margaret E. Bauer, Indiana University School of Medicine, USA,

Ashu Sharma, University at Buffalo, State University of New York, USA; Dakshina Jandhyala, Tufts Medical Center, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4036060/

■■■

..."AA [arachidonic acid] is involved in many pathologic conditions, such as inflammation, asthma, cancer, diabetes, hypertension, and the pathogenesis of kidney disease. The aim of this study was to define whether the dialysis type affects the concentration of AA derivatives in patients with chronic kidney disease."...

-Department of Laboratory Medicine, Pomeranian Medical University in Szczecin, Poland

-Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University in Szczecin, Poland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7488457

…"Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) have been attributed to their ability to displace the omega-6 fatty acid, arachidonic acid [8], as molecular substrates during the cyclooxygenase and oxygenase pathways."…

-College of Agriculture, Environment and Nutrition Sciences, Tuskegee University, Tuskegee, Alabama, USA

-Department of Biology, Tuskegee University, Tuskegee, Alabama, USA

https://www.longdom.org/open-access/omega-omega-and-omega-fatty-acids-implications-for-cardiovascular-and-other-diseases-2153-0637.1000123.pdf

http://bit.do/diet369

CBD has been shown in research to inhibit 'pro-inflammatory' Omega-6s

…"Administration of CBD to cultured human sebocytes and human skin organ culture inhibited the lipogenic actions of various compounds, including arachidonic acid [omega-6] and a combination of linoleic acid and testosterone, and suppressed sebocyte proliferation via the activation of transient receptor potential vanilloid-4 (TRPV4) ion channels."…

-DE-MTA "Lendület" Cellular Physiology Research Group, Department of Physiology, University of Debrecen, Debrecen, Hungary.

-Laboratory for Ion Channel Research and TRP Research Platform Leuven, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium.

-Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan.

-Department of Dermatology, University of Lübeck, Lübeck, Germany.

-Neurobiology Research Group, Department of Physiology, University of Debrecen, Debrecen, Hungary.

-Laboratory of Cutaneous Physiopathology and Integrated Center of Metabolomics Research, San Gallicano Dermatologic Institute, IRCCS, Rome, Italy.

-Departments of Dermatology, Venereology, and Allergology and Immunology, Dessau Medical Center, Dessau, Germany.

-School of Translational Medicine, University of Manchester, Manchester, United Kingdom.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151231

…"The biomarker of %n-6 [omega-6] in HUFA indicates the propensity for arachidonate cascade overreactions and is a useful indicator for health risk assessment. For example, the incidence of heart attacks for the quintile of Americans maintaining about 62% n-6 in HUFA was nearly one-

half of that for those with median values near 80% [41]. Cross-cultural comparisons showed a very close association of CHD mortality with values from 32% to 80% n-6 in HUFA [41]. Knowing about n-6 mediators of inflammatory atherogenesis and of platelet-mediated thrombosis makes a change of 10% to 20% in this biomarker an important aspect in health conditions. Blasbalg et al. described the dramatic rise in n-6 linoleic acid consumption in the USA during the late 20th century [42]. The change reflects a widespread insertion of vegetable oils into many "modern" processed foods. That change was assessed by one research group [43] in these terms: "The widespread consumption of diets with more than 2% energy as LA should be recognized for what it is—a massive uncontrolled human experiment without adequate rationales or proven mechanisms." A constructive alternative to this situation would be to apply quantitative knowledge of the metabolic dynamics of dietary n-3 and n-6 nutrients to moderate the current propensity for unwanted overactive arachidonic acid cascade events."…

"Lowering the propensity for arachidonate cascade overreaction is important for most large USA employers that have large financial losses due to employees' health-related absenteeism, presenteeism, and medical and pharmacy expenses [66]. Many health conditions that cause major financial losses [67] are made worse by n-6 mediators in arachidonate cascade overreactions (Table 1). A simple wellness plan that informs employees of their health risk status from finger-tip blood-spot assays and informs them of Omega 3-6 Balance Scores of common foods may help employees voluntarily shift their HUFA balance toward the lower values of %n-6 in HUFA which have a lower propensity for arachidonate cascade overreactions [16]. An Omega 3-6 Balance Score App [68] lists over 5,000 foods in a searchable format."

- Professor Bill Lands (Professor of Biochemistry)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537720

Omega-6 vegetable oils as a driver of coronary heart disease: the oxidized linoleic acid hypothesis

-Department of Preventive Cardiology, Saint Luke's Mid America Heart Institute, Kansas City, Missouri, USA
https://openheart.bmj.com/content/5/2/e000898

Role of dietary fatty acids in mammary gland development and breast cancer

…"When pregnant rats were fed high-fat diets using oils high in n-6 [omega-6] PUFA, serum estradiol levels increased in the mothers and resulted in the female offspring having significantly higher incidence of mammary tumors (Table (Table1)1) [25,26]. The increase in tumor incidence was attributed to changes in the MG of the female offspring. The effects of the high n-6 PUFA diet

were similar to animals injected with estradiol during pregnancy, which suggests that n-6 PUFA induces adipose cells to produce and release estrogen in the body, leading to the promotion of tumor growth [25,26]. Additionally, female offspring exposed to maternal high -fat diets had earlier menarche than controls, which is a marker of increased BC risk, and is associated with significantly higher numbers of TEB (Table (Table1)1) [25,26]. Moreover, the MG of female rodents exposed to estradiol or a high n-6 PUFA diet developed TEB that persisted longer, and with reduced differentiation to alveolar buds (Table (Table1)1) [25]."…

-Department of Human Health and Nutritional Sciences, College of Biological Science, University of Guelph, , Ontario, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3096965

■■■

…"Arachidonic acid (AA) has been recognized as protumorigenic."…

-Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928987/

■■■

…"Arachidonic acid (AA, 20:4 ω-6) is one of the major polyunsaturated ω-6 fatty acids. AA is metabolized by three groups of oxygenases namely cyclooxygenases (COX), lipoxygenases (LOX) and cytochrome P450s (CYP) to a number of biologically active eicosanoids (Figure 1). "…

-Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928987/

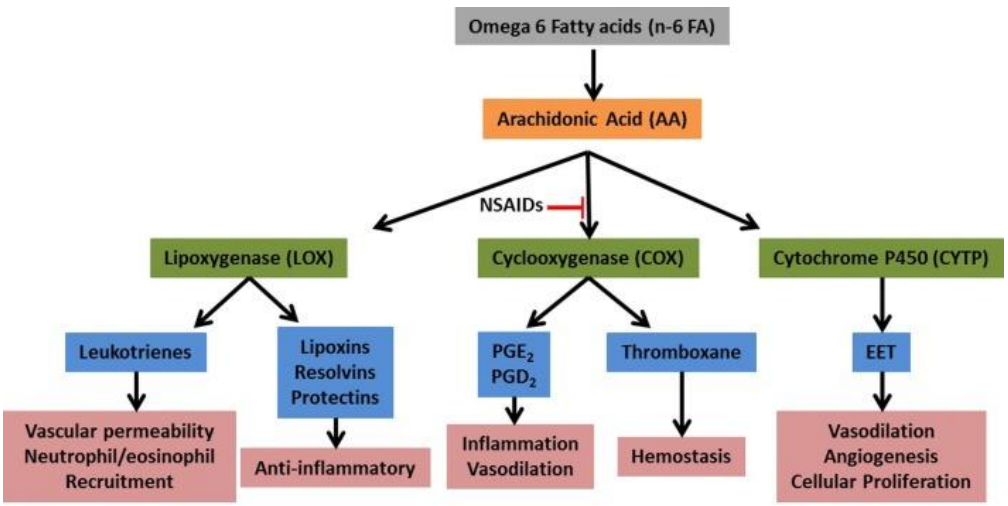
■■■

"Animal trials show that omega-3 fatty acid treatment decreases blood pressure, has anti-inflammatory effects, slows renal failure and moderates the side effects of hypertension (Imig et al. 2005; Zhao et al. 2004). This has been the basis for the study of the effects of omega-3 fatty acids on kidney disease. A recent literature review found that no definitive conclusions can be made about the effectiveness of omega-3 fatty acids for the prevention or treatment of kidney disease (Fassett et al. 2010).

However, just as in the review of effects on cardiovascular disease, the authors point out that there was substantial variability from study to study in the dosages, proportions of specific omega-3 fatty acids administered (i.e., formulations), duration of supplementation, sample sizes and specific outcomes assessed. This again suggests that further studies are needed to better understand the specific formulations, dosages and markers of effectiveness for omega-3 fatty

acid supplementation."

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/



…"Simplified eicosanoid metabolic pathway. Upon tissue damage or infection arachidonic acid (AA) is released from membrane stores by the activity of cytosolic phospholipase 2. The free AA is then acted upon by the primary metabolic enzymes (green) and converted to numerous bioactive compounds (blue)."…

-Department of Veterinary Pathobiology, University of Missouri, Columbia, MO, USA

-Edited by: Tanja Petnicki-Ocwieja, Tufts University School of Medicine and Tufts Medical Center, USA

-Reviewed by: Margaret E. Bauer, Indiana University School of Medicine, USA; Ashu Sharma, University at Buffalo, State University of New York, USA; Dakshina Jandhyala, Tufts Medical Center, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4036060

The acute inflammatory process, arachidonic acid metabolism and the mode of action of anti-inflammatory drugs

"Arachidonic acid is a polyunsaturated fatty acid covalently bound in esterified form in the cell membranes of most body cells. Following irritation or injury, arachidonic acid is released and oxygenated by enzyme systems leading to the formation of an important group of inflammatory mediators, the eicosanoids. It is now recognised that eicosanoid release is fundamental to the inflammatory process. For example, the prostaglandins and other prostanoids, products of the

cyclooxygenase enzyme pathway, have potent inflammatory properties and prostaglandin E2 is readily detectable in equine acute inflammatory exudates. The administration of nonsteroidal anti-inflammatory drugs results in inhibition of prostaglandin synthesis and this explains the mode of action of agents such as phenylbutazone and flunixin. Lipoxygenase enzymes metabolise arachidonic acid to a group of noncyclised eicosanoids, the leukotrienes, some of which are also important inflammatory mediators. They are probably of particular importance in leucocyte-mediated aspects of chronic inflammation. Currently available non-steroidal anti-inflammatory drugs, however, do not inhibit lipoxygenase activity. In the light of recent evidence, the inflammatory process is re-examined and the important emerging roles of both cyclo-oxygenase and lipoxygenase derived eicosanoids are explored. The mode of action of current and future anti-inflammatory drugs offered to the equine clinician can be explained by their interference with arachidonic acid metabolism."

-A J Higgins, P Lees
https://pubmed.ncbi.nlm.nih.gov/6428879/

Arachidonic acid: Physiological roles and potential health benefits – A review

"It is time to shift the arachidonic acid (ARA) paradigm from a harm-generating molecule to its status of polyunsaturated fatty acid essential for normal health. ARA is an integral constituent of biological cell membrane, conferring it with fluidity and flexibility, so necessary for the function of all cells, especially in nervous system, skeletal muscle, and immune system. Arachidonic acid is obtained from food or by desaturation and chain elongation of the plant-rich essential fatty acid, linoleic acid. Free ARA modulates the function of ion channels, several receptors and enzymes, via activation as well as inhibition. That explains its fundamental role in the proper function of the brain and muscles and its protective potential against Schistosoma mansoni and S. haematobium infection and tumor initiation, development, and metastasis. Arachidonic acid in cell membranes undergoes reacylation/deacylation cycles, which keep the concentration of free ARA in cells at a very low level and limit ARA availability to oxidation. Metabolites derived from ARA oxidation do not initiate but contribute to inflammation and most importantly lead to the generation of mediators responsible for resolving inflammation and wound healing. Endocannabinoids are oxidation-independent ARA derivatives, critically important for brain reward signaling, motivational processes, emotion, stress responses, pain, and energy balance. Free ARA and metabolites promote and modulate type 2 immune responses, which are critically important in resistance to parasites and allergens insult, directly via action on eosinophils, basophils, and mast cells and indirectly by binding to specific receptors on innate lymphoid cells. In conclusion, the present review advocates the innumerable ARA roles and considerable

importance for normal health."…

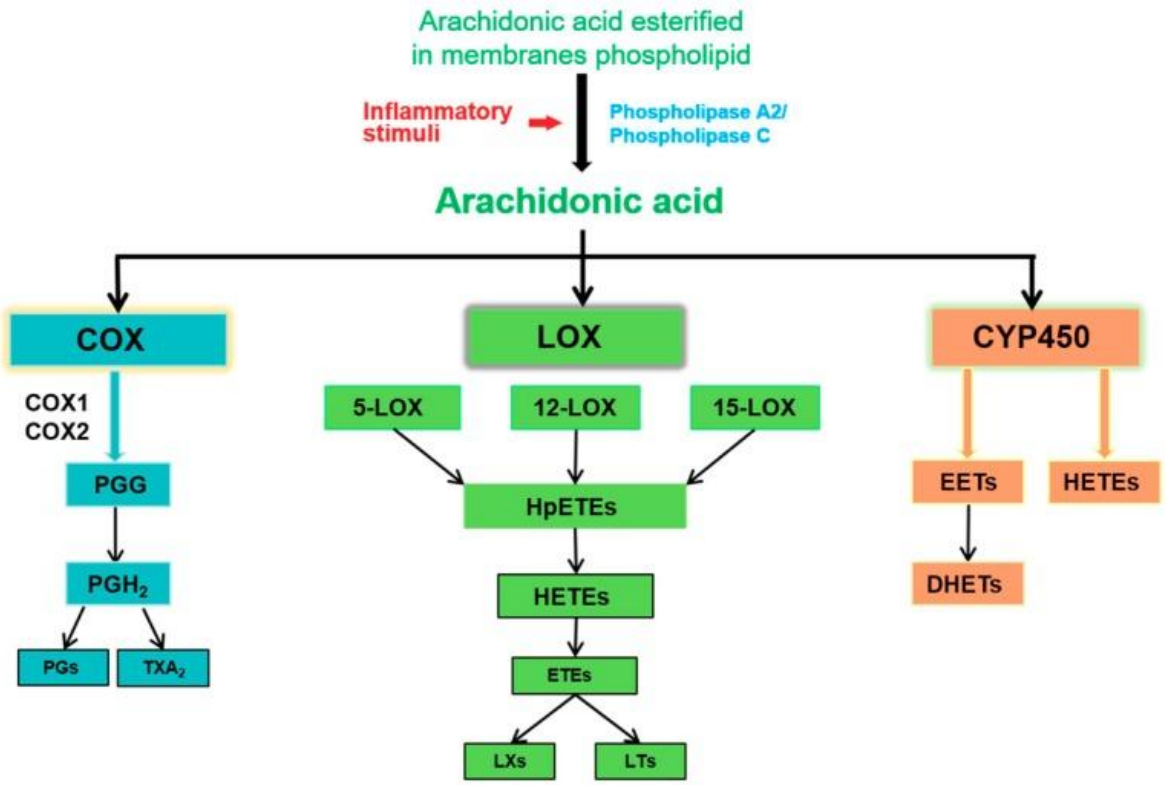
-Zoology Department, Faculty of Science, Cairo University, Giza 12613, Egypt

-Department of Chemistry, School of Science and Engineering, American University in Cairo, New Cairo 11835, Cairo, Egypt

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6052655/

The Release of AA [Arachidonic acid]

…"Normally, AA exists in the cell membrane in the form of phospholipids. When the cell membrane is subjected to stimuli, especially the inflammatory reaction, the phospholipids are released from the cell membrane. Through the hydrolysis of phospholipids by PLA2 and PLC [1,3,12], AA is released and then transformed into a bioactive metabolite with the help of different enzymes, thus promoting inflammatory cascades. At present, it is well known that at least three metabolic pathways (the COX pathway, LOX pathway and CYP450 pathway) are involved in the metabolism of AA, which are closely related to the occurrence, development, and regression of renal inflammation (Figure 1) [1]."…



-Traditional Chinese Medicine History and Literature, Institute for Literature and Culture of Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, China

-Institute for Literature and Culture of Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan

250355, China

-Key Laboratory of Traditional Chinese Medicine for Classical Theory, Ministry of Education, Shandong University of Traditional Chinese Medicine, Jinan 250355, China

-The Institute for Tissue Engineering and Regenerative Medicine, The Liaocheng University, Liaocheng 252000, China

-Research Institute of Biotechnology & Medical Converged Science, Dongguk University-Seoul, Goyangsi 10326, Korea

-Institute of Clinical Chemistry, University Hospital Zurich, University of Zurich, Wagistrasse 14, 8952 Schlieren, Switzerland

-Guizhou University of Traditional Chinese Medicine, Fei Shan Jie 32, Guiyang 550003, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6695795/

Arthritis

The association between omega-3 fatty acid biomarkers and inflammatory arthritis in an anti-citrullinated protein antibody positive population

"Higher circulating omega-3 fatty acids (n-3 FAs) are associated with a lower prevalence of anti-CCP antibodies and RF in subjects without RA. We examined whether, in anti-CCP+ subjects, n-3 FAs also play a role in development of inflammatory arthritis (IA)."

…"n-3 FAs may potentially lower the risk of transition from anti-CCP positivity to IA, an observation that warrants further investigation."

-Department of Epidemiology, Colorado School of Public Health

-Division of Rheumatology, University of Colorado, Aurora

-Nine Health Services, Inc., Denver, CO

-Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850337/

Higher Omega-6 to Omega-3 Fatty Acid Ratio Is Associated with Increased Odds of Inflammatory Arthritis in a Health Fair Population Positive for Anti-Citrullinated Protein Antibodies (ACPA)

"We previously found that lower levels of omega-3 fatty acids (n-3 FA) were associated with the presence of inflammatory arthritis (IA) as well as risk of developing incident IA in ACPA+ individuals without IA at baseline. Omega-6 fatty acids (n-6 FA) compete with n-3 FA for elongation and desaturation enzymes in the body that help determine the pro- and anti-inflammatory potential of these FA and their derivatives. Western diets tend to have a high n-6 to n-3 ratio that may promote the pathogenesis of inflammatory and autoimmune diseases. We

examined the association between n-6 FA levels and the presence of IA/rheumatoid arthritis (RA) in ACPA+ individuals."

…"Subjects with IA at baseline were more likely to be ever smokers and test positive for rheumatoid factor and C-reactive protein than those without IA (Table 1). In addition, we found that subjects with higher n-6 FA and linoleic acid levels had higher odds of IA (Table 2). Furthermore, analysis of the n-6 to n-3 ratio demonstrated that higher total n-6 FA % relative to total n-3 FA % in RBCs significantly increased the odds of IA by almost 3-fold (Table 2)."

…"We found that a higher n-6 to n-3 ratio was associated with prevalent IA [inflammatory arthritis] in this ACPA+ population. Building off our previous work, this suggests a potential beneficial role of n-3 FAs in decreasing the risk of transitioning from ACPA positivity to IA. Specifically, our findings herein suggest that decreasing the n-6 to n-3 FA ratio in the body, perhaps either via n-3 FA supplementation or diet may play a role in decreasing the transition from an ACPA+ state to IA, findings that warrant further investigation."

-Epidemiology, Colorado School of Public Health, Aurora, CO

-Colorado School of Public Health, University of Colorado Denver, Aurora, CO,

-Experimental Pathology, University of Florida, College of Medicine, Gainesville, FL, Rheumatology Division, University of Colorado School of Medicine, Aurora, CO,

-Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, Department of Epidemiology, Colorado School of Public Health, Aurora, CO

https://acrabstracts.org/abstract/higher-omega-6-to-omega-3-fatty-acid-ratio-is-associated-with-increased-odds-of-inflammatory-arthritis-in-a-health-fair-population-positive-for-anti-citrullinated-protein-antibodies-acpa/

Imbalance Between Omega-6- and Omega-3-Derived Bioactive Lipids in Arthritis in Older Adults

…"These results suggest that certain oxylipins may be key effectors in arthrtis in older adults and that the imbalance between n-6- and n-3-derived oxylipins might be related to pathobiology in this population."

-Roxana Coras, MD, Brian Pedersen, MD, Rekha Narasimhan, BS, Anahy Brandy, MD, Lourdes Mateo, MD, PhD, Agueda Prior-Español, MD, Arthur Kavanaugh, MD, Aaron M Armando, MS, Mohit Jain, MD, PhD, Oswald Quehenberger, PhD, Melania Martínez-Morillo, MD, PhD, Monica Guma, MD, PhD

-The Journals of Gerontology: Series A

https://academic.oup.com/biomedgerontology/advance-article-abstract/doi/10.1093/gerona/glaa113/5828417

…"Omega-3 fatty acid intake is associated with the improvement of rheumatoid arthritis, as omega-3 metabolites inhibit the production of inflammatory cytokines responsible for arthritic

pain [Zainal et al. 2009]. Supplementation with EPA and DHA is effective against arthritic pain as well as other symptoms, including joint stiffness [Goldberg and Katz 2007].”…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

Asperger Syndrome

“Autistic disorder is a behaviorally defined neurodevelopmental disorder of childhood characterized by deficits in social interaction, language, communication and repetitive behaviors that manifest in early postnatal life [1]. It belongs to a spectrum of closely related conditions also referred to as autism spectrum disorders (ASDs) that also includes pervasive developmental disorder not otherwise specified, Asperger’s syndrome, and childhood disintegrative disorder. The incidence of ASDs has increased significantly over the last decades and is currently 1 in 150, affecting boys four times more often than girls [2, 3].”…

During the last trimester of pregnancy and the first 2 years of life, human brain undergoes an immense growth during which unesterified omega-3 and omega-6 fatty acid content of the grey and white matters increase considerably [53, 54] . Because of the increased demand, sufficient supply of the essential PUFAs and proper ratio of AA to DHA particularly during early life is critical for proper development and function of the nervous system [16, 31, 55–59] . Both human and animal studies have correlated the presence of AA and DHA during critical period of development to enhanced visual, cognitive and motor functions [23, 60–63] . A link between imbalances in the AA to DHA composition and abnormalities of fatty acid metabolism have been shown to play a role in the pathology of various psychiatric disorders, including attention deficit hyperactivity disorder, dyslexia, dyspraxia, bipolar disorder and schizophrenia [51, 64–71] . Insufficient dietary intake of PUFA during early development and abnormal lipid metabolism have been shown to occur in ASDs as well. Current literature suggests that altered level of omega-6 fatty acids (i.e. AA) and omega-3 fatty acid (i.e. DHA) may result in an imbalance in the ratio between these PUFAs in the nervous system and potentially contribute to the behavioral outcomes seen in autism. A survey study reported that children who were not breastfed or fed on infant formula not supplemented with PUFAs were significantly more likely to develop autism [72] . Altered level of LA, DHA and AA and significantly higher AA:DHA ratio was reported in the blood samples (plasma and red blood cells) of autism patients compared to the control group [15] . Other studies have reported a significant reduction in AA and DHA levels in the plasma of autistic children compared to the levels in controls [73–75]. Decreased level of DHA and subsequently

higher AA:DHA ratio were also detected in the red blood cells of children with regressive autism and Asperger's syndrome compared to typically developing controls [14, 76] . Sliwinski et al.[77] observed an increase in the plasma omega-3 PUFAs, in particular DHA and an increase in the total omega-3 and omega-6 PUFA ratio in high-functioning males with autism compared to healthy controls. Moreover, other lipid biomarkers such as saturated and polyunsaturated very long-chain fatty acidcontaining phosphatidyl-ethanolamines and DHA-containing ethanolamine plasmalogens (PlsEtns) were also elevated in the plasma of subjects with autism [78]. The link between altered brain fatty acid metabolism and the occurrence of autism-like behavior has been also demonstrated in animal models. For example, various

studies reported that exposure to environmental agents such as propionic acid (PPA), derived from enteric bacteria or diet, may result in the appearance of autism-like behavior in rodents as a result of altered composition of brain phospholipids [79–81]. Intraventricular infusions of PPA, reduction in total monounsaturated fatty acids, omega-6 fatty acids and PlsEtns, decreased omega-6/omega-3 ratio, and increased level of total saturated fatty acids, which is consistent with reports observed in the blood of autistic patients [79, 82]. "…

-Department of Biology, b School of Kinesiology and Health Science
-Neuroscience Graduate Diploma Program,
-York University, Toronto, Ont. , Canada
https://www.karger.com/Article/pdf/323189

See also Autism

Astaxanthin

…"Astaxanthin is found in microalgae, yeast, salmon, trout, krill, shrimp, crayfish and crustacea. Astaxanthin is biosynthesized by microalgae or phytoplankton, which are consumed by zooplankton or crustacea. They accumulate astaxanthin and, in turn are ingested by fish which then accrue astaxanthin in the food chain.38 Therefore, astaxanthin has considerable potential and promising applications in human health and nutrition[39] and has been attributed an extraordinary potential for protecting the organism against a wide range of diseases (reviewed in refs. 40 and 41).

The UV protective effects of algal extract containing 14% of astaxanthin compaired to synthetic astaxanthin have also been tested. The authors of this study reported that preincubation with synthetic astaxanthin or an algal extract could prevent UVA-induced alterations in cellular superoxide dismutase activity and decrease in cellular glutathione content.[42]

In a study of Camera et al. the modulation of UVA-related injury by astaxanthin, canthaxanthin, and β-carotene for systemic photoprotection in human dermal fibroblasts has been compared.43 Astaxanthin showed a significant photoprotective effect and counteracted UVA-induced alterations to a great extent. The uptake of astaxanthin by fibroblasts was higher than that of canthaxanthin and β-carotene, which lead to the assumption that the effect of astaxanthin toward photooxidative changes was stronger than that of the other substances. A recent study of Suganuma et al. showed that astaxanthin could interfere with UVA-induced matrix-metalloproteinase-1 and skin fibroblast elastase/neutral endopeptidase expression.[44] Both studies suggest that effects of UVA radiation, such as skin sagging or wrinkling can be prevented or at least minimized by topical or oral administration of astaxanthin.[36,42,44]"…

-Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center; Dessau, Germany
-Laboratory for Biogerontology, Dermato-Pharmacology and Dermato-Endocrinology; Institute of Clinical Pharmacology and Toxicology; Charité Universitaetsmedizin Berlin; Berlin, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3583891

Natural products and body weight control

"Natural ingredients are effective and practical remedies for treatment of obesity, and relatively safe. The most popular supplements are catechins, capsaicin, soy isoflavone, fucoxanthin, glabridin, conjugated linoleic acid, astaxanthin, cyaniding-3-glucoside etc."…

"Astaxanthin is a natural antioxidant carotenoid that occurs in a wide variety of living organisms. It has many highly potent pharmacological effects, including antioxidant, anti-tumor and anti-cancer, anti-diabetic, and anti-inflammatory activities."…

"Recent animal studies have also shown that astaxanthin may have a beneficial effect on body weight control. Fifty 4 week old female ddY mice were divided into five groups (n=10), normal diet (control group), high-fat diet group (placebo) and the other three groups were high-fat diet supplemented with 1.2, 6, 30 mg/kg body weight of astaxanthin, respectively. Astaxanthin at levels of 6 mg/kg or 30 mg/kg body weight significantly reduced the body weight gain induced by the high-fat diet. In addition, astaxanthin reduced liver weight, liver triacyglycerol, plasma triacyglycerol and total cholesterol[48]. Another study with similar design from the same research group found that astaxanthin treatment stimulated an enhancement of fatty acid utilization in mice[49]. Further studies are warranted to elucidate the mechanisms of astaxanthin on body weight management."

-Department of Research & Development, Beijing Gingko Group, Beijing, China 100081
-Department of Food Science & Nutrition, Zhejiang University, Hangzhou, China 310058
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3336927

…"Many phytochemicals, particularly carotenoids and flavonoids, are well-known of capability in cellular redox imbalance modulation, as well as the endothelial and metabolic processes regarding the pathogenesis of inflammatory. Astaxanthin is one of the most common carotenoids and found in the red pigment in crustacean shells (crabs, shrimps, for example), salmon, and Asteroidean [14]. Moreover, astaxanthin, as a nutraceutical, has been reported to possess the potential preventive capacity associated with health benefits [15] partly due to its free radical antioxidant activity up to 100-fold stronger than vitamin E [16]. Additionally, previous studies demonstrated that astaxanthin intake as a nutritional supplement can prevent oxidative damages resulting in a decrease in some chronic diseases [17,18,19], exhibit anti-tumor activity [20], inhibit proliferation of breast and colon cancer [21,22], and reduce significantly chronic inflammatory diseases [23,24,25]. Since the common source, like Haematococcus pluvialis, is not able to be cultivated in Thailand, an interesting alternative source of astaxanthin is Litopenaeus vannamei, which plays an enormous role in national exportation. Large amount of crustacean shells are however wastefully left out. Additionally, any scientific supports for astaxanthin from have not yet been established. Herein the present study reported the anti-inflammatory activities of astaxanthin extracted from the white shrimp shell (Litopenaeus vannamei) mostly found in Thailand."…

-Department of Physiology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, Thailand;
-Center for Advanced Studies for Agriculture and Food, Kasetsart University, Bangkok, Thailand;
-Department of Biomedical Sciences, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6272999

"The consumption of marine fishes and general seafood has long been recommended by several medical authorities as a long-term nutritional intervention to preserve mental health, hinder neurodegenerative processes, and sustain cognitive capacities in humans. Most of the neurological benefits provided by frequent seafood consumption comes from adequate uptake of omega-3 and omega-6 polyunsaturated fatty acids, n-3/n-6 PUFAs, and antioxidants. Optimal n-3/n-6 PUFAs ratios allow efficient inflammatory responses that prevent the initiation and progression of many neurological disorders. Moreover, interesting in vivo and clinical studies with the marine antioxidant carotenoid astaxanthin (present in salmon, shrimp, and lobster) have shown promising results against free radical-promoted neurodegenerative processes and cognition loss. This review presents the state-of-the-art applications of n-3/n-6 PUFAs and astaxanthin as nutraceuticals against neurodegenerative diseases associated with exacerbated oxidative stress in CNS. The fundamental "neurohormesis" principle is discussed throughout this

paper. Finally, new perspectives for the application of a natural combination of the aforementioned anti-inflammatory and antioxidant agents (found in krill oil) are also presented herewith."…

-Institute of Physical Activity and Sports Science (ICAFE), Cruzeiro do Sul University, Brazil
-Graduation Program in Health Sciences, Cruzeiro do Sul University, Brazil;
-Department of Veterinary Medicine, University Paulista (UNIP), Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3967194/

Asthma

Ratio of omega-6 to omega-3 fatty acids and childhood asthma.

"Asthma is a leading cause of morbidity for children and is a major public health problem in Australia. Ecological and temporal data suggest that dietary factors may have a role in recent increases in the prevalence of asthma."

…."The aim of conducting this study was to investigate whether childhood asthma was associated with the ratio of omega 6 (n-6) to omega-3 (n-3) fatty acids in the diet (n-6:n-3)."

…."We found evidence for a modulatory effect of the dietary n-6:n-3 fatty acid ratio on the presence of asthma in children. Our results provide evidence that promotion of a diet with increased n-3 fatty acids and reduced n-6 fatty acids to protect children against symptoms of asthma is warranted."

-Department of Nutrition, Dietetics and Food Science, Curtin University of Technology, Perth, Western Australia, Australia
https://www.ncbi.nlm.nih.gov/pubmed/15260465/

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"Due to the immunomodulatory effect of cannabinoids, a significant variety of studies were focused on their possible therapeutic potential on inflammatory diseases like asthma [43,67,68,92,93,104,109,110,111,112,113,114]. The molecular mechanisms mediating the effects of cannabinoids in allergic airway responses mainly depend on their effects on immune cells and the related release of cytokines [115]. In mice, treatment with the plant-derived cannabinoids, cannabinol and THC, was able to inhibit the expression of critical T cell cytokines and inflammatory response in ovalbumin-induced experimental allergic airway inflammation [116]. Using the ovalbumin model, Braun et al., have demonstrated that THC can inhibit cell proliferation, suppress cytokine and chemokine production, and stimulate regulatory T cells [112]. However, they have also suggested

that these effects are probably mediated by cannabinoid receptor-independent mechanisms [112]."

-Department of Pharmacology, Faculty of Pharmacy, Hacettepe University
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943521/

Arachidonic acid metabolites: mediators of inflammation in asthma

"Asthma is increasingly recognized as a mediator-driven inflammatory process in the lungs. The leukotrienes (LTs) and prostaglandins (PGs), two families of proinflammatory mediators arising via arachidonic acid metabolism, have been implicated in the inflammatory cascade that occurs in asthmatic airways. The PG pathway normally maintains a balance in the airways; both PGD2 and thromboxane A2 are bronchoconstrictors, whereas PGE2 and prostacyclin are bronchoprotective. The actions of the LTs, however, appear to be exclusively proinflammatory in nature. The dihydroxy-LT, LTB4, may play an important role in attracting neutrophils and eosinophils into the airways, whereas the sulfidopeptide leukotrienes (LTC4, LTD4, and LTE4) produce effects that are characteristic of asthma, such as potent bronchoconstriction, increased endothelial membrane permeability leading to airway edema, and enhanced secretion of thick, viscous mucus. Given the significant role of the inflammatory process in asthma, newer pharmacologic agents, such as the sulfidopeptide-LT antagonists, zafirlukast, montelukast, and pranlukast and the 5-lipoxygenase (5-LO) inhibitor, zileuton, have been developed with the goal of targeting specific elements of the inflammatory cascade. These drugs appear to represent improvements to the existing therapeutic armamentarium. In addition, the results of clinical trials with these agents have helped to expand our understanding of the pathogenesis of asthma."

-National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206-1900, USA.
https://pubmed.ncbi.nlm.nih.gov/9017783/

Ataxia

"Ataxia describes a lack of muscle control or coordination of voluntary movements, such as walking or picking up objects. A sign of an underlying condition, ataxia can affect various movements, creating difficulties with speech, eye movement and swallowing.

Persistent ataxia usually results from damage to the part of your brain that controls muscle coordination (cerebellum). Many conditions can cause ataxia, including alcohol abuse, certain medications, stroke, tumor, cerebral palsy, brain degeneration and multiple sclerosis. Inherited defective genes also can cause the condition.

Treatment for ataxia depends on the cause. Adaptive devices, such as walkers or canes, might help you maintain your independence. Physical therapy, occupational therapy, speech therapy and regular aerobic exercise also might help."

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/ataxia/symptoms-causes/syc-20355652

Does modulation of the endocannabinoid system have potential therapeutic utility in cerebellar ataxia?

"Cerebellar ataxias represent a spectrum of disorders which are, however, linked by common symptoms of motor incoordination and typically associated with deficiency in Purkinje cell firing activity and, often, degeneration. Cerebellar ataxias currently lack a curative agent. The endocannabinoid (eCB) system includes eCB compounds and their associated metabolic enzymes, together with cannabinoid receptors, predominantly the cannabinoid CB1 receptor (CB1R) in the cerebellum; activation of this system in the cerebellar cortex is associated with deficits in motor coordination characteristic of ataxia, effects which can be prevented by CB1R antagonists. Of further interest are various findings that CB1R deficits may also induce a progressive ataxic phenotype. Together these studies suggest that motor coordination is reliant on maintaining the correct balance in eCB system signalling. Recent work also demonstrates deficient cannabinoid signalling in the mouse 'ducky^{2J}' model of ataxia. In light of these points, the potential mechanisms whereby cannabinoids may modulate the eCB system to ameliorate dysfunction associated with cerebellar ataxias are considered."

Professor G. J. Stephens - School of Pharmacy, University of Reading, Reading, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4983615/

Ataxia after Vaccination in United States, a Report from the CDC/FDA Vaccine Adverse Event Reporting System [1990–2010]

…"The report of most cases of ataxia within the first 6 weeks after vaccination (when the date of vaccination is known), reveals an unbalanced distribution of occurrence in this time period, with most cases reported in the first two weeks. This may suggest that some cases of ataxia are triggered by vaccination and warrants continuous and careful analysis of such cases after vaccination."

-Neurology New Jersey Medical School Newark NJ
https://n.neurology.org/content/78/1_Supplement/P05.016

Atherosclerosis

Also known as Arteriosclerosis, Hardening of arteries

"Atherosclerosis is a disease in which plaque builds up inside your arteries. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows your arteries. This limits the flow of oxygen-rich blood to your organs and other parts of your body. Atherosclerosis can lead to serious problems, including heart attack, stroke, or even death."

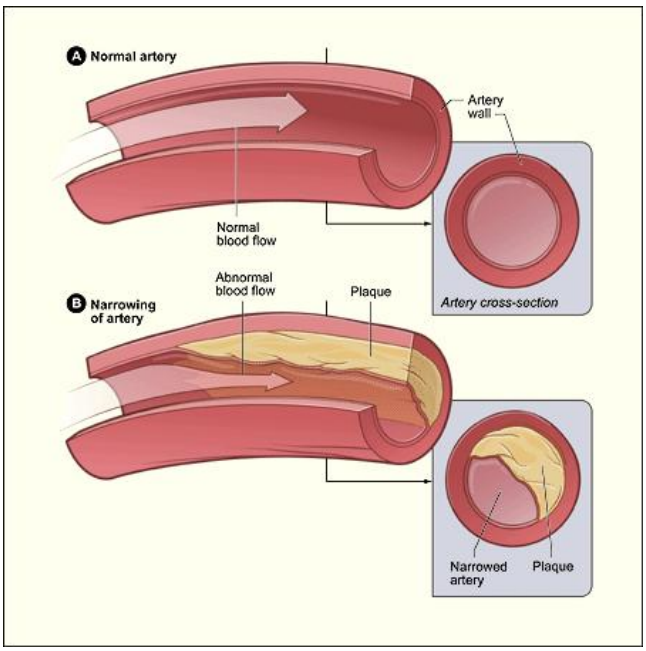

Figure A - shows a normal artery with normal blood flow. The inset image shows a cross-section of a normal artery.
Figure B - shows an artery with plaque buildup. The inset image shows a cross-section of an artery with plaque buildup.

- *National Institute of Health (NIH)*
https://www.nhlbi.nih.gov/health-topics/atherosclerosis

Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice

"Atherosclerosis is a chronic inflammatory disease, and is the primary cause of heart disease and

stroke in Western countries. Derivatives of cannabinoids such as delta-9-tetrahydrocannabinol (THC) modulate immune functions and therefore have potential for the treatment of inflammatory diseases. We investigated the effects of THC in a murine model of established atherosclerosis. Oral administration of THC (1 mg kg(-1) per day) resulted in significant inhibition of disease progression. This effective dose is lower than the dose usually associated with psychotropic effects of THC. Furthermore, we detected the CB2 receptor (the main cannabinoid receptor expressed on immune cells) in both human and mouse atherosclerotic plaques. Lymphoid cells isolated from THC-treated mice showed diminished proliferation capacity and decreased interferon-gamma secretion. Macrophage chemotaxis, which is a crucial step for the development of atherosclerosis, was also inhibited in vitro by THC. All these effects were completely blocked by a specific CB2 receptor antagonist. Our data demonstrate that oral treatment with a low dose of THC inhibits atherosclerosis progression in the apolipoprotein E knockout mouse model, through pleiotropic immunomodulatory effects on lymphoid and myeloid cells. Thus, THC or cannabinoids with activity at the CB2 receptor may be valuable targets for treating atherosclerosis."

-Division of Cardiology, Department of Medicine, Foundation for Medical Research, University Hospital, Faculty of Medicine, 1211 Geneva, Switzerland.

https://pubmed.ncbi.nlm.nih.gov/15815632

Iron and Atherosclerosis: Nailing Down a Novel Target with Magnetic Resonance

"Atherosclerosis is a proliferative, inflammatory disease affecting the arteries. Plaque disruption and subsequent thrombosis from the exposure of plaque contents to circulating blood is the underlying cause of acute coronary syndromes and ischemic strokes. Current preventive strategies focus on management of traditional risk factors such as dyslipidemia, diabetes, hypertension and smoking, and current treatment strategies of more advanced disease employ mechanical relief of stenosis in conjunction with lipid-lowering, anti-platelet and anti-ischemic medications. Yet, despite significant reduction of morbidity and mortality afforded by these strategies, atherosclerosis persists as a leading cause of death worldwide [1].

Atherosclerosis may develop insidiously prior to causing clinically-apparent events like heart attack and stroke; reducing such events requires better mechanistic understanding of disease onset and progression, and improved identification and treatment of subclinical disease. The ability to detect subclinical arterial wall disease holds promise for more timely diagnosis, more effective therapies and better outcomes, particularly if based on a proven contributor to atherosclerosis that also can be measured in vivo. This review focuses on iron as both a

biomarker and biomechanistic contributor to the pathogenesis of atherosclerosis. There is now considerable evidence supporting iron's role in both atherosclerosis initiation and progression (Figure 1), plus recent clinical trial evidence that targeting iron excess in atherosclerosis may be beneficial. "

-The Ohio State University, Columbus, Ohio, Davis Heart and Lung Research Institute
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4101028/

Stress, inflammation and cardiovascular disease

"Various psychosocial factors have been implicated in the etiology and pathogenesis of certain cardiovascular diseases such as atherosclerosis, now considered to be the result of a chronic inflammatory process. In this article, we review the evidence that repeated episodes of acute psychological stress, or chronic psychologic stress, may induce a chronic inflammatory process culminating in atherosclerosis. These inflammatory events, caused by stress, may account for the approximately 40% of atherosclerotic patients with no other known risk factors. Stress, by activating the sympathetic nervous system, the hypothalamic-pituitary axis, and the renin-angiotensin system, causes the release of various stress hormones such as catecholamines, corticosteroids, glucagon, growth hormone, and renin, and elevated levels of homocysteine, which induce a heightened state of cardiovascular activity, injured endothelium, and induction of adhesion molecules on endothelial cells to which recruited inflammatory cells adhere and translocate to the arterial wall. An acute phase response (APR), similar to that associated with inflammation, is also engendered, which is characterized by macrophage activation, the production of cytokines, other inflammatory mediators, acute phase proteins (APPs), and mast cell activation, all of which promote the inflammatory process. Stress also induces an atherosclerotic lipid profile with oxidation of lipids and, if chronic, a hypercoagulable state that may result in arterial thromboses. Shedding of adhesion molecules and the appearance of cytokines, and APPs in the blood are early indicators of a stress-induced APR, may appear in the blood of asymptomatic people, and be predictors of future cardiovascular disease. The inflammatory response is contained within the stress response, which evolved later and is adaptive in that an animal may be better able to react to an organism introduced during combat. The argument is made that humans reacting to stressors, which are not life-threatening but are "perceived" as such, mount similar stress/inflammatory responses in the arteries, and which, if repetitive or chronic, may culminate in atherosclerosis."

-Department of Microbiology, Boston University School of Medicine, Boston, MA
https://pubmed.ncbi.nlm.nih.gov/11801260/

A Plant-Based Diet, Atherogenesis, and Coronary Artery Disease Prevention

"A plant-based diet is increasingly becoming recognized as a healthier alternative to a diet laden with meat. Atherosclerosis associated with high dietary intake of meat, fat, and carbohydrates remains the leading cause of mortality in the US. This condition results from progressive damage to the endothelial cells lining the vascular system, including the heart, leading to endothelial dysfunction. In addition to genetic factors associated with endothelial dysfunction, many dietary and other lifestyle factors, such as tobacco use, high meat and fat intake, and oxidative stress, are implicated in atherogenesis."....

-Dr. Phillip Tuso, MD, FACP, FASN - Physician Leader for Total Health in Southern California.

-Dr. Scott R Stoll, MD - Physician for Coordinated Health in Bethlehem, PA

-Dr. William W Li, MD - President and Medical Director of the Angiogenesis Foundation of the Institute for Advance Studies in Cambridge, MA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315380/

The role of the endocannabinoid system in atherosclerosis

"Our current understanding of the pathophysiology of atherosclerosis suggests a prominent role for immune responses from its initiation through its complications. Given the increasing prevalence of cardiovascular risk factors worldwide, there is an urgent need to better understand the underlying mechanisms to improve current treatment protocols. **A growing body of evidence suggests that endocannabinoid signalling plays a critical role in the pathogenesis of atherogenesis and its clinical manifestations.** Blocking CB(1) receptors has been shown to mediate not only weight reduction, but also several cardiometabolic effects in rodents and humans, indicating a potential relevance for the process of atherosclerosis. Activation of CB(2) receptors with Delta(9)-tetrahydrocannabinol (THC) has been shown to inhibit atherosclerotic plaque progression in mice, mainly by inhibiting macrophage recruitment. Endocannabinoids released from endothelial cells, macrophages or platelets, reduce hypertension in rodents, a major risk factor for atherosclerosis. In addition, anandamide inhibits inflammatory gene expression in endothelial cells, and consequently monocyte adhesion. Conversely, endocannabinoids might also mediate pro-atherosclerotic effects by inducing platelet activation. In conclusion, the precise role of the endocannabinoid system during atherosclerosis is not yet understood. Whether increased endocannabinoid signalling is associated with disease progression and increased risk of acute thrombotic events remains to be determined."

-Division of Cardiology, Foundation for Medical Researches, University Hospital, Geneva, Switzerland.

https://pubmed.ncbi.nlm.nih.gov/18426500/

…"Atherosclerosis (a risk factor for ischemic stroke) results from accumulation of LDL-derived lipids in the arterial wall. Pro-inflammatory cytokines (TNF-α and IL-1), secretory phospholipase A2 IIA and lipoprotein-PLA2 are implicated in vascular inflammation. These inflammatory responses promote atherosclerotic plaques, formation and release of the blood clot that can induce ischemic stroke."…

"Atherosclerosis is believed to be predominantly an inflammatory condition produced as a response to injury (Elkind, 2006). "

- Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- Cardiovascular Research Center, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- Neuroscience Training Program, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- William S. Middleton Veterans Affairs Hospital, Madison, WI.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2293298/

The activated endocannabinoid system in atherosclerosis: driving force or protective mechanism?

"Atherosclerosis and its major acute complications, myocardial infarction and stroke, are the leading causes of death and morbidity worldwide. Despite major advances in cardiovascular intervention and healthcare, improving preventive care and treatment remains a continuous mission for cardiovascular research. Within the last 10 to 15 years, the endocannabinoid system has emerged as an important lipid signaling system involved in many biological processes. Growing evidence suggests that an overactive endocannabinoid-CB1 receptor signaling promotes the development of cardiovascular risk factors such as obesity, insulin resistance and dyslipidemia. This prompted an increasing interest in studying the role of the endocannabinoid system in atherosclerosis. As opposed to the detrimental actions of CB1 signaling, the endocannabinoid-CB2 receptor axis exhibits an anti-inflammatory and atheroprotective role. We will review recent findings from experimental and clinical studies aimed at understanding the complex actions of endocannabinoid signaling in cardiovascular disease. This is followed by an outlook on emerging targets for possible therapeutic intervention."

-Institute for Cardiovascular Prevention, Munich, Germany.
https://pubmed.ncbi.nlm.nih.gov/25469884/

Endocannabinoid Signalling in Atherosclerosis and Related Metabolic Complications

"Endocannabinoids are a group of arachidonic acid-derived lipid mediators binding to cannabinoid receptors CB1 [cannabinoid 1 receptor] and CB2 [cannabinoid 2 receptor]. An overactivity of the endocannabinoid system plays a pathophysiological role in the development of visceral obesity and insulin resistance. Moreover, elevated circulating endocannabinoid levels are also prevalent in atherosclerosis. The pathophysiological increase of endocannabinoid levels is due to an altered expression of endocannabinoid synthesizing and degrading enzymes induced by inflammatory mediators such as cytokines or lipids. Emerging experimental evidence suggests that enhanced endocannabinoid signalling affects atherosclerosis via multiple effects, including a modulation of vascular inflammation, leukocyte recruitment, macrophage cholesterol metabolism and consequently atherosclerotic plaque stability. In addition, recent findings in various metabolic disease models highlight the relevance of peripheral CB1 cannabinoid receptors in adipose tissue, liver and pancreas, which crucially regulate lipid and glucose metabolism as well as macrophage properties in these organs. This suggests that targeting the endocannabinoid system in the vasculature and peripheral organs might have a therapeutic potential for atherosclerosis by inhibiting vascular inflammation and improving metabolic risk factors. This review will provide a brief update on the effects of endocannabinoid signalling in atherosclerosis and related metabolic complications."

-Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians-University (LMU) Munich, Munich, Germany.
-Institute for Diabetes and Cancer, Helmholtz Center Munich, Neuherberg, Germany.
-Joint Heidelberg-IDC Translational Diabetes Program, Inner Medicine I, Heidelberg University Hospital, Heidelberg, Germany.
-Molecular Metabolic Control, Technical University Munich, Munich, Germany.
-German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany.

https://pubmed.ncbi.nlm.nih.gov/30769363/

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.."Cardiovascular disease, and its underlying pathology, atherosclerosis, is the major cause of death and disability worldwide [84, 85]. By 2030, almost 23.6 million people are projected to die annually from cardiovascular disorders [86, 87]. Inflammatory mediators play key roles in atherosclerosis, from initial leukocyte recruitment through rupture of the atherosclerotic plaque [88–91]. Inflammation is also an early event in cardiac stress. Elevated levels of endothelial adhesion molecules and increased inflammatory cytokine and chemokine production and release are observed in affected cardiac tissues [92]."...

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, Chengdu, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

New Insight into the Dietary Cause of Atherosclerosis: Implications for Pharmacology

"At present, the guideline approach to the medical treatment and prevention of atherosclerotic cardiovascular disease (ASCVD) is to classify patients by risk and treat the known risk factors (contributory causes), e.g., hypertension, diabetes, obesity, smoking, and poor diet, as appropriate. All high-risk patients should receive statins. This approach has had substantial success but ASCVD still remains the number one cause of death in the United States. Until recently, the underlying cause of ASCVD remained unknown, although a potential dietary cause was suggested by the fact that vegetarians, especially vegans, have a much lower incidence of ASCVD than animal flesh eaters. Recently, consistent with the vegetarian data, substantial evidence for a cause of ASCVD in animals and humans has been discovered. Trimethylamine (TMA)-containing dietary compounds in meat, milk, and other animal foods (e.g., lecithin, choline, and carnitine) are converted by closely related gut bacterial TMA lyases to TMA, which is absorbed and converted predominantly by flavin mono-oxygenase 3 to the toxic trimethylamine N-oxide (TMAO). TMAO causes atherosclerosis in animals and is elevated in patients with coronary heart disease. Inhibition of bacterial lyases in mice prevents TMA and secondarily TMAO formation and atherosclerosis, strong evidence for the TMAO hypothesis."

-Department of Medicine, Robert Wood Johnson Medical School, Piscataway, New Jersey

https://pubmed.ncbi.nlm.nih.gov/27189968

Mediterranean diet and carotid atherosclerosis in the Northern Manhattan Study

.."Moderate and strict adherence to a MeDi [mediterranean style diet] may protect against a higher burden of carotid atherosclerotic plaque, which may mediate the protection against clinical vascular events. Efforts to improve adherence to a MeDi are critical to reducing the burden of atherosclerotic disease."…

-Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA

-Department of Neurology, Sergievsky Center, Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA

-Department of Social Medicine, Psychiatry, and Neurology, National and Kapodistrian University of Athens, Athens, Greece

-Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, USA
-Department of Neurology, Columbia University College of Physicians and Surgeons, New York,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4370624

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…"Arterial stiffness is increased in children and young adults treated with the ketogenic diet, before the increase of the intima media thickness. This supports that arterial stiffness is an early marker of vascular damage."…

-Child and Adolescent Neuropsychiatry, Medical School, University of Salerno, Italy
-Cardiology Department, Second University of Naples, Ospedale dei Colli, Naples, Italy
-Department of Biochemistry & Biophysics "F. Cedrangolo", Second University of Naples, Italy
-Alberto Verrotti, Department of Pediatrics, University of Perugia, Italy
https://www.sciencedirect.com/science/article/pii/S1059131113003397

Cannabinoid receptors in atherosclerosis

"**Purpose of review:** Recent findings suggesting that cannabinoid receptors are potential targets for the treatment of atherosclerosis are reviewed.

Recent findings: Cannabinoids, such as Delta9-tetrahydrocannabinol, the major psychoactive compound of marijuana, their synthetic analogs and endogenous cannabinoid ligands, produce their biological effects by interacting with specific receptors. In the apolipoprotein E knockout mouse model of atherosclerosis, Delta9-tetrahydrocannabinol was shown to inhibit disease progression through pleiotropic effects on inflammatory cells. Blocking of cannabinoid receptor CB2, the main cannabinoid receptor expressed on immune cells, abolished the observed effects. The development of novel cannabinoid receptor ligands that selectively target CB2 receptors or pharmacological modulation of the endocannabinoid system might offer novel therapeutic strategies in the treatment of atherosclerosis. Several reports demonstrating an implication of the endocannabinoid system in different inflammatory conditions support this hypothesis.

Summary: The immunomodulatory capacity of cannabinoids is now well established and suggests a broad therapeutic potential of cannabinoids for a variety of conditions, including atherosclerosis. New strategies based on nonpsychotropic cannabinoid receptor ligands or compounds modulating endocannabinoid synthesis or stability might solve the problem of the unwanted side effects associated with cannabinoid administration."

-Division of Cardiology, Department of Medicine, University Hospital, Foundation for Medical Research, 64 Avenue Roseraie, 1211 Geneva, Switzerland.
https://pubmed.ncbi.nlm.nih.gov/16960500

Lower brain and blood nutrient status in Alzheimer's disease: Results from meta-analyses

…"The current data show that patients with AD have lower CSF/brain availability of DHA, choline, vitamin B12, folate, vitamin C, and vitamin E. Directionally, brain nutrient status appears to parallel the lower circulatory nutrient status; however, more studies are required measuring simultaneously circulatory and central nutrient status to obtain better insight in this observation. The brain is dependent on nutrient supply from the circulation, which in combination with nutrient involvement in AD-pathophysiological mechanisms suggests that patients with AD may have specific nutritional requirements. This hypothesis could be tested using a multicomponent nutritional intervention."…

-Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, The Netherlands

-Gerontopole and UMR INSERM 1027 University Paul Sabatier, Toulouse University Hospital, Toulouse, France

https://alz-journals.onlinelibrary.wiley.com/doi/pdf/10.1016/j.trci.2017.06.002

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…"Atherosclerosis is a chronic inflammatory disease characterized by the presence of plaques, composed of lipids and other cellular debris, within arterial walls. The most common way to study atherosclerosis in vivo is by use of mice that have genetic modifications resulting in hypercholesterolemia. While almost ten different murine models of atherosclerosis exist, the most widely used are knockout mice that are deficient in either the low-density lipoprotein (LDL) receptor (Ldlr−/−) or apolipoprotein-E (ApoE−/−), the first gene-knockout mice shown to develop atherosclerosis coupled with severe hypercholesterolemia. "…

-Department of Biomedical Sciences, Center for Inflammation, Infectious Disease and Immunity, Quillen College of Medicine, East Tennessee State University, Johnson City, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020134/

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…"Atherosclerosis is a chronic inflammatory disease of the vascular wall [(1)] during which macrophages in the vascular intima ingest atherogenic lipoproteins, such as modified LDLs, and transform into cholesteryl ester-laden foam cells [(2)]."…

-Department of Biochemistry and Molecular Biology, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, TN

-the Department of Biological Sciences, California State Polytechnic University, Pomona, CA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2563213/

See also Thrombosis , Tumor Necrosis Factor-alpha (TNF-a)

Atopic Dermatitis

…"Atopic dermatitis (AD), also designated atopic eczema, is a chronic inflammatory skin disease marked by pruritus (often intense) and characteristic eczematous lesions with erythema, fine scaling, and thickening of the epidermis. The disease is complex with several subgroups and frequently associated with allergic rhinitis, asthma, and immunoglobulin E (IgE)-mediated food reactions (Bieber 2008). Genetic factors, such as those leading to an impaired skin barrier, play an important role in the development of AD. However, environmental factors, such as lifestyle and exposure to microbes, most likely contribute to the increased frequency of the disease (Bieber 2010). The prevalence of AD has rapidly increased, estimated today at 15%–30% in children and 2%–10% in adults, with the highest prevalence in industrialized countries.
Many studies have found that Malassezia is a microbial trigger that exacerbates AD, especially when the disorder is localized to the head and neck, sebum-rich areas frequently colonized by Malassezia."…

-School of Biological Sciences, University of Missouri–Kansas City, Kansas City, Missouri

-Social and Behavioral Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland

-Procter & Gamble Company, Singapore

-Department of Medicine Solna, Translational Immunology Unit, Karolinska Institutet and University Hospital, Stockholm, Sweden

-CBS-KNAW Fungal Biodiversity Centre, The Netherlands

-Broad Institute of MIT and Harvard, Cambridge, Massachusetts

-Procter & Gamble Company, Mason, Ohio

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4109575/

Review of evidence for dietary influences on atopic dermatitis

"Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting children and adolescents worldwide. The relationship of AD to diet has been a matter of curiosity for many years. Here we look at the evidence in the literature of the association between AD and diet, and the effectiveness of elimination diets and diet supplementation in the management of AD. Several studies have found an association between clinical food allergy and AD, and more recent investigations have also suggested that dietary elements may promote late AD exacerbations.

Diet elimination trials in select patients who are clinically allergic to eggs have shown promise in reducing symptoms. Additionally, elimination of food additives in a subgroup of patients was found to be beneficial. Finally, diet supplementations with evening primrose oil and an omega-3 fatty acid (docosahexaenoic acid) may be appropriate in certain AD candidates."

-Dermatology and Internal Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, USA.

https://pubmed.ncbi.nlm.nih.gov/25188523

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…"Dermatitis [is] a universal term describing inflammation of the skin; as most skin diseases, dermatitis can be induced by various factors such as, for example, allergens (allergic dermatitis), infections, eczema (atopic dermatitis), external compounds (contact dermatitis) and so on."…

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary

-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ, USA

-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck, Germany

-School of Translational Medicine, University of Manchester, Manchester, UK

-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

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…"The first findings on a favorable influence of fatty acids on the animal and human skin with AD [Atopic Dermatitis] come from the 1930s [16]. For the next decades, various preparations containing LC-PUFA were used to treat this disease, especially, those containing compounds with the various content of LA and GLA, usually improving the skin condition [23, 27]. Ω-3 [omega-3] and ω-6 [omega-6] fatty acids provide the appropriate structure, elasticity and functionality of cell membranes and are vital for the synthesis of intracellular lipids in the corneous layer in the epithelium."…

-Department of Pediatrics, Gastroenterology and Allergology, Medical University of Bialystok, Poland. Head: Prof. Maciej Kaczmarski MD, PhD

-University Children's Teaching Hospital, Bialystok, Poland. Head: Janusz Pomaski MD, PhD

-Department of Pediatric Oncology and Hematology, Medical University of Bialystok, Poland. Head: Prof. Maryna Krawczuk-Rybak MD, PhD

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3834680

Atrophy

The endocannabinoid signaling system: a marriage of PUFA and musculoskeletal health

"The role of diet in health and diseases related to muscle and bone has been an area of active study. Recently, endocannabinoids (EC), endogenous derivatives of arachidonic acid, an omega-6 (n-6) polyunsaturated fatty acid (PUFA), have been discovered to play regulatory roles in bone mass and muscle energy metabolism. This signaling system consists of the G-protein coupled cannabinoid receptors, CB1 and CB2, expressed in central and peripheral tissues and cells, which are variably activated by the production and on demand release of endogenous and synthetic agonists and antagonists. We propose that the balance between omega-6 and omega-3 (n-3) PUFA is an important modifier for the activation and suppression of endocannabinoid receptors and therefore, downstream signaling actions in cells. The potential of dietary PUFA to regulate this signaling system to influence the metabolic and physiological outcomes favorable to musculoskeletal health is the purpose of this review. The important role of n-3 PUFA in metabolic and physiological processes that attenuate muscle and bone loss under conditions of disease and stress is one aspect described herein. In this review, we first introduce the EC agonists (ligands) and their receptors (CB1 and CB2) and the general actions of EC signaling in various organs and systems. Second, we describe EC signaling in bone and muscle and how dietary PUFA influence the levels of endogenous agonists. Third, we discuss the potential implications of how dietary PUFA impact this system to minimize muscle atrophy and osteopenia and support healthy muscle development and bone modeling."

-Lipid Chemistry and Molecular Biology Laboratory, School of Agriculture, West Lafayette, IN 47907, USA.
https://pubmed.ncbi.nlm.nih.gov/20934863/

Autism

Lower circulating endocannabinoid levels in children with autism spectrum disorder

"The Endocannabinoid System (ECS) is a major regulator of synaptic plasticity and neuromodulation. Alterations of the ECS have been demonstrated in several animal models of autism spectrum disorder (ASD). In some of these models, activating the ECS rescued the social deficits. Evidence for dysregulations of the ECS in human ASD are emerging, but comprehensive assessments and correlations with disease characteristics have not been reported yet."…

Conclusions

"We found lower serum levels of AEA [anandamide], PEA [N-palmitoylethanolamine], and OEA [N-oleoylethanolamine] in children with ASD. Further studies are needed to determine whether circulating endocannabinoid levels can be used as stratification biomarkers that identify clinically significant subgroups within the autism spectrum and if they reflect lower endocannabinoid "tone" in the brain, as found in animal models of ASD."

-Neuropediatric Unit, Shaare Zedek Medical Center, 12 Bayit Street, 91031 Jerusalem, Israel
-Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
-Department of Nutritional Sciences, Tel Hai Academic College, Upper Galilee, 1220800 Kiryat Shmona, Israel
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6354384

Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study.

…"The results of this study provide preliminary evidence that omega-3 fatty acids may be an effective treatment for children with autism."

-Department of Child and Adolescent Neuropsychiatry, Medical University of Vienna, Vienna, Austria
https://www.ncbi.nlm.nih.gov/pubmed/16920077

Relationship between Long Chain n-3 Polyunsaturated Fatty Acids and Autism Spectrum Disorder: Systematic Review and Meta-Analysis of Case-Control and Randomised Controlled Trials

…"Populations with ASD [Autism Spectrum Disorder] have lower n-3 LCPUFA status and n-3 LCPUFA supplementation can potentially improve some ASD symptoms. Further research with large sample size and adequate study duration is warranted to confirm the efficacy of n-3 LCPUFA."…

"Because DHA, EPA and ARA are amongst the most reported fatty acids of n-3 LCPUFAs and n-6 LCPUFAs categories, respectively, and have been shown to be more biologically active in the brain and been linked to neurodevelopment disorders, we focused on these fatty acids as well as the ratio of ARA to EPA and DHA and the ratio of n-6 LCPUFA to n-3 LCPUFA [41,42]. "…

"Another plausible mechanism supporting the association between LCPUFA and ASD is the anti- and pro-inflammatory properties of LCPUFA metabolic products. Eicosanoids (a collective name for prostaglandins, thromboxanes, leukotrienes and a variety of hydroxyl and hydroproxy fatty acid) are the enzymatic metabolic products of PUFA, and have important roles in inflammation [20]. While EPA or DHA derived eicosanoids have anti-inflammatory properties, those derived

from ARA have pro-inflammatory properties [20]. Elevated levels of several peripheral pro-inflammatory cytokines and nuclear factor Kappa B (NF-κB, a transcription factor involved in inflammatory signaling pathways) has been reported in children with ASD [122,123,124]. Brigandi et al. [24] reported children with ASD having significantly higher plasma levels of PGE2 than healthy controls, a finding confirmed by El-Ansary and Al-Ayadhi (2012) [125] who also reported higher levels of leukotriene and 8-isoprostane together with PGE2 in children with ASD. In addition, lower levels of antioxidant proteins and increased levels of oxidative stress markers was associated with more severe ASD symptoms, including sensory issues [14,124,126]. Supplementation with n-3 PUFA, on the other hand, decreased the gene expression of NF-κB, IL-12 and IL-13 [127], macrophage inflammatory protein-2 (MIP2), IL-6 [128] and tumor necrosis factor-α (TNF-α) [128,129,130].

Decreased antioxidant capacity and increased lipid peroxidation may result in RBC LCPUFA instability and decrease these fatty acids in autism [23,74]. Instability in RBC LCPUFA composition has been shown by a great loss in PUFA levels when the blood samples of autistic children were stored at −20 °C, a finding not observed in the blood sample of healthy controls [62]. The reason for such instability could be related to cellular phospholipase activity. Tostes et al. (2013) [68] and Bell et al. (2004) [66] reported children with ASD having significantly higher phospholipase A2 (PLA2) activity than typically developing controls that was reduced by EPA supplementation [66]. PLA2 is responsible for releasing fatty acids, more particularly ARA, from phospholipids [66].

Finally, the role of LCPUFA in ASD could be explained by defects in enzymes involved in the conversion of LCPUFA from their precursors or deficits in the process of incorporation of LCPUFA into the cell membrane [24,25,26]. Gene variants in fatty acid desaturase (FADS)—one of the strongest genome wide associated signals—have been shown to enhance the conversion of ARA from its precursor and to be sex- and ethnicity-specific [131,132]. The effect of FADS genotype has been shown to be more pronounced in African Americans than Europeans (approximately two fold higher) [131]. "…

-Massey Institute of Food Science and Technology, School of Food and Nutrition, Massey University, New Zealand;
-Commonwealth Scientific Industrial Research Organisation (CSIRO) Food, Nutrition and Bioproducts, Australia
-Massey Institute of Food Science and Technology, School of Food and Nutrition, Massey University, New Zealand
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5331586/

Endocannabinoid Signaling in Autism.

"Autism spectrum disorder (ASD) is a complex behavioral condition with onset during early childhood and a lifelong course in the vast majority of cases. To date, no behavioral, genetic, brain imaging, or electrophysiological test can specifically validate a clinical diagnosis of ASD.

However, these medical procedures are often implemented in order to screen for syndromic forms of the disorder (i.e., autism comorbid with known medical conditions). In the last 25 years a good deal of information has been accumulated on the main components of the "endocannabinoid (eCB) system", a rather complex ensemble of lipid signals ("endocannabinoids"), their target receptors, purported transporters, and metabolic enzymes. It has been clearly documented that eCB signaling plays a key role in many human health and disease conditions of the central nervous system, thus opening the avenue to the therapeutic exploitation of eCB-oriented drugs for the treatment of psychiatric, neurodegenerative, and neuroinflammatory disorders. Here we present a modern view of the eCB system, and alterations of its main components in human patients and animal models relevant to ASD. This review will thus provide a critical perspective necessary to explore the potential exploitation of distinct elements of eCB system as targets of innovative therapeutics against ASD."

-Centre for Integrative Neuroscience and Neurodynamics, School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK.

-Center of Integrated Research and School of Medicine, Campus Bio-Medico University of Rome, Via Alvaro del Portillo 21, 00128, Rome, Italy.

-Mafalda Luce Center for Pervasive Developmental Disorders, Milan, Italy.

-Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Teramo, Italy.

-Center of Integrated Research and School of Medicine, Campus Bio-Medico University of Rome, Via Alvaro del Portillo 21, 00128, Rome, Italy.

-European Center for Brain Research (CERC)/Santa Lucia Foundation, Rome, Italy

https://www.ncbi.nlm.nih.gov/m/pubmed/26216231/

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"Marijuana exerts profound effects on human social behavior, but the neural substrates underlying such effects are unknown. Here we report that social contact increases, whereas isolation decreases, the mobilization of the endogenous marijuana-like neurotransmitter, anandamide, in the mouse nucleus accumbens (NAc), a brain structure that regulates motivated behavior. Pharmacological and genetic experiments show that anandamide mobilization and consequent activation of CB1 cannabinoid receptors are necessary and sufficient to express the rewarding properties of social interactions, assessed using a socially conditioned place preference test. We further show that oxytocin, a neuropeptide that reinforces parental and social bonding, drives anandamide mobilization in the NAc. Pharmacological blockade of oxytocin receptors stops this response, whereas chemogenetic, site-selective activation of oxytocin neurons in the paraventricular nucleus of the hypothalamus stimulates it. Genetic or pharmacological interruption of anandamide degradation offsets the effects of oxytocin receptor

blockade on both social place preference and cFos expression in the NAc. The results indicate that anandamide-mediated signaling at CB1 receptors, driven by oxytocin, controls social reward. Deficits in this signaling mechanism may contribute to social impairment in autism spectrum disorders and might offer an avenue to treat these conditions."

-Department of Anatomy and Neurobiology, University of California, Irvine, CA 92697;

-Department of Pharmacology, School of Medicine, University of the Basque Country, Barrio Sarriena s/n, Leioa 48940, Spain;

-Program in Neurogenetics, Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, CA 90095; Center for Autism Research and Treatment and Center for Neurobehavioral Genetics, Jane and Terry Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA 90095;

-Department of Anatomy and Neurobiology, University of California, Irvine, CA 92697; Department of Biological Chemistry, University of California, Irvine, Irvine, CA 92697; Unit of Drug Discovery and Development, Istituto Italiano di Tecnologia, Genova 16163, Italy

https://pubmed.ncbi.nlm.nih.gov/26504214/

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"Autism is a neurodevelopmental disorder characterized by impairments in communication and reciprocal social interaction, coupled with repetitive behavior, which typically manifests by 3 years of age. Multiple genes and early exposure to environmental factors are the etiological determinants of the disorder that contribute to variable expression of autism-related traits. Increasing evidence indicates that altered fatty acid metabolic pathways may affect proper function of the nervous system and contribute to autism spectrum disorders. This review provides an overview of the reported abnormalities associated with the synthesis of membrane fatty acids in individuals with autism as a result of insufficient dietary supplementation or genetic defects. Moreover, we discuss deficits associated with the release of arachidonic acid [omega-6] from the membrane phospholipids and its subsequent metabolism to bioactive prostaglandins via phospholipase A 2 -cyclooxygenase biosynthetic pathway in autism spectrum disorders. The existing evidence for the involvement of lipid neurobiology in the pathology of neurodevelopmental disorders such as autism is compelling and opens up an interesting possibility for further investigation of this metabolic pathway."…

-Department of Biology, School of Kinesiology and Health Science, Neuroscience Graduate Diploma Program, York University, Toronto, , Canada

https://www.karger.com/Article/pdf/323189

Targeting anandamide metabolism rescues core and associated autistic-like symptoms in rats prenatally exposed to valproic acid

"Autism spectrum disorders (ASD) are characterized by altered sociability, compromised

communication and stereotyped/repetitive behaviors, for which no specific treatments are currently available. Prenatal exposure to valproic acid (VPA) is a known, although still underestimated, environmental risk factor for ASD. Altered endocannabinoid activity has been observed in autistic patients, and endocannabinoids are known to modulate behavioral traits that are typically affected in ASD. On this basis, we tested the hypothesis that changes in the endocannabinoid tone contribute to the altered phenotype induced by prenatal VPA exposure in rats, with focus on behavioral features that resemble the core and associated symptoms of ASD. In the course of development, VPA-exposed rats showed early deficits in social communication and discrimination, compromised sociability and social play behavior, stereotypies and increased anxiety, thus providing preclinical proof of the long-lasting deleterious effects induced by prenatal VPA exposure. At the neurochemical level, VPA-exposed rats displayed altered phosphorylation of CB1 cannabinoid receptors in different brain areas, associated with changes in anandamide metabolism from infancy to adulthood. Interestingly, enhancing anandamide signaling through inhibition of its degradation rescued the behavioral deficits displayed by VPA-exposed rats at infancy, adolescence and adulthood. This study therefore shows that abnormalities in anandamide activity may underlie the deleterious impact of environmental risk factors on ASD-relevant behaviors and that the endocannabinoid system may represent a therapeutic target for the core and associated symptoms displayed by autistic patients."…

-Department of Science, Section of Biomedical Sciences and Technologies, University "Roma Tre", Rome, Italy
-Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5048215/

The role of the endocannabinoid system as a therapeutic target for autism spectrum disorder: Lessons from behavioral studies on mouse models

"Recent years have seen an impressive amount of research devoted to understanding the etiopathology of Autism Spectrum Disorder (ASD) and developing therapies for this syndrome. Because of the lack of biomarkers of ASD, this work has been largely based on the behavioral characterization of rodent models, based on a multitude of genetic and environmental manipulations. Here we highlight how the endocannabinoid system (ECS) has recently emerged within this context of mouse behavioral studies as an etiopathological factor in ASD and a valid potential therapeutic target. We summarize the most recent results showing alterations of the ECS in rodent models of ASD, and demonstrating ASD-like behaviors in mice with altered ECS, induced either by genetic or pharmacological manipulations. We also give a critical overview of the most relevant advances in designing treatments and novel mouse models for ASD targeting the ECS, highlighting the relevance of thorough and innovative behavioral approaches to

investigate the mechanisms acting underneath the complex features of ASD."

-Univ. Bordeaux, CNRS, EPHE, INCIA, UMR 5287, Bordeaux, France.
-INSERM, U1215 NeuroCentre Magendie, Bordeaux Cedex, France.
https://pubmed.ncbi.nlm.nih.gov/34813825/

The Autism-Psychosis Continuum Conundrum: Exploring the Role of the Endocannabinoid System

"Evidence indicates shared physiopathological mechanisms between autism and psychosis. In this regard, the endocannabinoid system has been suggested to modulate neural circuits during the early stage of neurodevelopment, with implications for both autism and psychosis. Nevertheless, such potential common markers of disease have been investigated in both autism and psychosis spectrum disorders, without considering the conundrum of differentiating the two groups of conditions in terms of diagnosis and treatment. Here, we systematically review all human and animal studies examining the endocannabinoid system and its biobehavioral correlates in the association between autism and psychosis. Studies indicate overlapping biobehavioral aberrancies between autism and schizophrenia, subject to correction by modulation of the endocannabinoid system. In addition, common cannabinoid-based pharmacological strategies have been identified, exerting epigenetic effects across genes controlling neural mechanisms shared between autism and schizophrenia. Interestingly, a developmental and transgenerational trajectory between autism and schizophrenia is supported by evidence that exogenous alteration of the endocannabinoid system promotes progression to inheritable psychosis phenotypes in the context of biobehavioral autism vulnerability. However, evidence for a diametral association between autism and psychosis is scant. Several clinical implications follow from evidence of a developmental continuum between autism and psychosis as a function of the endocannabinoid system dysregulation."

-Unit of Psychiatry, Department of Medicine (DAME), University of Udine, Italy.
-Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.
-Child and Adolescent Neuropsychiatry Unit, Maternal-Child Integrated Care Department, Integrated University Hospital of Verona, Verona, Italy.
-Community Mental Health Team, Friuli Centrale University Health Service (ASUFC), Palmanova, Italy.
https://pubmed.ncbi.nlm.nih.gov/35565034/

Autism and associated disorders: cannabis as a potential therapy

"Autism spectrum disorder (ASD) is a group of disabilities with impairments in physical, verbal,

and behavior areas. Regardless the growing frequency of autism, no medicine has been formed for the management of the ASD primary symptoms. The most frequently prescribed drugs are off-label. Therefore, there is necessity for an advance tactic for the treatment of autism. The endocannabinoid system has a central role in ruling emotion and social behaviors. Dysfunctions of the system donate to the behavioral deficits in autism. Therefore, the endocannabinoid system represents a potential target for the development of a novel autism therapy. Cannabis and associated compounds have produced substantial research attention as a capable therapy in neurobehavioral and neurological syndromes. In this review we examine the potential benefits of medical cannabis and related compounds in the treatment of ASD and concurrent disorders."

-Department of Biomedical and Pharmaceutical Sciences, Touro College of Pharmacy, New York, NY, USA.

-Department of Medicinal Chemistry, School of Pharmacy, College of Health Sciences, Mekelle University, Tigray, Ethiopia.

-Department of Pathology, Microbiology and Immunology, New York Medical College, Valhalla, NY, USA.

https://pubmed.ncbi.nlm.nih.gov/35320905/

The Endocannabinoids-Microbiota Partnership in Gut-Brain Axis Homeostasis: Implications for Autism Spectrum Disorders

"The latest years have witnessed a growing interest towards the relationship between neuropsychiatric disease in children with autism spectrum disorders (ASD) and severe alterations in gut microbiota composition. In parallel, an increasing literature has focused the attention towards the association between derangement of the endocannabinoids machinery and some mechanisms and symptoms identified in ASD pathophysiology, such as alteration of neural development, immune system dysfunction, defective social interaction and stereotypic behavior. In this narrative review, we put together the vast ground of endocannabinoids and their partnership with gut microbiota, pursuing the hypothesis that the crosstalk between these two complex homeostatic systems (bioactive lipid mediators, receptors, biosynthetic and hydrolytic enzymes and the entire bacterial gut ecosystem, signaling molecules, metabolites and short chain fatty acids) may disclose new ideas and functional connections for the development of synergic treatments combining "gut-therapy," nutritional intervention and pharmacological approaches. The two separate domains of the literature have been examined looking for all the plausible (and so far known) overlapping points, describing the mutual changes induced by acting either on the endocannabinoid system or on gut bacteria population and their relevance for the understanding of ASD pathophysiology. Both human pathology and symptoms relief in ASD subjects, as well as multiple ASD-like animal models, have been taken into consideration in order to provide evidence of the relevance of the endocannabinoids-microbiota crosstalk in this

major neurodevelopmental disorder."

…"Increasing the intake of LA might alter the eCBs levels (Berger et al., 2001; Alvheim et al., 2013; Alvheim et al., 2014), and CB1 receptor function in selected brain areas (prefrontal cortex and nucleus accumbens) can be permanently altered by feeding animals with a n-3 deficient diet during gestation and lactation (Lafourcade et al., 2011). Moreover, there is evidence that the beneficial impact on cognition, or the attenuation of cognitive decline provided by the decrease of dietary n-6/n-3 ratio via n-3 PUFAs dietary supplementation can be preserved both during adolescence and adulthood (Muldoon et al., 2010; Luchtman and Song, 2013), although negative results have also been reported (Stough et al., 2012). The anti-neuroinflammatory and anti-depressive potential of DHA and EPA has been studied in the recent literature in both animal models (Minogue et al., 2007; Moranis et al., 2012) and clinical reports (Rees et al., 2006; Liao et al., 2019), along with their use in dietary supplementation as nutritional guideline to slow down age-associated cognitive decline through preservation of neurogenesis and synaptic plasticity (Dyall, 2015). The levels of dietary LA can affect brain content of 2-AG and AEA and increase liability to obesity (Massiera et al., 2010; Alvheim et al., 2012) but, on the other hand, the different composition of dietary fatty acids can be exploited as anti-obesity agent by both reduction of 2-AG levels (Banni et al., 2011) and the modulation of NAEs concentrations (Pu et al., 2016). Most importantly, the composition of dietary n-3 and n-6 PUFAs and therefore ALA or LA is able to shape the huge microbial community composing the gut microbiota (Marrone and Coccurello, 2019; Wolters et al., 2019). Gut dysbiosis, low-grade inflammation and gut permeability are indeed leading causes for obesity development (Levy et al., 2017; Sun et al., 2018). In obesity, the systemic elevation of the eCB tone (brain included) as well as the upregulation of the CB1 receptor in adipose tissue, liver and muscle have been extensively demonstrated (Matias and Di Marzo, 2006; Starowicz et al., 2008; Silvestri and Di Marzo, 2013). Accordingly, blockade of CB1 receptors may revert both systemic inflammation and dysbiosis induced in obese mice by chronic high-fat diet (HFD) regimen (Mehrpouya-Bahrami et al., 2017)."

-Institute for Complex Systems (ISC), National Council of Research (CNR), Rome, Italy.
-European Center for Brain Research/Santa Lucia Foundation IRCCS, Rome, Italy.
-Ministry of University and Research, Mission Unity for Recovery and Resilience Plan, Rome, Italy.
-Department of Biotechnological and Applied Clinical and Sciences, University of L'Aquila, L'Aquila, Italy.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9204215/

See also

Asperger Syndrome , Cerebral Palsy , Endocannabinoid System , Social Functioning

Autoimmune Diseases

The Endocannabinoid System and Plant-Derived Cannabinoids in Diabetes and Diabetic Complications

…"There is also considerable interest in the use of certain natural and similar synthetic cannabinoid ligands to modulate a wide variety of immune responses, including T-lymphocyte activation and subsequent cytokine production.[17,46] THC was shown to attenuate the severity of autoimmune responses in an experimental model of autoimmune diabetes as evidenced by the significantly lower number of infiltrating lymphocytic cells and reduced expression levels of interferon-γ, interleukin-12, and tumor necrosis factor-α (TNF-α).[47] The treatment also preserved pancreatic insulin content and led to lower blood glucose levels compared with the untreated diabetic group. Even though THC shows excellent immunosuppressive ability, the psychoactive effects of the compound limit its usefulness for therapeutic purposes. This is the reason why the study[10] that showed that CBD exerts similar beneficial effects is crucially important. CBD reduced the incidence of diabetes in nonobese diabetic mice, the mouse model of type 1 diabetes. The effect was paired with reduced insulitis, which was due to a shift of the immune response from Th1 to Th2 dominance, resulting in decreased levels of proinflammatory cytokines, such as interferon-γ and TNF-α. CBD was also able to ameliorate the disease when given at the time of the development of initial symptoms of diabetes in nonobese diabetic mice.[11]"…

-Section on Oxidative Stress and Tissue Injury, Laboratory of Physiological Studies, National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

-Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest, Hungary

-Department of Surgery, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3349875/

…"Cannabinoids can modulate immune cell function, activity, and secretion of cytokines [10, 11]. Compounds that activate CB2R are of particular interest for their immunomodulatory activity because these receptors are predominantly expressed in the immune system. CB2R is expressed in human leukocytes, B cells, basophils, dendritic cells, eosinophils, mast cells, macrophages, microglia, monocytes, natural killer cells, neutrophils, platelets, and T cells, highlighting its potential in immune modulation [9]. The complexity of the immune system means it has ample opportunity to fall out of balance and be under- or overactive. The role of the ECS in immune regulation—overall function, tone, and activity—is very important. Inflammation plays a crucial role in the immune system's defensive response to harmful stimuli, such as pathogens and injury.

Autoimmune diseases frequently involve a chronic hyperinflammatory response. Endogenous cannabinoids can modulate inflammation both through direct cannabinoid receptor binding and other mechanisms [12]. Emerging evidence shows that phytocannabinoids also exert regulatory control over immune and inflammatory responses [13–16]. It is likely that the subtle but significant role of the ECS in immune regulation can be exploited in the management of human disease.

Both CB1R and CB2R are distributed in various organs and tissues throughout the body, affecting every major organ of the body and whose expression changes in disease states [17]. It is well known that these receptors and the molecules that interact with them have a significant signaling and regulatory effect on cells, tissues, organs, and organ systems [18]. Indeed, the ECS is vital for human survival and plays a critical role in maintaining homeostasis so much so that some consider it the "master regulator" of the human body [19]."…

-dōTERRA International, LLC
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7246407/

Molecular mechanisms underlying prostaglandin E2-exacerbated inflammation and immune diseases

"Prostaglandins (PGs) are the major lipid mediators in animals and which are biosynthesized from arachidonic acid by the cyclooxygenases (COX-1 or COX-2) as the rate-limiting enzymes. Prostaglandin E2 (PGE2), which is the most abundantly detected PG in various tissues, exerts versatile physiological and pathological actions via four receptor subtypes (EP1-4). Non-steroidal anti-inflammatory drugs, such as aspirin and indomethacin, exert potent anti-inflammatory actions by the inhibition of COX activity and the resulting suppression of PG production. Therefore, PGE2 has been shown to exacerbate several inflammatory responses and immune diseases. Recently, studies using mice deficient in each PG receptor subtype have clarified the detailed mechanisms underlying PGE2-associated inflammation and autoimmune diseases involving each EP receptor. **Here, we review the recent advances in our understanding of the roles of PGE2 receptors in the progression of acute and chronic inflammation and autoimmune diseases. PGE2 induces acute inflammation through mast cell activation via the EP3 receptor. PGE2 also induces chronic inflammation and various autoimmune diseases** through T helper 1 (Th1)-cell differentiation, Th17-cell proliferation and IL-22 production from Th22 cells via the EP2 and EP4 receptors. The possibility of EP receptor-targeted drug development for the treatment of immune diseases is also discussed."

-Department of Regenerative Medicine Research, Faculty of Pharmaceutical Sciences, Sanyo-Onoda City University, Sanyo-Onoda, Yamaguchi, Japan.
-Department of Pharmaceutical Biochemistry, Graduate School of Pharmaceutical Sciences, Kumamoto University,

Chuo-ku, Kumamoto, Japan.
-Japan Agency for Medical Research and Development-Core Research for Evolutional Science and Technology, Chiyoda-ku, Tokyo, Japan.
https://pubmed.ncbi.nlm.nih.gov/30926983/

Role of "Western Diet" in Inflammatory Autoimmune Diseases

"Developed societies, although having successfully reduced the burden of infectious disease, constitute an environment where metabolic, cardiovascular, and autoimmune diseases thrive. Living in westernized countries has not fundamentally changed the genetic basis on which these diseases emerge, but has strong impact on lifestyle and pathogen exposure. In particular, nutritional patterns collectively termed the "Western diet", including high-fat and cholesterol, high-protein, high-sugar, and excess salt intake, as well as frequent consumption of processed and 'fast foods', promote obesity, metabolic syndrome, and cardiovascular disease. These factors have also gained high interest as possible promoters of autoimmune diseases. Underlying metabolic and immunologic mechanisms are currently being intensively explored. This review discusses the current knowledge relative to the association of "Western diet" with autoimmunity, and highlights the role of T cells as central players linking dietary influences to autoimmune pathology."

…"Autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), type 1 diabetes (T1D), and psoriasis (Ps) are a heterogeneous set of diseases that share common hallmarks including multifactorial aetiologies, involvement of T cell-mediated autoimmune pathomechanisms, and a chronic clinical course that often requires life-long disease management. Genetic factors clearly predispose to the development of inflammatory autoimmune diseases [1, 2], but a relatively low concordance rate for most of the diseases between monozygotic twins [3] suggests environmental factors as important triggers of disease. This view is corroborated by the striking increase of autoimmune diseases in recent decades, whereas the genetic basis in affected populations has remained arguably constant [4]. Notably, there is a high prevalence in Western societies and established market economies as opposed to a lower prevalence in the Eastern world and developing countries [4, 5]. It is of interest that there are also some high prevalence areas today that display a stable or even slightly declining occurrence of some autoimmune diseases [6, 7], while there is certainly a steep incline in former low prevalence regions [8–11]. The trend towards a higher prevalence often coincides with a high pace of socio-economic improvement and westernization in these countries [4, 5]. There are multiple explanations of how the "Western lifestyle" favors the development of autoimmunity. The hygiene hypothesis states that high standards of hygiene and good health care reduce the

burden of infections, but can also limit exposure to pathogens that are potentially beneficial for proper function of the immune system [4, 5, 12]. Psychosocial stress generated by high demands on productivity, as well as smoking and alcohol consumption, may be additional lifestyle-associated risk and severity factors for autoimmune diseases [13–15]. Finally, lack of physical activity in combination with excess calorie intake and frequent consumption of 'fast food' causes a high prevalence of obesity in developed societies [16]. Obesity in turn predisposes to metabolic and cardiovascular disease [17], and it is becoming increasingly clear that the dietary habits in Western societies ("too much", "too fatty", "too salty") and a high body mass index (BMI) also constitute risk factors for autoimmune diseases [18]. In this review, we briefly summarize the evidence provided by epidemiological and experimental studies linking nutrition to autoimmunity. Exploring possible mechanisms, we then discuss the nexus of nutrition, gut mucosal immunity, and systemic autoimmune responses. Here, T helper cells emerge as central players linking dietary perturbations to the modulation of autoimmune pathology."

-Department of Neurology, University of Erlangen, Erlangen, Germany

-Experimental and Clinical Research Center, a joint cooperation between the Charitè Medical Faculty and the Max-Delbruck Center for Molecular Medicine, Berlin, Germany

-Departments of Neurology and Immunobiology, Yale School of Medicine, New Haven, Connecticut, USA

-Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

-Division of Comparative Medicine, Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts, USA

-Department of Clinical Pathobiochemistry, Dresden University of Technology (TUD), Dresden, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4034518/

Omega-3 fatty acids in inflammation and autoimmune diseases.

"Among the fatty acids, it is the omega-3 polyunsaturated fatty acids (PUFA) which possess the most potent immunomodulatory activities, and among the omega-3 PUFA, those from fish oil-eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)--are more biologically potent than alpha-linolenic acid (ALA). Some of the effects of omega-3 PUFA are brought about by modulation of the amount and types of eicosanoids made, and other effects are elicited by eicosanoid-independent mechanisms, including actions upon intracellular signaling pathways, transcription factor activity and gene expression. Animal experiments and clinical intervention studies indicate that omega-3 fatty acids have anti-inflammatory properties and, therefore, might be useful in the management of inflammatory and autoimmune diseases. Coronary heart disease, major depression, aging and cancer are characterized by an increased level of interleukin 1 (IL-1), a proinflammatory cytokine. Similarly, arthritis, Crohn's disease, ulcerative colitis and lupus erythematosis are autoimmune diseases characterized by a high level of IL-1 and the proinflammatory leukotriene $LTB^{(4)}$ produced by omega-6 fatty acids. There have been a

number of clinical trials assessing the benefits of dietary supplementation with fish oils in several inflammatory and autoimmune diseases in humans, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, lupus erythematosus, multiple sclerosis and migraine headaches. Many of the placebo-controlled trials of fish oil in chronic inflammatory diseases reveal significant benefit, including decreased disease activity and a lowered use of anti-inflammatory drugs."

-The Center for Genetics, Nutrition and Health, Washington, DC, USA
https://www.ncbi.nlm.nih.gov/pubmed/12480795

Regulation of Inflammation in Autoimmune Disease

"Inflammation is a normal physiological defense against pathogen infection and tissue damage and quickly ends under normal circumstances. However, in many chronic conditions, the inflammatory response continues and leads to significant tissue and organ damage. Recently, increasing evidences have shown that the abnormal inflammatory response is closely associated with many chronic diseases, especially in autoimmune diseases, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), gout, and diabetes [1–3]. Although the importance of inflammatory dysregulation in chronic illnesses has been reported in recent studies, the pathogenesis of inflammation dysfunction in the autoimmune diseases remains elusive. Knowledge of the mechanism of inflammation regulation will lead to significant clinical benefits for the treatment of autoimmune disease. This special issue showcases a number of original research articles and review papers on the topic of inflammatory regulation in autoimmune diseases."

-Department of Rheumatology and Clinical Immunology, Jiangxi Provincial People's Hospital, Nanchang, China
-School of Medicine, Case Western Reserve University, Cleveland, USA
-Department of Internal Medicine, Patan Academy of Health Sciences, Nepal
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6421792/

The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Inflammatory Cytokine Storms

…"Inflammation is important in treating infections and wounds as it promotes tissue healing and the killing of pathogens. The omega-6 fat linoleic acid, and arachidonic acid (AA) formed from it, are important in responses such as redness, swelling, heat, and pain.[1] However, acute inflammatory responses are meant to be quickly suppressed by resolvins formed from the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Thus, a

balance in the dietary omega-6/3 ratio may be important for ensuring that an excessive and prolonged inflammatory response does not occur, which could lead to tissue damage and potentially to autoimmune disease."…

-MSMA member since 2003, Saint Luke's Mid America Heart Institute, Kansas City, Missouri.
-Dr James J. DiNicolantonio
-Dr. James O'Keefe, MD
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7721408

■■■

…"It has been noted that rheumatoid arthritis and autoimmune inflammatory disease are associated with an increased risk for cardiovascular disease.[1] "…

-Dr Joseph Lamb, M.D
- Director of Intramural Clinical Research, Metagenics
-Anti-Aging Medical News - The Future of Medicine Today (2014)
https://www.a4m.com/assets/pdf/medical-news/medical-news-winter-2014.pdf

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"Your body's immune system protects you from disease and infection. But if you have an autoimmune disease, your immune system attacks healthy cells in your body by mistake. Autoimmune diseases can affect many parts of the body.

No one is sure what causes autoimmune diseases. They do tend to run in families. Women - particularly African American, Hispanic American, and Native American women - have a higher risk for some autoimmune diseases.

There are more than 80 types of autoimmune diseases, and some have similar symptoms. This makes it hard for your health care provider to know if you really have one of these diseases, and if so, which one. Getting a diagnosis can be frustrating and stressful. Often, the first symptoms are fatigue, muscle aches and a low fever. **The classic sign of an autoimmune disease is inflammation, which can cause redness, heat, pain and swelling**.

The diseases may also have flare-ups, when they get worse, and remissions, when symptoms get better or disappear. Treatment depends on the disease, but in most cases one important goal is to reduce inflammation. Sometimes doctors prescribe corticosteroids or other drugs that reduce your immune response."

- Medline Plus
- United States National Library of Medicine
https://medlineplus.gov/autoimmunediseases.html

Therapeutic Potential of ω-3 Polyunsaturated Fatty Acids in Human Autoimmune Diseases

"The recognition of ω-3 polyunsaturated acids (PUFAs) as essential fatty acids to normal growth and health was realized more than 80 years ago. However, the awareness of the long-term nutritional intake of ω-3 PUFAs in lowering the risk of a variety of chronic human diseases has grown exponentially only since the 1980s [1, 2]. Despite the overwhelming epidemiological evidence, many attempts of using fish-oil supplementation to intervene human diseases have generated conflicting and often ambiguous outcomes; null or weak supporting conclusions were sometimes derived in the subsequent META analysis. Different dosages, as well as the sources of fish-oil, may have contributed to the conflicting outcomes of intervention carried out at different clinics. However, over the past decade, mounting evidence generated from genetic mouse models and clinical studies has shed new light on the functions and the underlying mechanisms of ω-3 PUFAs and their metabolites in the prevention and treatment of rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis, and type 1 diabetes. In this review, we have summarized the current understanding of the effects as well as the underlying mechanisms of ω-3 PUFAs on autoimmune diseases."…

"Polyunsaturated fatty acids (PUFAs) can be divided into two major classes: ω-3 PUFAs and ω-6 PUFAs, with the primary structural difference at the positions of their double bonds on the carbon chain. ω-6 PUFAs have the first double bonds starting at the sixth carbon, while ω-3 PUFAs starting at the third carbon, from the methyl end of the carbon chain (the ω-carbon) (3). The two major ω-6 PUFAs that are typically consumed in the diet are linoleic acid (18:2; ω-6; LA) and arachidonic acid (20:4; ω-6; AA). **Western diets are dominated by ω-6 PUFAs but contain only small amounts of ω-3 PUFAs with the ratio of ω-6/ω-3 reaching as high as 20–30** (4). "….

-The School of Biomedical and Pharmaceutical Sciences, Guangdong University of Technology, Guangzhou, China

-Department of Immunology, Nanjing Medical University, Nanjing, China

-Edited by: Allen Jay Rosenspire, Wayne State University, United States

-Reviewed by: Philip Calder, University of Southampton, United Kingdom; Melissa Bates, Michigan Medicine, University of Michigan, United States

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776881

Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon?

"Autoimmune diseases, including multiple sclerosis and type 1 diabetes mellitus, affect about 5%

of the worldwide population. **In the last decade, reports have accumulated on various autoimmune disorders, such as idiopathic thrombocytopenia purpura, myopericarditis, primary ovarian failure, and systemic lupus erythematosus (SLE), following vaccination.** In this review, we discuss the possible underlying mechanisms of autoimmune reactions following vaccinations and review cases of autoimmune diseases that have been correlated with vaccination. Molecular mimicry and bystander activation are reported as possible mechanisms by which vaccines can cause autoimmune reactions. The individuals who might be susceptible to develop these reactions could be especially not only those with previous post-vaccination phenomena and those with allergies but also in individuals who are prone to develop autoimmune diseases, such as those with a family history of autoimmunity or with known autoantibodies, and the genetic predisposed individuals. Further research is encouraged into the direct associations between vaccines and autoimmune conditions, and the biological mechanisms behind them."

-Department of General Surgery and Surgical Specialties, Medical School, Surgical Clinic, University of Modena and Reggio Emilia, Modena, Italy

-Network of the Second Opinion, Modena, MO Italy

-Department of Pediatrics, ASST Melegnano e Martesana, Milano, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5607155

Eicosapentaenoic acid (EPA) induces peroxisome proliferator-activated receptors and ameliorates experimental autoimmune encephalomyelitis

“Eicosapentaenoic acid (EPA), one of the n-3 polyunsaturated fatty acids, is a neuroprotective lipid with anti-inflammatory properties. We investigated the possible therapeutic effect of EPA on experimental autoimmune encephalomyelitis (EAE). EAE mice were fed a diet with or without EPA. The clinical EAE scores of the EPA-fed mice were significantly lower than those of the non-EPA mice. In the EPA-treated mice, IFN-γ and IL-17 productions were remarkably inhibited and the expression levels of peroxisome proliferator-activated receptors were significantly enhanced in the CNS-infiltrating CD4T cells. Thus EPA shows promise as a potential new therapeutic agent against multiple sclerosis.”

-Department of Internal Medicine I, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka, 569-0801, Japan.

https://pubmed.ncbi.nlm.nih.gov/23276800

See also Arthritis , Cardiovascular Disease , Rheumatoid Arthritis

Autonomic Neuropathy Diabetic (Diabetic Neuropathy)

Avascular necrosis (Aseptic Necrosis)
Avian Flu (Avian Influenza (Bird Flu))
Avian Influenza (Bird Flu)

B

B Hemophilia (Hemophilia)
Baby Colic (Colic)
Baby Formulas (Infant Formulas)
Back Surgery (Minimally Invasive Lumbar Spinal Fusion)
Baclofen Pump Therapy
Bacterial Vaginosis (Causes, Symptoms, Treatment)
Bad Breath
Bad Cholesterol Test (Cholesterol Test)
Baker Cyst
Bakers Cyst (Baker Cyst)
Balamuthia mandrillaris
Balanitis (Penis Disorder)
Balanitis Contagious (Is Balanitis Contagious)
Balloon Angioplasty Of Heart (Coronary Angioplasty)
Balloon Endoscopy
Balloon Enteroscopy (Balloon Endoscopy)
Balloon Valvuloplasty (Heart Valve Disease Treatment)
Barium Enema
Barium Swallow (Upper GI Series)
Barlow syndrome (Mitral Valve Prolapse)
Barrett's Esophagus
Barretts Esophagus (Barrett's Esophagus)
Barrier Methods of Birth Control
Basal Body Temperature Method of Birth Control (Natural Methods of Birth Control)

Basal Ganglia

“Damage to the basal ganglia cells may cause problems controlling speech, movement, and posture. This combination of symptoms is called parkinsonism. A person with basal ganglia dysfunction may have difficulty starting, stopping, or sustaining movement. Depending on which area of the brain is affected, there may also be problems with memory and other thought processes.

In general, symptoms vary and may include:

- Movement changes, such as involuntary or slowed movements
- Increased muscle tone
- Muscle spasms and muscle rigidity
- Problems finding words
- Tremor
- Uncontrollable, repeated movements, speech, or cries (tics)
- Walking difficulty"

-Medline Plus
-U.S National Library of Medicine
https://medlineplus.gov/ency/article/001069.htm

Cannabinoid control of motor function at the basal ganglia

"Classic and novel data strengthen the idea of a prominent role for the endocannabinoid signaling system in the control of movement. This finding is supported by three-fold evidence: (1) the abundance of the cannabinoid CB1 receptor subtype, but also of CB2 and vanilloid VR1 receptors, as well as of endocannabinoids in the basal ganglia and the cerebellum, the areas that control movement; (2) the demonstration of a powerful action, mostly of an inhibitory nature, of plant-derived, synthetic, and endogenous cannabinoids on motor activity, exerted by modulating the activity of various classic neurotransmitters; and (3) the occurrence of marked changes in endocannabinoid transmission in the basal ganglia of humans affected by several motor disorders, an event corroborated in animal models of these neurological diseases. This three-fold evidence has provided support to the idea that cannabinoid-based compounds, which act at key steps of the endocannabinoid transmission [receptors, transporter, fatty acid amide hydrolase (FAAH)], might be of interest because of their potential ability to alleviate motor symptoms and/or provide neuroprotection in a variety of neurological pathologies directly affecting basal ganglia structures, such as Parkinson's disease and Huntington's chorea, or indirectly, such as multiple sclerosis and Alzheimer's disease. The present chapter will review the knowledge on this issue, trying to establish future lines for research into the therapeutic potential of the endocannabinoid system in motor disorders."

-Department of Biochemistry and Molecular Biology III, Faculty of Medicine, Complutense University, Ciudad Universitaria
https://pubmed.ncbi.nlm.nih.gov/16596785/

Endocannabinoids and basal ganglia functionality

”In recent years, our knowledge on the cannabinoid pharmacology has shown a significant rise in terms of both quantity (more compounds and more targets) and quality (more selective compounds). This allows to consider cannabinoids and related compounds as a promising new line of research for therapeutic treatment of a variety of conditions, such as brain injury, chronic pain, glaucoma, asthma, cancer and AIDS-associated effects and other pathologies. Motor disorders are another promising field for the therapeutic application of cannabinoid-related compounds, since the control of movement is one of the more relevant physiological roles of the endocannabinoid transmission in the brain. There are two pathologies, Parkinson's disease and Huntington's chorea, which are particularly interesting from a clinical point of view due to the direct relationship of endocannabinoids and their receptors with neurons that degenerate in those disorders. However, other neurological pathologies, such as Alzheimer's disease or multiple sclerosis, which are not motor disorders in origin, but present a strong alteration in the control of movement, have also been a subject of interesting research for a cannabinoid therapy. This review will summarize our current knowledge on the role of these endogenous substances in the control of movement and, in particular, on the possible therapeutic usefulness of these compounds in the treatment of motor pathologies.”

-Department of Biochemistry and Molecular Biology III, Faculty of Medicine, Complutense University, Ciudad Universitaria

https://pubmed.ncbi.nlm.nih.gov/12052041/

The endocannabinoid system as a target for the treatment of motor dysfunction

“There is evidence that cannabinoid-based medicines that are selective for different targets in the cannabinoid signalling system (e.g. receptors, inactivation mechanism, enzymes) might be beneficial in basal ganglia disorders, namely Parkinson's disease (PD) and Huntington's disease (HD). These benefits not only include the alleviation of specific motor symptoms [e.g. choreic movements with cannabinoid receptor type 1 (CB1)/transient receptor potential vanilloid type 1 agonists in HD; bradykinesia with CB1 antagonists and tremor with CB1 agonists in PD], but also the delay of disease progression due to the neuroprotective properties demonstrated for cannabinoids (e.g. CB1 agonists reduce excitotoxicity; CB2 agonists limit the toxicity of reactive microglia; and antioxidant cannabinoids attenuate oxidative damage). In addition, extensive biochemical, anatomical, physiological and pharmacological studies have demonstrated that: (i) the different elements of the cannabinoid system are abundant in basal ganglia structures and they are affected by these disorders; (ii) the cannabinoid system plays a prominent role in basal

ganglia function by modulating the neurotransmitters that operate in the basal ganglia circuits, both in healthy and pathological conditions; and (iii) the activation and/or inhibition of the cannabinoid system is associated with important motor responses that are maintained and even enhanced in conditions of malfunctioning and/or degeneration."….

"The studies reviewed here support the view that the cannabinoid signalling system is a key modulatory element in the activity of the basal ganglia. This concept is supported by different anatomical, electrophysiological, pharmacological and biochemical data. Indeed, we have shown that the cannabinoid system is impaired in different disorders that directly or indirectly affect the basal ganglia, which supports the idea of developing novel pharmacotherapies with compounds that selectively target specific elements of the cannabinoid system. The development of such compounds would not only provide novel therapeutic agents capable of minimizing the frequent side effects observed when classic cannabinoids are used in patients, but also help to elucidate the exact role played by the cannabinoid system in the pathogenesis of these disorders. In the light of the neuroprotectant/neuroregenerative properties demonstrated for certain cannabinoids, these treatments should not only aim to alleviate specific symptoms (e.g. hyperkinesia in HD, tremor and bradykinesia in PD), but also attempt to delay/arrest disease progression and to repair the damaged structures. However, most of the studies that have examined the therapeutic potential of these compounds in basal ganglia disorders have been conducted in animal models, with very few clinical trials carried out to date. Therefore, the importance of this intercellular signalling system needs further clinical research to be carried out in patients with the aim of validating the results found in animal and cellular models."…

-Department of Biochemistry and Molecular Biology and Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), Faculty of Medicine, Complutense University, Madrid, Spain
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697699/

This research paper above mentions side effects in relation to cannabinoid use. However the research doesn't clarify which side effect and whether or not they are referring to synthetic cannabinoids. Researchers will often classify the "runner's high" experienced from the phytocannabinoid THC as a side effect, however this is the cell signaling of the body which is the also activated during exercise.

See also Exercise & Training

Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the 'runner's high'

https://jeb.biologists.org/content/215/8/1331

Basedows disease (Graves' Disease)

See Thyroid Disease

B-cell Deficiency

See T-Cell & B-Cells

Beta-Arrestins

Also referred to as β-arrestins, β-arr, β-arr2

…"Data obtained from the experiments presented herein demonstrate that AEA and virodhamine modulate agonist-mediated recruitment of βarr2. AEA and virodhamine act as partial agonists; enhancing the agonist effect at low concentrations and inhibiting it at high concentrations"…

-Department of Anatomy and Cell Biology and Center for Substance Abuse Research, Temple University, Philadelphia, Pennsylvania, United States

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3669693/

Multifaceted role of β-arrestins in inflammation and disease

"Arrestins are intracellular scaffolding proteins known to regulate a range of biochemical processes including G-protein coupled receptor (GPCR) desensitization, signal attenuation, receptor turnover and downstream signaling cascades. Their roles in regulation of signaling network have lately been extended to receptors outside of the GPCR family, demonstrating their roles as important scaffolding proteins in various physiological processes including proliferation, differentiation, and apoptosis. Recent studies have demonstrated a critical role for arrestins in immunological processes including key functions in inflammatory signaling pathways. In this review, we provide a comprehensive analysis of the different functions of the arrestin family of proteins especially related to immunity and inflammatory diseases."…

"The canonical role of β-arrestins involves receptor desensitization and internalization wherein they act as scaffolds for proteins involved in the life-cycle of the GPCR"…

-Department of Physiology and Division of Pathology Michigan State University East Lansing, MI
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4670277/

Beta-arrestins and cell signaling

"Upon their discovery, beta-arrestins 1 and 2 were named for their capacity to sterically hinder the G protein coupling of agonist-activated seven-transmembrane receptors, ultimately resulting in receptor desensitization. Surprisingly, recent evidence shows that beta-arrestins can also function to activate signaling cascades independently of G protein activation. By serving as multiprotein scaffolds, the beta-arrestins bring elements of specific signaling pathways into close proximity. beta-Arrestin regulation has been demonstrated for an ever-increasing number of signaling molecules, including the mitogen-activated protein kinases ERK, JNK, and p38 as well as Akt, PI3 kinase, and RhoA. In addition, investigators are discovering new roles for beta-arrestins in nuclear functions. Here, we review the signaling capacities of these versatile adapter molecules and discuss the possible implications for cellular processes such as chemotaxis and apoptosis."

-Howard Hughes Medical Institute and Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA.
https://pubmed.ncbi.nlm.nih.gov/17305471

Beta-caryophyllene (β-caryophyllene)

…"It is the most commonly occurring form of beta-caryophyllene, occurring in many essential oils, particularly oil of cloves. It has a role as a non-steroidal anti-inflammatory drug, a fragrance and a metabolite."…

- U.S National Library of Medicine
https://pubchem.ncbi.nlm.nih.gov/compound/beta-caryophyllene

The Endocannabinoid System, Cannabinoids, and Pain

"The terpene β-caryophyllene is found in a number of commonly available plants, including black pepper, cinnamon, clove, and other spices. It selectively binds to the CB2 receptor at nanomolar concentrations and acts as a full agonist. β-Caryophyllene and cannabidiol occur abundantly in Cannabis sativa. So this plant species produces at least two entirely different chemical substances able to target CB2 receptors differentially. While studies on the pharmacokinetics of

β-caryophyllene are still on-going, it is already clear that this terpene is readily bioavailable. Unlike many polyphenolic natural products, it is not metabolized immediately but shows a Tmax >1 h after one single oral administration. Orally administered β-caryophyllene (<5 mg·kg−1) produces strong anti-inflammatory and analgesic effects in wild-type mice but not in CB2 receptor knock-out mice, which is a clear indication that it may be a functional CB2 ligand.[107]

On-going studies show that β-caryophyllene is effective at reducing neuropathic pain in a CB2 receptor-dependent manner.[108] Like other CB2 ligands β-caryophylleneinhibits the pathways triggered by activation of the toll-like receptor complex CD14/TLR4/MD2, which typically leads to the expression of pro-inflammatory cytokines (e.g. IL-1 beta, IL-6, IL-8, and TNF alpha) and promotes a Th1 immune response that plays a critical role in neuroinflammation, sensitization, and pain.[109] Therefore, the FDA-approved food additive β-caryophyllene seems an attractive candidate for clinical trials targeting the CB2 receptor. Indeed, in cases of intractable or difficult-to-control pain, combination therapy with small doses of opioid and non-psychoactive cannabinoid receptor agonists may be an alternative way to circumvent the undesirable side effects of opioids yet obtain far greater analgesic efficacy than achieved with cannabinoids alone.[56,110]"

-Professor of Anesthesiology, Pain Research and Management Centers, Department of Anesthesiology, School of Medicine, University of Utah, Salt Lake City, Utah, USA; and
-Chief Executive Officer, ISA Scientific, Draper, Utah, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3820295/

β-caryophyllene and β-caryophyllene oxide—natural compounds of anticancer and analgesic properties

"Natural bicyclic sesquiterpenes, β-caryophyllene (BCP) and β-caryophyllene oxide (BCPO), are present in a large number of plants worldwide. Both BCP and BCPO (BCP(O)) possess significant anticancer activities, affecting growth and proliferation of numerous cancer cells. Nevertheless, their antineoplastic effects have hardly been investigated in vivo. In addition, both compounds potentiate the classical drug efficacy by augmenting their concentrations inside the cells. The mechanisms underlying the anticancer activities of these sesquiterpenes are poorly described. BCP is a phytocannabinoid with strong affinity to cannabinoid receptor type 2 (CB 2), but not cannabinoid receptor type 1 (CB 1). In opposite, BCP oxidation derivative, BCPO, does not exhibit CB 1/2 binding, thus the mechanism of its action is not related to endocannabinoid system (ECS) machinery. It is known that BCPO alters several key pathways for cancer development, such as mitogen-activated protein kinase (MAPK), PI3K/AKT/mTOR/S6K1 and STAT3 pathways. In addition, treatment with this compound reduces the expression of procancer genes/proteins,

while increases the levels of those with proapoptotic properties. The selective activation of CB 2 may be considered a novel strategy in pain treatment, devoid of psychoactive side effects associated with CB 1 stimulation. Thus, BCP as selective CB 2 activator may be taken into account as potential natural analgesic drug. Moreover, due to the fact that chronic pain is often an element of cancer disease, the double activity of BCP, anticancer and analgesic, as well as its beneficial influence on the efficacy of classical chemotherapeutics, is particularly valuable in oncology. This review is focused on anticancer and analgesic activities of BCP and BCPO, the mechanisms of their actions, and potential therapeutic utility."

-Laboratory of Tumor Molecular Immunobiology, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, 12 Rudolf Weigl, Wroclaw, Poland

-The Faculty of Food Science, Department of Chemistry, Wrocław University of Environmental and Life Sciences, 25/27 C.K. Norwida, Wroclaw, Poland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5083753/

Binswanger's Disease

…"Binswanger disease is caused by arteriosclerosis, thromboembolism and other diseases that obstruct blood vessels that supply the deep structures of the brain. Hypertension, smoking, hypercholesterolemia, heart disease and diabetes mellitus are risk factors for Binswanger disease. Rare hereditary diseases such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) also cause Binswanger disease. Thus, Binswanger disease is actually a clinical syndrome of vascular dementia with multiple causes, not a specific disease. The reduced blood flow in brain tissue appears to produce secondary inflammation that may be a target for treatment."…

-NORD - National Organization for Rare Diseases

-NORD gratefully acknowledges Rodger J. Elble, MD, PhD, Professor of Neurology, Director, Parkinson Disease and Movement Disorders Center, Southern Illinois University School of Medicine, for assistance in the preparation of this report.

https://rarediseases.org/rare-diseases/binswanger-disease/

See also Atherosclerosis , Heart Disease , Thrombosis

Bipolar Disorder

…"Unipolar depression and bipolar disorder are considered distinct psychiatric conditions,

although major depression occurs in both. A 2016 meta-analysis of eight case-control studies that compared the PUFA composition of red blood cell membranes between patients with bipolar disorder and healthy subjects showed abnormally low red blood cell DHA concentrations with bipolar disorder (196). As with major depression, reviews of trials indicated that omega-3 supplementation may have a positive effect as an adjunct to therapy in patients with bipolar disorder (192, 194). Additionally, a 2016 randomized, placebo-controlled trial in 100 participants with bipolar disorder reported a reduction in the severity of manic episodes with daily supplementation of 1,000 mg omega-3 PUFA for three months (197).”…

- Oregon State University
https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids#neuropsychiatric-disorders-treatment

■■■

“**Background**: The basis for carbamazepine's efficacy in treating bipolar disorder is not agreed on. One hypothesis is that, similar to lithium and valproate (antibipolar drugs), carbamazepine might selectively decrease the kinetics of arachidonic acid (AA) in brain phospholipids.”…

“**Results**: Chronic carbamazepine, compared with vehicle, decreased the rate of incorporation of AA-CoA (27%-29%) and turnover of AA (25%-27%) but not of DHA-CoA or DHA in brain phospholipids.

Conclusions: The results, which are comparable to published findings after chronic administration of lithium and valproic acid to rats, support the hypothesis that drugs effective against mania in bipolar disorder act by selectively downregulating the incorporation rate of AA-CoA and turnover of AA in brain phospholipids.”

-Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA.
https://pubmed.ncbi.nlm.nih.gov/16182257

Antimanic therapies target brain arachidonic acid [omega-6] signaling: lessons learned about the regulation of brain fatty acid metabolism

“Bipolar disorder is a major medical, social and economic burden worldwide. However, the biochemical basis of the disorder and the mechanisms of action of effective antibipolar disorder drugs remain elusive. In this paper, we review how combining a kinetic approach to studying the turnover of fatty acids within brain phospholipids of unanesthetized rats along with chronic administration of antimanic drugs (lithium, valproate and carbamazepine) at therapeutically

relevant doses, shows that the brain arachidonic acid cascade is a common target of these drugs. **The overlapping effects of the three drugs are decreased turnover of arachidonic acid but not of docosahexaenoic acid in rat brain phospholipids, and decreased brain cyclooxygenase-2 and prostaglandin E(2).** Whereas lithium and carbamazepine target the transcription of the arachidonic acid-selective calcium-dependent cytosolic phospholipase A(2), valproate is a non-competitive inhibitor of an arachidonic acid-selective acyl-CoA synthetase. Two potential models of bipolar disorder, chronic N-methyl-d-aspartate and n-3 polyunsaturated fatty acid deprivation, opposite to the antimanic drugs, increase the turnover and markers of the arachidonic acid cascade in rat brain. **These observations support the hypothesis proposed by Rapoport and colleagues that the arachidonic acid cascade is a common target of mood stabilizers and that by targeting substrate-specific enzymes the turnover of individual fatty acids can be regulated within the brain.**"

-Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA.

https://pubmed.ncbi.nlm.nih.gov/18042366

See also Social Functioning

Black Pepper

See Beta-caryophyllene (β-caryophyllene)

Bladder Cancer

Bladder cancer cell growth and motility implicate cannabinoid 2 receptor-mediated modifications of sphingolipids metabolism

…"CB2 [cannabinoid receptor 2] activation led to ceramide-mediated BC [bladder cancer] cell apoptosis independently of SL constitutive composition, which instead was modulated by CB2 agonists to reduce cell motility."

-Division of Experimental Oncology/Unit of Urology; URI; IRCCS Ospedale San Raffaele, Milan, Italy.
-Department of Medical Biotechnology and Translational Medicine, University of Milano, Segrate, Italy.
-Department of Pathology, IRCCS Ospedale San Raffaele, Milan, Italy.
-Department of Medicine, University of Stony Brook, Stony Brook, New York 11794, USA.

-Department of Clinical Pharmacology, Linköping University, Sweden.
-Università Vita-Salute San Raffaele, Milan, Italy.
https://pubmed.ncbi.nlm.nih.gov/28191815/

Capsaicin-induced apoptosis and reduced release of reactive oxygen species in MBT-2 Murine Bladder Tumor cells

"Bladder cancer is a common cancer with high risk of recurrence and mortality. Intravesicle chemotherapy after trans-urethral resection is required to prevent tumor recurrence and progression. It has been known that antioxidants enhance the antitumor effect of bacillus Calmette-Guerin (BCG), the most effective intravesical bladder cancer treatment. Capsaicin, the major pungent ingredient in genusCapsicum, has recently been tried as an intravesical drug for overactive bladder and it has also been shown to induce apoptotic cell death in many cancer cells. In this study, we investigated the apoptosis-inducing effect and alterations in the cellular redox state of capsaicin in MBT-2 murine bladder tumor cells. Capsaicin induced apoptotic MBT-2 cell death in a time- and dose-dependent manner. The capsaicin-induced apoptosis was blocked by the pretreatment with Z-VAD-fmk, a broad-range caspase inhibitor, or AcDEVD-CHO, a caspase-3 inhibitor. In addition to the caspase-3 activation, capsaicin also induced cytochrome c release and decrease in Bcl-2 protein expression with no changes in the level of Bax. Furthermore, capsaicin at the concentration of inducing apoptosis also markedly reduced the level of reactive oxygen species and lipid peroxidation, implying that capsaicin may enhance the antitumor effect of BCG in bladder cancer treatment. These results further suggest that capsaicin may be a valuable intravesical chemotherapeutic agent for bladder cancers."

- College of Pharmacy, Yeungnam University, Gyongsan, Korea.
https://link.springer.com/article/10.1007/BF02975121

Honokiol induces apoptotic cell death by oxidative burst and mitochondrial hyperpolarization of bladder cancer cells

"Bladder cancer is one of the most common types of malignant tumor worldwide. Current treatments, including chemo- /radiotherapy, only have limited efficacy on bladder cancer progression. Honokiol is an active component of Magnolia officinalis with multiple biological effects that may provide promising health benefits. In the present study, the anti- cancer properties of honokiol against bladder cancer cells were investigated by flow cytometric analysis. The results revealed that honokiol exhibited significant anti- proliferative effects on bladder cancer cell lines, particularly on BFTC- 905 human transitional cell carcinoma cells. Furthermore,

honokiol at low doses (≤25 μM) induced cell cycle arrest in G0/G1 phase, while it induced significant apoptotic cell death at high doses (≥50 μM; P<0.05). Furthermore, a significant accumulation of reactive oxygen species was identified in honokiol- treated cells. In addition, honokiol induced hyperpolarization of the mitochondrial membrane, which may lead to mitochondrial dysfunction. Finally, caspase- 3/7 activation was identified in high- dose honokiol- treated bladder cancer cells. These results suggest that honokiol induces apoptosis via the mitochondrial pathway and honokiol- containing traditional herbal remedies may have a potential clinical application in the treatment of bladder cancer."

-Department of Urology, Wan Fang Hospital, Taipei 11696, Taiwan R.O.C.

-Cancer Center, Wan Fang Hospital, Taipei 11696, Taiwan R.O.C.

-Center for Cell Therapy, Department of Medical Research, China Medical University Hospital, Taichung 40447, Taiwan R.O.C.

https://www.spandidos-publications.com/10.3892/etm.2019.7419

apoptosis - the death of cells which occurs as a normal and controlled part of an organism's growth or development. (Oxford Languages / Google)

capsaicin - a compound that is responsible for the pungency of capsicums. ***capsicums*** - A tropical American pepper plant of the nightshade family with fruits containing many seeds. Many cultivated varieties with edible, pungent fruits have been developed. (Oxford Languages / Google)

Bladder Stone Disease

"Supplementation of basal mixture or pumpkin seeds snack gave a higher level of inhibitor of crystal formation or aggregation than the control period. Moreover, pumpkin seeds snack showed inhibition effect to a greater extent than basal mixture. In the light of this study, it is suggested that pumpkin seeds snack, a high nutritive mixture, is satisfactory to improve the nutrients and increase the level of inhibitors of crystal formation or aggregation which will subsequently reduce the risk of bladder stone disease in Thailand."

-Division of Experimental Nutrition, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

https://www.ncbi.nlm.nih.gov/pubmed/7964254

Blood Brain Barrier (BBB)

Barrier Mechanisms in the Developing Brain

"The adult brain functions within a well-controlled stable environment, the properties of which are determined by cellular exchange mechanisms superimposed on the diffusion restraint provided by tight junctions at interfaces between blood, brain and cerebrospinal fluid (CSF). These interfaces are referred to as "the" blood–brain barrier. It is widely believed that in embryos and newborns, this barrier is immature or "leaky," rendering the developing brain more vulnerable to drugs or toxins entering the fetal circulation from the mother. New evidence shows that many adult mechanisms, including functionally effective tight junctions are present in embryonic brain and some transporters are more active during development than in the adult. Additionally, some mechanisms present in embryos are not present in adults, e.g., specific transport of plasma proteins across the blood–CSF barrier and embryo-specific intercellular junctions between neuroependymal cells lining the ventricles. However developing cerebral vessels appear to be more fragile than in the adult. Together these properties may render developing brains more vulnerable to drugs, toxins, and pathological conditions, contributing to cerebral damage and later neurological disorders. In addition, after birth loss of protection by efflux transporters in placenta may also render the neonatal brain more vulnerable than in the fetus."

-Department of Pharmacology, The University of Melbourne, Parkville, VIC, Australia
-Edited by: Joana A. Palha, University of Minho, Portugal
-Reviewed by: Jason B. Wu, Cedars-Sinai Medical Center, USA; Adam Chodobski, Brown University, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314990/

Endocannabinoids modulate human blood–brain barrier permeability in vitro

"Anandamide [AEA] (10 μM) and oleoylethanolamide (OEA, 10 μM) decreased BBB [Blood Brain Barrier] permeability (i.e. increased resistance). "…

"The endocannabinoids may play an important modulatory role in normal BBB physiology, and also afford protection to the BBB during ischaemic stroke, through a number of target sites."…

-School of Medicine, University of Nottingham, Royal Derby Hospital, Derby, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4459020/

Blood Cancers

"The three main types of blood cancer are leukemia, lymphoma and myeloma:

Leukemia is a blood cancer that originates in the blood and bone marrow. It occurs when the body creates too many abnormal white blood cells and interferes with the bone marrow's ability to make red blood cells and platelets.

Non-Hodgkin lymphoma is a blood cancer that develops in the lymphatic system from cells called lymphocytes, a type of white blood cell that helps the body fight infections.

Hodgkin lymphoma is a blood cancer that develops in the lymphatic system from cells called lymphocytes. Hodgkin lymphoma is characterized by the presence of an abnormal lymphocyte called the Reed-Sternberg cell.

Multiple myeloma is a blood cancer that begins in the blood's plasma cells, a type of white blood cell made in the bone marrow."

-Cancer Treatment Centers of America
https://www.cancercenter.com/blood-cancers

Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease

"In the current study, we examined whether ligation of CB2 receptors would lead to induction of apoptosis in tumors of immune origin and whether CB2 agonist could be used to treat such cancers. Exposure of murine tumors EL-4, LSA, and P815 to delta-9-tetrahydrocannabinol (THC) in vitro led to a significant reduction in cell viability and an increase in apoptosis. **Exposure of EL-4 tumor cells to the synthetic cannabinoid HU-210 and the endogenous cannabinoid anandamide led to significant induction of apoptosis**, whereas exposure to WIN55212 was not effective. **Treatment of EL-4 tumor-bearing mice with THC in vivo led to a significant reduction in tumor load, increase in tumor-cell apoptosis, and increase in survival of tumor-bearing mice**. Examination of a number of human leukemia and lymphoma cell lines, including Jurkat, Molt-4, and Sup-T1, revealed that they expressed CB2 receptors but not CB1. **These human tumor cells were also susceptible to apoptosis induced by THC, HU-210, anandamide, and the CB2-selective agonist JWH-015**. This effect was mediated at least in part through the CB2 receptors because pretreatment with the CB2 antagonist SR144528 partially reversed the THC-induced apoptosis. **Culture of primary acute lymphoblastic leukemia cells with THC in vitro reduced cell viability and induced apoptosis. Together, the current data demonstrate that CB2 cannabinoid receptors**

expressed on malignancies of the immune system may serve as potential targets for the induction of apoptosis. Also, because CB2 agonists lack psychotropic effects, they may serve as novel anticancer agents to selectively target and kill tumors of immune origin."

-Department of Microbiology and Immunology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298, USA.

https://pubmed.ncbi.nlm.nih.gov/12091357/

Delta9-tetrahydrocannabinol-induced apoptosis in Jurkat leukemia T cells is regulated by translocation of Bad to mitochondria

"Plant-derived cannabinoids, including Delta9-tetrahydrocannabinol (THC), induce apoptosis in leukemic cells, although the precise mechanism remains unclear. In the current study, we investigated the effect of THC on the upstream and downstream events that modulate the extracellular signal-regulated kinase (ERK) module of mitogen-activated protein kinase pathways primarily in human Jurkat leukemia T cells. The data showed that THC down-regulated Raf-1/mitogen-activated protein kinase/ERK kinase (MEK)/ERK/RSK pathway leading to translocation of Bad to mitochondria. THC also decreased the phosphorylation of Akt. However, no significant association of Bad translocation with phosphatidylinositol 3-kinase/Akt and protein kinase A signaling pathways was noted when treated cells were examined in relation to phosphorylation status of Bad by Western blot and localization of Bad to mitochondria by confocal analysis. Furthermore, THC treatment decreased the Bad phosphorylation at Ser(112) but failed to alter the level of phospho-Bad on site Ser(136) that has been reported to be associated with phosphatidylinositol 3-kinase/Akt signal pathway. Jurkat cells expressing a constitutively active MEK construct were found to be resistant to THC-mediated apoptosis and failed to exhibit decreased phospho-Bad on Ser(112) as well as Bad translocation to mitochondria. Finally, use of Bad small interfering RNA reduced the expression of Bad in Jurkat cells leading to increased resistance to THC-mediated apoptosis. Together, these data suggested that Raf-1/MEK/ERK/RSK-mediated Bad translocation played a critical role in THC-induced apoptosis in Jurkat cells."

-Department of Pharmacology and Toxicology, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, USA.

https://pubmed.ncbi.nlm.nih.gov/16908594/

■■■

"Studies show that exposure of murine lymphoma tumors EL-4, LSA, and P815 to Δ(9)-tetrahydrocannabinol in vitro led to a significant reduction in cell viability and an increase in apoptosis, and EL-4 tumor–bearing mice led to a significant reduction in tumor load, increase in

tumor-cell apoptosis, and increase in survival of tumor-bearing mice (ref. 20 and references therein). Similar observations were made by Flygare et al. (20) who treated mantle cell lymphoma (MCL) cells with cannabinoid receptor ligands and found a decrease in cell viability, whereas control cells lacking CB1 were not affected. Recently, Gustafsson et al. (3) reported that cannabinoid receptor–mediated apoptosis induced by (R)-methanandamide and WIN-55,212-2 in MCL was associated with ceramide accumulation and p38. These data suggest that targeting CB1 and CB2 receptors by their agonists may have therapeutic potential for the treatment of lymphoma."

-Chemoprevention Program, Paul P. Carbone Comprehensive Cancer Center and Department of Dermatology, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin USA.

https://pubmed.ncbi.nlm.nih.gov/18199524/

p38 MAPK is involved in CB2 receptor-induced apoptosis of human leukaemia cells

"Cannabinoids have been shown to inhibit the growth of a broad spectrum of tumour cells. However, the molecular mechanisms involved in that effect have not been completely elucidated. Here, we investigated the possible involvement of mitogen-activated protein kinases (MAPKs) in CB2 receptor-induced apoptosis of human leukaemia cells. Results show that stimulation of the CB2 receptor leads to p38 MAPK activation and that inhibition of this kinase attenuates CB2 receptor-induced caspase activation and apoptosis. These findings support a role for p38 MAPK in CB2 receptor-induced apoptosis of human leukaemia cells."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, c/José Antonio Novais s/n, 28040 Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/16139274/

The CB2 cannabinoid receptor signals apoptosis via ceramide-dependent activation of the mitochondrial intrinsic pathway

"Delta9-tetrahydrocannabinol and other cannabinoids exert pro-apoptotic actions in tumor cells via the CB2 cannabinoid receptor. However, the molecular mechanism involved in this effect has remained elusive. Here we used the human leukemia cell line Jurkat-that expresses CB2 as the unique CB receptor-to investigate this mechanism. Our results show that incubation with the selective CB2 antagonist SR144528 abrogated the pro-apoptotic effect of Delta9-tetrahydrocannabinol. Cannabinoid treatment led to a CB2 receptor-dependent stimulation of ceramide biosynthesis and inhibition of this pathway prevented Delta9-tetrahydrocannabinol-

induced mitochondrial hypopolarization and cytochrome c release, indicating that ceramide acts at a pre-mitochondrial level. Inhibition of ceramide synthesis de novo also prevented caspase activation and apoptosis. Caspase 8 activation-an event typically related with the extrinsic apoptotic pathway-was also evident in this model. However, activation of this protease was post-mitochondrial since (i) a pan-caspase inhibitor as well as a selective caspase 8 inhibitor were unable to prevent Delta9-tetrahydrocannabinol-induced loss of mitochondrial-membrane transmembrane potential, and (ii) cannabinoid-induced caspase 8 activation was not observed in Bcl-xL over-expressing cells. In summary, results presented here show that CB2 receptor activation signals apoptosis via a ceramide-dependent stimulation of the mitochondrial intrinsic pathway."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, c/José Antonio Novais s/n, 28040 Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/16624285

Effects of omega-3 fatty acids on regulatory T cells in hematologic neoplasms

"The development of leukemia and lymphomas is related to the increase in inflammatory process modulators. These, in turn, have divergent actions on the neoplastic process. Populations of T cells have different roles in the neoplastic environment; while interferon-gamma positive T cells have antitumor activity, the FoxP3+interleukin-10 positive population present a pro-tumor activity. Simultaneously, the inflammatory process promotes the mobilization of fatty acids from the cell membrane to produce lipid mediators, which also participate of the inflammatory response. Eicosapentaenoic (EPA) and docosahexaenoic (DHA) omega-3 fatty acids, when incorporated in the plasmatic membrane, decrease the arachidonic acid (AA) metabolism and the production of eicosanoids derived from it. Thus, an alternative family of lipid mediators are produced that are often less inflammatory than those produced from arachidonic acid. Fatty acids can also influence the production of peptide mediators such as cytokines, and the expression of transcription factors, which can determine the production patterns of eicosanoids and cytokines as well as cell differentiation. Due to these properties, the objective of this literature review was to investigate studies published over the last 15 years on the effects of using omega-3 fatty acids on inflammatory markers in leukemia and lymphomas."…

-Federal University of Santa Catarina - UFSC, Florianópolis, SC, Brazil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3672122/

Targeting cannabinoid receptors to treat leukemia: role of cross-talk between extrinsic and intrinsic pathways in Delta9-tetrahydrocannabinol (THC)-induced apoptosis of Jurkat cells

"Targeting cannabinoid receptors has recently been shown to trigger apoptosis and offers a novel treatment modality against malignancies of the immune system. However, the precise mechanism of apoptosis in such cancers has not been previously addressed. In this study, we used human Jurkat leukemia cell lines with defects in intrinsic and extrinsic signaling pathways to elucidate the mechanism of apoptosis induced by Delta9-tetrahydrocannabinol (THC). We observed that Jurkat cells deficient in FADD or caspase-8 were partially resistant to apoptosis, while dominant-negative caspase-9 mutant cells were completely resistant to apoptosis. Use of caspase inhibitors confirmed these results. Furthermore, overexpression of Bcl-2 rendered the cells resistant to THC at early time points but not upon prolonged exposure. THC treatment led to loss of Deltapsi(m), in both wild-type and FADD-deficient Jurkat cells thereby suggesting that THC-induced intrinsic pathway was independent of FADD. THC treatment of wild-type Jurkat cells caused cytochrome c release, and cleavage of caspase-8, -9, -2, -10, and Bid. Caspase-2 inhibitor blocked THC-induced caspase-3 in wild-type Jurkat cells but not loss of Deltapsi(m). Together, these data suggest that the intrinsic pathway plays a more critical role in THC-induced apoptosis while the extrinsic pathway may facilitate apoptosis via cross-talk with the intrinsic pathway."

-Department of Microbiology and Immunology, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, VA, USA.

https://pubmed.ncbi.nlm.nih.gov/15978942/

Chronic stress enhances progression of acute lymphoblastic leukemia via β-adrenergic signaling

"Clinical studies suggest that stress-related biobehavioral factors can accelerate progression of hematopoietic cancers such as acute lymphoblastic leukemia (ALL), but it is unclear whether such effects are causal or what biological pathways mediate such effects. Given the network of sympathetic nervous system (SNS) fibers that innervates the bone marrow to regulate normal (non-leukemic) hematopoietic progenitor cells, we tested the possibility that stress-induced SNS signaling might also affect ALL progression. In an orthotopic mouse model, Nalm-6 human pre-B ALL cells were transduced with the luciferase gene for longitudinal bioluminescent imaging and injected i.v. into male SCID mice for bone marrow engraftment. Two weeks of daily restraint stress significantly enhanced ALL tumor burden and dissemination in comparison to controls, and this effect was blocked by the β-adrenergic antagonist, propranolol. Although Nalm-6 ALL cells expressed mRNA for β1- and β3-adrengeric receptors, they showed no evidence of cAMP

signaling in response to norepinephrine, and norepinephrine failed to enhance Nalm-6 proliferation in vitro. These results show that chronic stress can accelerate the progression of human pre-B ALL tumor load via a β-adrenergic signaling pathway that likely involves indirect regulation of ALL biology via alterations in the function of other host cell types such as immune cells or the bone marrow microenvironment."

-Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, USA

-Monash Institute of Pharmaceutical Sciences, Monash University, Australia

-Jonsson Comprehensive Cancer Center, University of California, Los Angeles, USA

-Division of Hematology-Oncology, David Geffen School of Medicine, University of California, Los Angeles, USA

-UCLA Molecular Biology Institute, USA

-Corresponding Author: Donald M. Lamkin, Ph.D. University of California

-Institute for Neuroscience and Human Behavior Cousins Center for Psychoneuroimmunology 300 Medical Plaza, Room 3160 Los Angeles, CA 90095

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322262

p38 MAPK is involved in CB2 receptor-induced apoptosis of human leukaemia cells

"Cannabinoids have been shown to inhibit the growth of a broad spectrum of tumour cells. However, the molecular mechanisms involved in that effect have not been completely elucidated. Here, we investigated the possible involvement of mitogen-activated protein kinases (MAPKs) in CB2 receptor-induced apoptosis of human leukaemia cells. Results show that stimulation of the CB2 receptor leads to p38 MAPK activation and that inhibition of this kinase attenuates CB2 receptor-induced caspase activation and apoptosis. These findings support a role for p38 MAPK in CB2 receptor-induced apoptosis of human leukaemia cells."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, c/José Antonio Novais s/n, 28040 Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/16139274/

Blood Cells

"Endocannabinoids are blood borne and may also be secreted by the endothelium. Accordingly, there has been interest in the interactions between (endo)cannabinoids and blood cells. There is certainly evidence that (endo)cannabinoids may promote platelet activation, indicating that they may be thrombogenic. Platelets are involved both in the metabolism and release of

endocannabinoids, and so it is possible that their circulating levels may be regulated by platelets. This process is altered in disease states such that platelet-derived endocannabinoids contribute towards hypotension in cardiovascular shock. Not only may endocannabinoids regulate platelet function and possibly lead to thrombogenesis, but they may also influence haematopoiesis. Given these emerging roles, the aim of this review is to examine the interactions between cannabinoids and blood."

…"The production of blood cells is a tightly regulated process and is designed to maintain physiological levels of cells but also to respond to pathophysiology. Valk et al. (1997), reported that in vitro anandamide (at low micromolar concentrations) acted via cannabinoid CB2 receptors to synergize with colony-stimulating factors (CSFs), interleukin-3 and erythropoietin to stimulate haematopoesis. This finding at low concentrations may suggest a role in the modulation of blood cell production, while the effects on white cells may contribute towards their established role in immune responses. More recently, the same group has also reported that 2-AG acts via cannabinoid CB2 receptors to cause haematopoietic cell migration and this effect was synergistic with interleukin-3 and granulocyte-CSF (Jorda et al., 2002). This may indicate that 2-AG is important in immune cell mobilization."…

…"The effects of cannabinoids and the physiological/pathophysiological actions of endocannabinoids on blood cells is clearly an important and fertile area for research. To date, much work in this area has emanated from Professor Maccarrone's group and includes important findings such as endocannabinoids being thrombogenic. However, platelets may also act as an important site of endocannabinoid metabolism, perhaps regulating their circulating levels. It is tempting to speculate that role of endocannabinoids in both vascular control and thrombosis may be governed by the relationship between the endothelium and platelets (Figure 1)."

- *School of Biomedical Sciences, University of Nottingham Medical School, Nottingham, UK*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2190025/

Endothelium - the tissue which forms a single layer of cells lining various organs and cavities of the body, especially the blood vessels, heart, and lymphatic vessels. It is formed from the embryonic mesoderm. *(Oxford/Google)*
thrombogenesis / thrombogenic - the formation of a thrombus (blood clotting) *(Merriam-webster)*
haematopoiesis - the production of blood cells and platelets, which occurs in the bone marrow. (Oxford/Google)

Blood Brain Barrier

Endocannabinoids modulate human blood-brain barrier permeability in vitro.

"Anandamide (10 µM) and oleoylethanolamide (OEA, 10 µM) decreased BBB [Blood Brain Barrier]

permeability (i.e. increased resistance). "…

-School of Medicine, University of Nottingham, Royal Derby Hospital, Derby, UK
https://www.ncbi.nlm.nih.gov/pubmed/25651941

Barrier Mechanisms in the Developing Brain

"These interfaces are referred to as "the" blood–brain barrier. It is widely believed that in embryos and newborns, this barrier is immature or "leaky," rendering the developing brain more vulnerable to drugs or toxins entering the fetal circulation from the mother."

-Department of Pharmacology, The University of Melbourne, Parkville, VIC, Australia
-Edited by: Joana A. Palha, University of Minho, Portugal
-Reviewed by: Jason B. Wu, Cedars-Sinai Medical Center, USA
-Adam Chodobski, Brown University, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314990/

Bone Loss & Fractures

Endocannabinoids and the regulation of bone metabolism

"In mammals, including humans, bone metabolism is manifested as an ongoing modelling/remodelling process whereby the bone mineralised matrix is being continuously renewed. Recently, the main components of the endocannabinoid system have been reported in the skeleton. Osteoblasts, the bone forming cells, and other cells of the osteoblastic lineage, as well as osteoclasts, the bone resorbing cells, and their precursors, synthesise the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG). CB(1) cannabinoid receptors are present in sympathetic nerve terminals in close proximity to osteoblasts. Activation of these CB(1) receptors by elevated bone 2-AG levels communicates brain-to-bone signals as exemplified by traumatic brain injury-induced stimulation of bone formation. In this process, the retrograde CB(1) signalling inhibits noradrenaline release and alleviates the tonic sympathetic restrain of bone formation. CB(2) receptors are expressed by osteoblasts and osteoclasts. Their activation stimulates bone formation and suppresses bone resorption. CB(2)-deficient mice display a markedly accelerated age-related bone loss. Ovariectomy-induced bone loss can be both prevented and rescued by a CB(2) specific agonist. Hence, synthetic CB(2) ligands, which are stable and orally available, provide a basis for developing novel anti-osteoporotic therapies, free of psychotropic effects. The CNR2 gene (encoding CB(2)) in women is associated with low bone mineral density, offering an assay for identifying females at risk of developing osteoporosis."

-Bone Laboratory, The Hebrew University of Jerusalem, Jerusalem, Israel.
https://pubmed.ncbi.nlm.nih.gov/18426503

Regulation of skeletal remodeling by the endocannabinoid system

"Since the discovery of the endocannabinoid system, its presence and involvement have been reported in a handful of biological systems. Recently, the skeleton has been identified as a major endocannabinoid target through both the neuronal CB1 and predominantly peripheral CB2 cannabinoid receptors. CB1 is present in sympathetic nerve terminals in bone, whereas CB2 is expressed in osteoblasts and osteoclasts, the respective bone-forming and -resorbing cells. Furthermore, the skeleton appears as the main system physiologically regulated by CB2. CB2-deficient mice show a markedly accelerated age-related bone loss and the CB2 locus in women is associated with low bone density and osteoporotic fractures. Since activation of CB2 attenuates experimentally induced bone loss by inhibiting bone resorption and stimulating bone formation, and because synthetic cannabinoids are stable and orally available, a therapy based on synthetic CB2 agonists is a promising novel target for antiosteoporotic drug development."

-Bone Laboratory, The Hebrew University of Jerusalem, Jerusalem, Israel.
https://pubmed.ncbi.nlm.nih.gov/17646266/

Bone Health and Osteoporosis: A Report of the Surgeon General.
The Basics of Bone in Health and Disease

"Many bone disorders are local, affecting only a small region of the skeleton. Inflammation can lead to bone loss, probably through the production of local resorbing factors by the inflammatory white cells. This process can occur around the affected joints in patients with arthritis. Bacterial infections, such as severe gum inflammation or periodontal disease, can produce loss of the bones around the teeth, and osteomyelitis can produce a loss of bone at the site of infection. This type of bone loss is due to the direct damaging effect of bacterial products as well as the production of resorbing factors by white cells. Paget's disease is a multifaceted condition in which the first change is the formation of large, highly active, and unregulated osteoclasts that produce abnormal bone resorption. The precise cause of Paget's disease is not known, but it appears to be the consequence of both genetic factors and environmental factors, possibly a viral infection. The osteoblasts try to repair this damage by increasing bone formation. However, the normal bone architecture has been disrupted, leading to weak bones and the potential for fractures and deformities (even though the bones may appear dense on an x-ray). One reason for this is that the new bone formed is disorderly, "woven" bone, which does not

have the proper alignment of mineral crystals and collagen matrix. In addition, the new bone may not be in the right place to provide strength."…

-Office of the Surgeon General (US). Rockville (MD): Office of the Surgeon General (US); 2004.
https://www.ncbi.nlm.nih.gov/books/NBK45504/

The role of cyclooxygenase-2 in bone repair

"Prostaglandins are important mediators of bone repair, and cyclooxygenases are required for prostaglandin production. Data from animal studies suggest that both non-specific and specific inhibitors of cyclooxygenases impair fracture healing but that this is due to the inhibition of COX-2 and not COX-1. Although these data raise concerns about the use of COX-2-specific inhibitors as anti-inflammatory or anti-analgesic drugs in patients undergoing bone repair, clinical reports have been inconclusive. Because animal data suggest that the effects of COX-2 inhibitors are both dose-dependent and reversible, in the absence of scientifically sound clinical evidence it is suggested that physicians consider short-term administration or other drugs in the management of these patients."…

"Bone repair is a complex process involving the participation of several cell types, signal transduction pathways and biochemical events [1]. Because it is initiated by a skeletal injury, which induces an inflammatory response, chemical mediators of inflammation are also involved in this process [2]. Prostaglandins, a class of compounds known to mediate inflammation and shown to have effects on bone formation and resorption, are essential in bone repair [3]."…

"The role of COX-2 in bone repair has received recent attention because drugs that inhibit prostaglandin production have been shown to inhibit experimental fracture healing [10–12]. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide and are indicated in the treatment of several forms of arthritis, menstrual pain and headache. Their ability to decrease inflammation by inhibiting cyclooxygenase has improved the quality of many people's lives but their use has been limited by gastrointestinal side effects such as dyspepsia, abdominal pain, and, in some instances, gastric or duodenal perforation or bleeding. The development of COX-2 inhibitors (coxibs) was a response to the need for drugs that inhibit prostaglandin production without side effects [13]. Because most NSAIDs inhibit COX-1 and COX-2 with almost equal potency, it was hoped that the development of COX-2-selective drugs would be better tolerated and equally efficacious in managing inflammation. However, whereas the selectivity of this group of compounds might allow inflammation to be inhibited with minimal effects on certain homeostatic mechanisms, their role in bone metabolism and repair remains unclear."…

-Dr. Thomas A Einhorn MD

-Arthritis Research & Therapy
https://arthritis-research.biomedcentral.com/articles/10.1186/ar607

Bone Remodeling

Role of cannabinoids in the regulation of bone remodeling

…"Recent studies have implicated the endocannabinoid system in the regulation of bone cell activity and bone remodeling. These studies showed that endogenous cannabinoid ligands, cannabinoid receptors, and the enzymes responsible for ligand synthesis and breakdown all play important roles in bone mass and in the regulation of bone disease. These findings suggest that the endocannabinoid pathway could be of value as a therapeutic target for the prevention and treatment of bone diseases. Here, we review the role of the skeletal endocannabinoid system in the regulation of bone remodeling in health and disease."

…"Endocannabinoids and their receptors are involved in the regulation of osteoblast differentiation and bone formation. Mice with targeted deletion of the CB1 receptor have been found to develop osteoporosis with increasing age due to reduced bone formation and accumulation of adipocytes in the bone marrow space (Idris et al., 2009). "

…"There is a steadily growing body of evidence suggesting that the skeletal endocannabinoid system plays a significant role in regulating bone mass and bone turnover."…

-Bone and Cancer Group, Edinburgh Cancer Research Centre, The University of Edinburgh, Edinburgh, UK
-Rheumatic Disease Unit, The Centre for Molecular Medicine, The University of Edinburgh, Edinburgh, UK
-Edited by: Vicky E. MacRae, The University of Edinburgh, UK
-Reviewed by: Paula H. Stern, Northwestern University Feinberg School of Medicine, USA; Alun Hughes, University of St Andrews, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499879/

Peripheral cannabinoid receptor, CB2, regulates bone mass.

"These results demonstrate that the endocannabinoid system is essential for the maintenance of normal bone mass by osteoblastic and osteoclastic CB2 signaling. Hence, CB2 offers a molecular target for the diagnosis and treatment of osteoporosis, the most prevalent degenerative disease in developed countries."

Bone Laboratory, Hebrew University of Jerusalem, Jerusalem 91120, Israel.
https://www.ncbi.nlm.nih.gov/pubmed/16407142

Bone Spurs
Bone tumor (Bone Cancer Overview)
Borderline Personality Disorder
Botox Injections (Botox Treatment)
Botox to Treat Multiple Sclerosis (MS)
Botox Treatment
Botox Treatment (Botox Treatment)
Botulism
Bourbon Virus
bovine spongiform encephalopathy (Mad Cow Disease)
Bowel Diversion Surgery Ileostomy, Colostomy
Bp-Br
BPD (Borderline Personality Disorder)
BPH (Benign Prostatic Hyperplasia)
BPH vs. Prostatitis (Prostatitis vs BPH Enlarged Prostate Gland)
Braces and Retainers (Dental Braces)
Brachytherapy
Bradley Method for Childbirth (Childbirth Class Options)

Brain

Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA

..."Thus, DHA is quantitatively the most important omega-3 PUFA in the brain."...

-Faculty of Health and Social Sciences, Bournemouth University, Bournemouth, UK

https://www.frontiersin.org/articles/10.3389/fnagi.2015.00052/full

Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain

"Cannabinoid receptors were distributed in a heterogeneous fashion throughout the adult human brain and spinal cord. The allocortex contained very high concentrations of cannabinoid receptor binding sites in the dentate gyrus, Ammons's horn and subiculum of the hippocampal formation; high concentrations of receptors were also present in the entorhinal cortex and amygdaloid complex. Cannabinoid receptor binding sites were also present throughout all regions of the neocortex, where they showed a marked variation in density between the primary, secondary and associational cortical regions: the greatest densities of receptors were present in

the associational cortical regions of the frontal and limbic lobes, with moderate densities in the secondary sensory and motor cortical regions, and with the lowest densities of receptors in the primary sensory and motor cortical regions. Relatively high concentrations of cannabinoid receptors were consistently seen in cortical regions of the left (dominant) hemisphere, known to be associated with verbal language functions. In all of the cortical regions, the pattern and density of receptor labelling followed the neocortical laminar organization, with the greatest density of receptors localized in two discrete bands--a clearly delineated narrow superficial band which coincided with lamina I and a deeper broader, conspicuous band of labelling which corresponded to laminae V and VI. Labelling in the intervening cortical laminae (II-IV) showed lower densities, with a well delineated narrow band of label in the middle of laminae IV in the associational cortical regions. The thalamus showed a distinctive heterogeneous distribution of cannabinoid receptors, with the highest concentration of receptors localized in the mediodorsal nucleus, anterior nuclear complex, and in the midline and intralaminar complex of nuclei, i.e. in thalamic nuclei which have connectional affiliations with the associational cortical areas. The basal ganglia showed a distinctive heterogeneous pattern of receptor binding, with the very highest concentrations in the globus pallidus internus, moderate concentrations in the globus pallidus externus and ventral pallidum, and moderately low levels of binding throughout the striatal complex. In the midbrain, some of the highest levels of cannabinoid receptor binding sites in the human brain were present in the substantia nigra pars reticulata, with very low levels of labelling in all other midbrain areas. The highest densities of cannabinoid receptor binding in the hindbrain were localized in the molecular layer of the cerebellar cortex and the dorsal motor nucleus of the vagus, with moderate densities of receptors in the nucleus of the solitary tract. The spinal cord showed very low levels of receptor binding. Studies on the distribution of cannabinoid receptors in the fetal and neonatal human brain showed similar patterns of receptor distribution to that observed in the adult human brain, except that the density of receptor binding was generally markedly higher, especially in the basal ganglia and substantia nigra. The pattern of cannabinoid receptor labelling in the striatum showed a striking patchy pattern of organization which was especially conspicuous in the fetal brain. These results show that cannabinoid receptor binding sites in the human brain are localized mainly in: forebrain areas associated with higher cognitive functions; forebrain, midbrain and hindbrain areas associated with the control of movement; and in hindbrain areas associated with the control of motor and sensory functions of the autonomic nervous system. “

-Department of Anatomy, School of Medicine, University of Auckland, New Zealand.
https://pubmed.ncbi.nlm.nih.gov/9472392/

Oiling the Brain: A Review of Randomized Controlled Trials of Omega-3 Fatty Acids in Psychopathology across the Lifespan

…"Studies have further indicated that n-3 PUFA may affect receptor properties or activation of signal transduction by receptors [30]. Electrical impulse conduction is dependent on the exchange of ions through the cell membrane, which relies on the fluidity and physiological structure of cell membranes. Furthermore, there are indications that PUFA are involved in the synthesis and activities of brain peptides [19], which are involved in modulating the activities of neurotransmitters [32]. n-3 PUFA are also thought to influence gene expression of a range of enzymes required for important neural functions including synaptic transduction, ion channel formation, energy metabolism and formulation of proteins vital for brain development and function [22].

Regular delivery of oxygen and nutrients via the blood is also critical for optimal brain function, and psychopathology is associated with both reduced cerebral blood flow and transportation of glucose, the brain's primary energy source, to brain regions as required. In this regard, n-3 PUFA are associated with production of nitric oxide [33], as well as anti-inflammatory and vasodilatory eicosanoids (notably PGI2), and are known to assist in endothelial-dependent vasodilation [10]. They have also been associated with substantially increased transport of glucose across the blood-brain barrier [34,35]. Therefore, it is also possible that their primary influence on brain function includes improved cerebral blood flow and blood-brain barrier integrity [36]. This notion is supported by the high co-morbidity between cardiovascular disease and psychopathology, indicative of a common underlying vascular pathology that may be mediated by lifestyle factors such as suboptimal levels of n-3 PUFA [37].

A review of controlled animal studies [30] concluded that there is sufficient evidence of a role for n-3 PUFA in improving learning and behavior. A large body of research has investigated n-3 PUFA in infant development, which is also reviewed elsewhere [38]."…

-Nutritional Physiology Research Centre, Sansom Institute for Health Research, University of South Australia
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257637/

Evolutionary aspects of diet: the omega-6/omega-3 ratio and the brain

"Several sources of information suggest that human beings evolved on a diet that had a ratio of omega-6 to omega-3 fatty acids (FA) of about 1/1; whereas today, Western diets have a ratio of 10/1 to 20-25/1, indicating that Western diets are deficient in omega-3 FA compared with the diet on which humans evolved and their genetic patterns were established. Omega-6 and omega-3 FA are not interconvertible in the human body and are important components of

practically all cell membranes. Studies with nonhuman primates and human newborns indicate that docosahexaenoic acid (DHA) is essential for the normal functional development of the brain and retina, particularly in premature infants. DHA accounts for 40% of the membrane phospholipid FA in the brain. Both eicosapentaenoic acid (EPA) and DHA have an effect on membrane receptor function and even neurotransmitter generation and metabolism. There is growing evidence that EPA and DHA could play a role in hostility and violence in addition to the beneficial effects in substance abuse disorders and alcoholism. The balance of omega-6 and omega-3 FA is important for homeostasis and normal development throughout the life cycle."

-The Center for Genetics, Nutrition and Health, Washington, DC, USA
https://pubmed.ncbi.nlm.nih.gov/21279554

Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain

"Two well-characterized cannabinoid receptors (CBrs), CB1 and CB2, mediate the effects of cannabinoids and marijuana use, with functional evidence for other CBrs. CB1 receptors are expressed primarily in brain and peripheral tissues. For over a decade several laboratories were unable to detect CB2 receptors in brain and were known to be intensely expressed in peripheral and immune tissues and have traditionally been referred to as peripheral CB2 CBrs. We have reported the discovery and functional presence of CB2 cannabinoid receptors in mammalian brain that may be involved in depression and drug abuse and this was supported by reports of identification of neuronal CB2 receptors that are involved in emesis. We used RT-PCR, immunoblotting, hippocampal cultures, immunohistochemistry, transmission electron microscopy, and stereotaxic techniques with behavioral assays to determine the functional expression of CB2 CBrs in rat brain and mice brain exposed to chronic mild stress (CMS) or those treated with abused drugs. RT-PCR analyses supported the expression of brain CB2 receptor transcripts at levels much lower than those of CB1 receptors. In situ hybridization revealed CB2 mRNA in cerebellar neurons of wild-type but not of CB2 knockout mice. Abundant CB2 receptor immunoreactivity (iCB2) in neuronal and glial processes was detected in brain and CB2 expression was detected in neuron-specific enolase (NSE) positive hippocampal cell cultures. The effect of direct CB2 antisense oligonucleotide injection into the brain and treatment with JWH015 in motor function and plus-maze tests also demonstrated the functional presence of CB2 cannabinoid receptors in the central nervous system (CNS). Thus, contrary to the prevailing view that CB2 CBrs are restricted to peripheral tissues and predominantly in immune cells, we demonstrated that CB2 CBrs and their gene transcripts are widely distributed in the brain. This multifocal expression of CB2 immunoreactivity in brain suggests that CB2 receptors may play

broader roles in the brain than previously anticipated and may be exploited as new targets in the treatment of depression and substance abuse."

-Department of Biology, William Paterson University, Wayne, NJ, USA.
https://pubmed.ncbi.nlm.nih.gov/17105950/

Roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during ageing

"Among various organs, in the brain, the fatty acids most extensively studied are omega-3 fatty acids. Alpha-linolenic acid (18:3omega3) deficiency alters the structure and function of membranes and induces minor cerebral dysfunctions, as demonstrated in animal models and subsequently in human infants. Even though the brain is materially an organ like any other, that is to say elaborated from substances present in the diet (sometimes exclusively), for long it was not accepted that food can have an influence on brain structure, and thus on its function. Lipids, and especially omega-3 fatty acids, provided the first coherent experimental demonstration of the effect of diet (nutrients) on the structure and function of the brain. In fact the brain, after adipose tissue, is the organ richest in lipids, whose only role is to participate in membrane structure. First it was shown that the differentiation and functioning of cultured brain cells requires not only alpha-linolenic acid (the major component of the omega-3, omega3 family), but also the very long omega-3 and omega-6 carbon chains (1). It was then demonstrated that alpha-linolenic acid deficiency alters the course of brain development, perturbs the composition and physicochemical properties of brain cell membranes, neurones, oligodendrocytes, and astrocytes (2). This leads to physicochemical modifications, induces biochemical and physiological perturbations, and results in neurosensory and behavioural upset (3). Consequently, the nature of polyunsaturated fatty acids (in particular omega-3) present in formula milks for infants (premature and term) conditions the visual and cerebral abilities, including intellectual. Moreover, dietary omega-3 fatty acids are certainly involved in the prevention of some aspects of cardiovascular disease (including at the level of cerebral vascularization), and in some neuropsychiatric disorders, particularly depression, as well as in dementia, notably Alzheimer's disease. Recent results have shown that dietary alpha-linolenic acid deficiency induces more marked abnormalities in certain cerebral structures than in others, as the frontal cortex and pituitary gland are more severely affected. These selective lesions are accompanied by behavioural disorders more particularly affecting certain tests (habituation, adaptation to new situations). Biochemical and behavioural abnormalities are partially reversed by a dietary phospholipid supplement, especially omega-3-rich egg yolk extracts or pig brain. A dose-effect study showed that animal phospholipids are more effective than plant phospholipids to reverse

the consequences of alpha-linolenic acid deficiency, partly because they provide very long preformed chains. Alpha-linolenic acid deficiency decreases the perception of pleasure, by slightly altering the efficacy of sensory organs and by affecting certain cerebral structures. Age-related impairment of hearing, vision and smell is due to both decreased efficacy of the parts of the brain concerned and disorders of sensory receptors, particularly of the inner ear or retina. For example, a given level of perception of a sweet taste requires a larger quantity of sugar in subjects with alpha-linolenic acid deficiency. In view of occidental eating habits, as omega-6 fatty acid deficiency has never been observed, its impact on the brain has not been studied. In contrast, omega-9 fatty acid deficiency, specifically oleic acid deficiency, induces a reduction of this fatty acid in many tissues, except the brain (but the sciatic nerve is affected). This fatty acid is therefore not synthesized in sufficient quantities, at least during pregnancy-lactation, implying a need for dietary intake. It must be remembered that organization of the neurons is almost complete several weeks before birth, and that these neurons remain for the subject's life time. Consequently, any disturbance of these neurons, an alteration of their connections, and impaired turnover of their constituents at any stage of life, will tend to accelerate ageing. The enzymatic activities of sytivities of synthesis of long-chain polyunsaturated fatty acids from linoleic and alpha-linolenic acids are very limited in the brain: this organ therefore depends on an exogenous supply. Consequently, fatty acids that are essential for the brain are arachidonic acid and cervonic acid, derived from the diet, unless they are synthesized by the liver from linoleic acid and alpha-linolenic acid. The age-related reduction of hepatic desaturase activities (which participate in the synthesis of long chains, together with elongases) can impair turnover of cerebral membranes. In many structures, especially in the frontal cortex, a reduction of cervonic and arachidonic acids is observed during ageing, predominantly associated with a reduction of phosphatidylethanolamines (mainly in the form of plasmalogens). Peroxisomal oxidation of polyunsaturated fatty acids decreases in the brain during ageing, participating in decreased turnover of membrane fatty acids, which are also less effectively protected against peroxidation by free radicals."

-INSERM Research Director. Unit U26 Neuro-pharmaco-nutrition. Hopital Fernand Widal, 200 rue du Faubourg Saint Denis

https://pubmed.ncbi.nlm.nih.gov/15129302/

■■■

…"Inflammatory responses occur in the brain in many central nervous system (CNS) diseases, including autoimmune diseases, neurodegenerative diseases like Alzheimer's (AD) and Parkinson's disease (PD), and epilepsy. Inflammatory responses in the brain can enhance neuronal excitability, injure cells, and increase blood-brain barrier permeability to various

molecules [159–161]. Inflammation-associated CNS diseases result from activation of the brain's resident immune cells and microglia, which produce pro-inflammatory markers [162]. These inflammation processes also involve both the innate and adaptive immune systems and resemble immune responses to systemic infection. Cytokines and TLRs are major inflammatory mediators in the transition between innate and adaptive. Inflammatory responses in the CNS may also be triggered by endogenous ligands recognized by TLRs. DAMPs, such as heat-shock proteins and extracellular matrix degradation molecules, entering the brain through a damaged blood-brain barrier may initiate inflammatory responses. The CNS inflammatory response is strong in reaction to both infectious agents and brain injury,such as tissue damage observed following ischemic, traumatic, or excitotoxic brain injury, or seizure [160, 163, 164].”...

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548

See also Aging , Microglial & Glial Cells

Brain Aneurysm

Also called Cerebral Aneurysm

“A cerebral aneurysm (also known as a brain aneurysm) is a weak or thin spot on an artery in the brain that balloons or bulges out and fills with blood. The bulging aneurysm can put pressure on the nerves or brain tissue. It may also burst or rupture, spilling blood into the surrounding tissue (called a hemorrhage).”....

- National Institute of Neurological Disorders

https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Cerebral-Aneurysms-Fact-Sheet

■■■

“A brain aneurysm (AN-yoo-riz-um) is a bulge or ballooning in a blood vessel in the brain. It often looks like a berry hanging on a stem. A brain aneurysm can leak or rupture, causing bleeding into the brain (hemorrhagic stroke). Most often a ruptured brain aneurysm occurs in the space

between the brain and the thin tissues covering the brain. This type of hemorrhagic stroke is called a subarachnoid hemorrhage."…

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/brain-aneurysm/symptoms-causes/syc-20361483

The Role of Omega-3 Polyunsaturated Fatty Acids in Stroke

"Stroke is the third commonest cause of death following cardiovascular diseases and cancer. In particular, in recent years, the morbidity and mortality of stroke keep remarkable growing. However, stroke still captures people attention far less than cardiovascular diseases and cancer. Past studies have shown that oxidative stress and inflammation play crucial roles in the progress of cerebral injury induced by stroke. Evidence is accumulating that the dietary supplementation of fish oil exhibits beneficial effects on several diseases, such as cardiovascular diseases, metabolic diseases, and cancer. Omega-3 polyunsaturated fatty acids (n-3 PUFAs), the major component of fish oil, have been found against oxidative stress and inflammation in cardiovascular diseases. And the potential of n-3 PUFAs in stroke treatment is attracting more and more attention. In this review, we will review the effects of n-3 PUFAs on stroke and mainly focus on the antioxidant and anti-inflammatory effects of n-3 PUFAs."

-Department of Neurosurgery & Brain and Nerve Research Laboratory, The First Affiliated Hospital of Soochow University, China.
https://pubmed.ncbi.nlm.nih.gov/27433289/

Brain Cancer

Importance of the Role of ω-3 and ω-6 Polyunsaturated Fatty Acids in the Progression of Brain Cancer

"Brain cancer is one of the most malignant types of cancer in both children and adults. Brain cancer patients tend to have a poor prognosis and a high rate of mortality. Additionally, 20–40% of all other types of cancer can develop brain metastasis. Numerous pieces of evidence suggest that omega-3-polyunsaturated fatty acids (ω-PUFAs) could potentially be used in the prevention and therapy of several types of cancer. PUFAs and oxylipins are fundamental in preserving physiological events in the nervous system; it is, therefore, necessary to maintain a certain ratio of ω-3 to ω-6 for normal nervous system function. Alterations in PUFAs signaling are involved in

the development of various pathologies of the nervous system, including cancer. It is well established that an omega-6-polyunsaturated fatty acid (ω-6 PUFA)-rich diet has a pro-tumoral effect, whereas the consumption of an ω-3 rich diet has an anti-tumoral effect. This review aims to offer a better understanding of brain cancer and PUFAs and to discuss the role and impact of PUFAs on the development of different types of brain cancer. Considering the difficulty of antitumor drugs in crossing the blood–brain barrier, the therapeutic role of ω-3/ω-6 PUFAs against brain cancer would be a good alternative to consider. We highlight our current understanding of the role of PUFAs and its metabolites (oxylipins) in different brain tumors, proliferation, apoptosis, invasion, angiogenesis, and immunosuppression by focusing on recent research in vitro and in vivo."

-Programa de Doctorado en Ciencias Biomédicas, Facultad de Medicina, Universidad Nacional Autónoma de Mexico (UNAM), Mexico City, Mexico

-Hospital Infantil de Mexico, Federico Gomez, Unidad de Investigacion en Enfermedades Oncologicas, Mexico City, Mexico;

-Molecular Toxicology Interdepartmental Program and Environmental Health Sciences, University of California, USA

-Department of Pathology & Laboratory Medicine, University of California, USA

-Departamento de Biología, Facultad de Química, Universidad Nacional Autonoma de Mexico (UNAM), Mexico City, Mexico

https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7349634/

Delta9-tetrahydrocannabinol [THC] induces apoptosis in C6 glioma cells

"delta9-Tetrahydrocannabinol (THC), the major active component of marijuana, induced apoptosis in C6.[9] glioma cells, as determined by DNA fragmentation and loss of plasma membrane asymmetry. THC stimulated sphingomyelin hydrolysis in C6.[9] glioma cells. THC and N-acetylsphingosine, a cell-permeable ceramide analog, induced apoptosis in several transformed neural cells but not in primary astrocytes or neurons. Although glioma C6.[9] cells expressed the CBI cannabinoid receptor, neither THC-induced apoptosis nor THC-induced sphingomyelin breakdown were prevented by SR141716, a specific antagonist of that receptor. Results thus show that THC-induced apoptosis in glioma C6.[9] cells may rely on a CBI receptor-independent stimulation of sphingomyelin breakdown."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/9771884/

Cannabinoids and gliomas

"Cannabinoids, the active components of Cannabis sativa L., act in the body by mimicking

endogenous substances--the endocannabinoids--that activate specific cell surface receptors. Cannabinoids exert various palliative effects in cancer patients. In addition, cannabinoids inhibit the growth of different types of tumor cells, including glioma cells, in laboratory animals. They do so by modulating key cell signaling pathways, mostly the endoplasmic reticulum stress response, thereby inducing antitumoral actions such as the apoptotic death of tumor cells and the inhibition of tumor angiogenesis. Of interest, cannabinoids seem to be selective antitumoral compounds, as they kill glioma cells, but not their non-transformed astroglial counterparts. On the basis of these preclinical findings, a pilot clinical study of Delta(9)-tetrahydrocannabinol (THC) in patients with recurrent glioblastoma multiforme has been recently run. The good safety profile of THC, together with its possible growth-inhibiting action on tumor cells, justifies the setting up of future trials aimed at evaluating the potential antitumoral activity of cannabinoids."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/17952650/

Cannabinoids as potential new therapy for the treatment of gliomas

"Gliomas constitute the most frequent and malignant primary brain tumors. Current standard therapeutic strategies (surgery, radiotherapy and chemotherapeutics, e.g., temozolomide, carmustin or carboplatin) for their treatment are only palliative and survival diagnosis is normally 6-12 months. The development of new therapeutic strategies for the management of gliomas is therefore essential. Interestingly, cannabinoids have been shown to exert antiproliferative effects on a wide spectrum of cells in culture. Of interest, cannabinoids have displayed a great potency in reducing glioma tumor growth either in vitro or in animal experimental models, curbing the growth of xenografts generated by subcutaneous or intratecal injection of glioma cells in immune-deficient mice. Moreover, cannabinoids appear to be selective antitumoral agents as they kill glioma cells without affecting the viability of nontransformed counterparts. A pilot clinical trial on patients with glioblastoma multiforme demonstrated their good safety profile together and remarkable antitumor effects, and may set the basis for further studies aimed at better evaluating the potential anticancer activity of cannabinoids."

-Department of Structural & Functional Biology, Pharmacology Section, Center of Neuroscience, University of Insubria, Via A da Giussano 10, Busto Arsizio (VA), Italy.
https://pubmed.ncbi.nlm.nih.gov/18088200/

Hypothesis: cannabinoid therapy for the treatment of gliomas?

"Gliomas, in particular glioblastoma multiforme or grade IV astrocytoma, are the most frequent

class of malignant primary brain tumours and one of the most aggressive forms of cancer. Current therapeutic strategies for the treatment of glioblastoma multiforme are usually ineffective or just palliative. During the last few years, several studies have shown that cannabinoids-the active components of the plant Cannabis sativa and their derivatives--slow the growth of different types of tumours, including gliomas, in laboratory animals. Cannabinoids induce apoptosis of glioma cells in culture via sustained ceramide accumulation, extracellular signal-regulated kinase activation and Akt inhibition. In addition, cannabinoid treatment inhibits angiogenesis of gliomas in vivo. Remarkably, cannabinoids kill glioma cells selectively and can protect non-transformed glial cells from death. These and other findings reviewed here might set the basis for a potential use of cannabinoids in the management of gliomas."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Avenida Complutense, Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/15275820/

Cannabinoids inhibit the vascular endothelial growth factor pathway in gliomas

"Cannabinoids inhibit tumor angiogenesis in mice, but the mechanism of their antiangiogenic action is still unknown. Because the vascular endothelial growth factor (VEGF) pathway plays a critical role in tumor angiogenesis, here we studied whether cannabinoids affect it. As a first approach, cDNA array analysis showed that cannabinoid administration to mice bearing s.c. gliomas lowered the expression of various VEGF pathway-related genes. The use of other methods (ELISA, Western blotting, and confocal microscopy) provided additional evidence that cannabinoids depressed the VEGF pathway by decreasing the production of VEGF and the activation of VEGF receptor (VEGFR)-2, the most prominent VEGF receptor, in cultured glioma cells and in mouse gliomas. Cannabinoid-induced inhibition of VEGF production and VEGFR-2 activation was abrogated both in vitro and in vivo by pharmacological blockade of ceramide biosynthesis. These changes in the VEGF pathway were paralleled by changes in tumor size. Moreover, intratumoral administration of the cannabinoid Delta9-tetrahydrocannabinol to two patients with glioblastoma multiforme (grade IV astrocytoma) decreased VEGF levels and VEGFR-2 activation in the tumors. Because blockade of the VEGF pathway constitutes one of the most promising antitumoral approaches currently available, the present findings provide a novel pharmacological target for cannabinoid-based therapies."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/15313899

Inhibition of tumor angiogenesis by cannabinoids

”Department Cannabinoids, the active components of marijuana and their derivatives, induce tumor regression in rodents (8). However, the mechanism of cannabinoid antitumoral action in vivo is as yet unknown. Here we show that local administration of a nonpsychoactive cannabinoid to mice inhibits angiogenesis of malignant gliomas as determined by immunohistochemical analyses and vascular permeability assays. In vitro and in vivo experiments show that at least two mechanisms may be involved in this cannabinoid action: the direct inhibition of vascular endothelial cell migration and survival as well as the decrease of the expression of proangiogenic factors (vascular endothelial growth factor and angiopoietin-2) and matrix metalloproteinase-2 in the tumors. Inhibition of tumor angiogenesis may allow new strategies for the design of cannabinoid-based antitumoral therapies. “

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/12514108/

Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation

“Delta9-Tetrahydrocannabinol, the main active component of marijuana, induces apoptosis of transformed neural cells in culture. Here, we show that intratumoral administration of Delta9-tetrahydrocannabinol and the synthetic cannabinoid agonist WIN-55,212-2 induced a considerable regression of malignant gliomas in Wistar rats and in mice deficient in recombination activating gene 2. Cannabinoid treatment did not produce any substantial neurotoxic effect in the conditions used. Experiments with two subclones of C6 glioma cells in culture showed that cannabinoids signal apoptosis by a pathway involving cannabinoid receptors, sustained ceramide accumulation and Raf1/extracellular signal-regulated kinase activation. These results may provide the basis for a new therapeutic approach for the treatment of malignant gliomas.”

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/10700234/

Cannabinoids inhibit glioma cell invasion by down-regulating matrix metalloproteinase-2 expression

“Cannabinoids, the active components of Cannabis sativa L. and their derivatives, inhibit tumor growth in laboratory animals by inducing apoptosis of tumor cells and impairing tumor

angiogenesis. It has also been reported that these compounds inhibit tumor cell spreading, but the molecular targets of this cannabinoid action remain elusive. Here, we evaluated the effect of cannabinoids on matrix metalloproteinase (MMP) expression and its effect on tumor cell invasion. Local administration of Delta(9)-tetrahydrocannabinol (THC), the major active ingredient of cannabis, down-regulated MMP-2 expression in gliomas generated in mice, as determined by Western blot, immunofluorescence, and real-time quantitative PCR analyses. This cannabinoid-induced inhibition of MMP-2 expression in gliomas (a) was MMP-2-selective, as levels of other MMP family members were unaffected; (b) was mimicked by JWH-133, a CB(2) cannabinoid receptor-selective agonist that is devoid of psychoactive side effects; (c) was abrogated by fumonisin B1, a selective inhibitor of ceramide biosynthesis; and (d) was also evident in two patients with recurrent glioblastoma multiforme. THC inhibited MMP-2 expression and cell invasion in cultured glioma cells. Manipulation of MMP-2 expression by RNA interference and cDNA overexpression experiments proved that down-regulation of this MMP plays a critical role in THC-mediated inhibition of cell invasion. Cannabinoid-induced inhibition of MMP-2 expression and cell invasion was prevented by blocking ceramide biosynthesis and by knocking-down the expression of the stress protein p8. As MMP-2 up-regulation is associated with high progression and poor prognosis of gliomas and many other tumors, MMP-2 down-regulation constitutes a new hallmark of cannabinoid antitumoral activity."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/18339876/

A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme

"Δ9-Tetrahydrocannabinol (THC) and other cannabinoids inhibit tumour growth and angiogenesis in animal models, so their potential application as antitumoral drugs has been suggested. However, the antitumoral effect of cannabinoids has never been tested in humans. Here we report the first clinical study aimed at assessing cannabinoid antitumoral action, specifically a pilot phase I trial in which nine patients with recurrent glioblastoma multiforme were administered THC intratumoraly. The patients had previously failed standard therapy (surgery and radiotherapy) and had clear evidence of tumour progression. The primary end point of the study was to determine the safety of intracranial THC administration. We also evaluated THC action on the length of survival and various tumour-cell parameters. A dose escalation regimen for THC administration was assessed. Cannabinoid delivery was safe and could be achieved without overt psychoactive effects. Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% confidence interval: 15–33). Δ9-

Tetrahydrocannabinol inhibited tumour-cell proliferation in vitro and decreased tumour-cell Ki67 immunostaining when administered to two patients. The fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain
-Department of Neurosurgery, Hospital Universitario de Canarias, La Laguna, Tenerife, Spain
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2360617/

Predominant CB2 receptor expression in endothelial cells of glioblastoma in humans

"Background and objectives: The most abundant malignant brain tumor in human is glioblastoma and patients with this type of tumor have a poor prognosis with high mortality. Glioblastoma are characterized particularly by fast growth and a dependence on blood vessel formation for survival. Cannabinoids (CBs) inhibit tumor growth by inducing apoptosis of tumor cells and impairing tumor angiogenesis. The distribution of CB1 and CB2 receptors in glioblastoma and associated endothelial vessels is still unknown."…

Conclusions: The abundant expression and distribution of CB2 receptors in glioblastoma and particularly endothelial cells of glioblastoma indicate that impaired tumor growth in presence of CB may be associated with CB2 activation. Selective CB2 agonists might become important targets attenuating vascular endothelial growth factor (VEGF) signalling and thereby diminishing neoangiogenesis and glioblastoma growth."

-Department of Anaesthesiology and Operative Intensive Care, Kantonsspital Lucerne, CH-6000 Lucerne 16, Switzerland.
https://pubmed.ncbi.nlm.nih.gov/19480992/

Opposite changes in cannabinoid CB1 and CB2 receptor expression in human gliomas

"Gliomas are the most important group of malignant primary brain tumors and one of the most aggressive forms of cancer. During the last years, several studies have demonstrated that cannabinoids induce apoptosis of glioma cells and inhibit angiogenesis of gliomas in vivo. As the effects of cannabinoids rely on CB(1) and CB(2) receptors activation, the aim of the present study was to investigate both receptors protein expression in cellular membrane homogenates of human glial tumors using specific antibodies raised against these proteins. Additionally, we studied the functionality of the cannabinoid receptors in glioblastomas by using WIN 55,212-2

stimulated [(35)S]GTPgammaS binding. Western blot analysis showed that CB(1) receptor immunoreactivity was significantly lower in glioblastoma multiforme (-43%, n=10; p<0.05) than in normal post-mortem brain tissue (n=16). No significant differences were found for astrocytoma (n=6) and meningioma (n=8) samples. Conversely, CB(2) receptor immunoreactivity was significantly greater in membranes of glioblastoma multiforme (765%, n=9; p<0.05) and astrocytoma (471%, n=4; p<0.05) than in control brain tissue (n=10). Finally, the maximal stimulation of [(35)S]GTPgammaS binding by WIN 55,212-2 was significantly lower in glioblastomas (134+/-4%) than in control membranes (183+/-2%; p<0.05). The basal [(35)S]GTPgammaS binding and the EC(50) values were not significantly different between both groups. The present results demonstrate opposite changes in CB(1) and CB(2) receptor protein expression in human gliomas. These changes may be of interest for further research about the therapeutic effects of cannabinoids in glial tumors."

-Department of Pharmacology, University of the Basque Country, Leioa, Bizkaia, Spain.
https://pubmed.ncbi.nlm.nih.gov/20307616/

Cannabinoid CB2 receptor: a new target for controlling neural cell survival?

"Two types of cannabinoid receptor have been cloned and characterized. Whereas CB1 receptors are ubiquitously expressed in neurons of the CNS, CB2 receptors have been thought to be absent from the CNS. Recent data now question this notion and support the expression of CB2 receptors in microglial cells, astrocytes and even some neuron subpopulations. This discrete distribution makes CB2 receptors interesting targets for treating neurological disorders because CB2-selective agonists lack psychoactivity. Here, we review evidence supporting the idea that CB2 receptors are implicated in the control of fundamental neural cell processes, such as proliferation and survival, and that their pharmacological manipulation might be useful for both delaying the progression of neurodegenerative disorders and inhibiting the growth of glial tumors."

-Department of Biochemistry and Molecular Biology, Faculty of Medicine, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/17141334/

Down-regulation of tissue inhibitor of metalloproteinases-1 in gliomas: a new marker of cannabinoid antitumoral activity?

"Cannabinoids, the active components of Cannabis sativa L. and their derivatives, inhibit tumor growth in laboratory animals by inducing apoptosis of tumor cells and inhibiting tumor angiogenesis. It has also been reported that cannabinoids inhibit tumor cell invasiveness, but the molecular targets of this cannabinoid action remain elusive. Here we evaluated the effects of

cannabinoids on the expression of tissue inhibitors of metalloproteinases (TIMPs), which play critical roles in the acquisition of migrating and invasive capacities by tumor cells. Local administration of Delta(9)-tetrahydrocannabinol (THC), the major active ingredient of cannabis, down-regulated TIMP-1 expression in mice bearing subcutaneous gliomas, as determined by Western blot and immunofluorescence analyses. This cannabinoid-induced inhibition of TIMP-1 expression in gliomas (i) was mimicked by JWH-133, a selective CB(2) cannabinoid receptor agonist that is devoid of psychoactive side effects, (ii) was abrogated by fumonisin B1, a selective inhibitor of ceramide synthesis de novo, and (iii) was also evident in two patients with recurrent glioblastoma multiforme (grade IV astrocytoma). THC also depressed TIMP-1 expression in cultures of various human glioma cell lines as well as in primary tumor cells obtained from a glioblastoma multiforme patient. This action was prevented by pharmacological blockade of ceramide biosynthesis and by knocking-down the expression of the stress protein p8. As TIMP-1 up-regulation is associated with high malignancy and negative prognosis of numerous cancers, TIMP-1 down-regulation may be a hallmark of cannabinoid-induced inhibition of glioma progression."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/17675107/

Distinctive pattern of cannabinoid receptor type II (CB2) expression in adult and pediatric brain tumors

"The efficacy of cannabinoids against high-grade glioma in animal models, mediated by two specific receptors, CB1 and CB2, raised promises for targeted treatment of the most frequent and malignant primary brain tumors. Unlike the abundantly expressed CB1, the CB2 receptor shows a restricted distribution in normal brain. Although brain tumors constitute the second most common malignancy in children and the prevalence of histological types of brain tumors vary significantly between the adult and pediatric populations, cannabinoid receptor expression in pediatric tumors remains unknown. In the present study, we compared the expression of the CB2 receptor in paraffin-embedded sections from primary brain tumors of adult and pediatric patients. Most glioblastomas expressed very high levels of CB2 receptors and the expression correlated with tumor grade. Interestingly, some benign pediatric astrocytic tumors, such as subependymal giant cell astrocytoma (SEGA), which may occasionally cause mortality owing to progressive growth, also displayed high CB2 immunoreactivity. The high levels of CB2 expression would predestine those tumors to be vulnerable to cannabinoid treatment. In contrast, all examined cases of embryonal tumors (medulloblastoma and S-PNET), the most frequently diagnosed malignant brain tumors in childhood, showed no or trace CB2 immunoreactivity. Our

results suggest that the CB2 receptor expression depends primarily on the histopathological origin of the brain tumor cells and differentiation state, reflecting the tumor grade."

-Department of Biochemistry and Clinical Chemistry, Medical University of Warsaw, Poland.
https://pubmed.ncbi.nlm.nih.gov/17239827/

Delta 9-tetrahydrocannabinol [THC] inhibits cell cycle progression by downregulation of E2F1 in human glioblastoma multiforme cells

"Background: The active components of Cannabis sativa L., Cannabinoids, traditionally used in the field of cancer for alleviation of pain, nausea, wasting and improvement of well-being have received renewed interest in recent years due to their diverse pharmacologic activities such as cell growth inhibition, anti-inflammatory activity and induction of tumor regression. Here we used several experimental approaches, which identified delta-9-tetrahydrocannabinol (Delta(9)-THC) as an essential mediator of cannabinoid antitumoral action."…

"Conclusions: Delta(9)-THC is shown to significantly affect viability of GBM [glioblastoma multiforme] cells via a mechanism that appears to elicit G(1) arrest due to downregulation of E2F1 and Cyclin A. Hence, it is suggested that Delta(9)-THC and other cannabinoids be implemented in future clinical evaluation as a therapeutic modality for brain tumors."

-The Mina and Everard Goodman Faculty of Life Science, Bar-Ilan University, Ramat-Gan, Israel.
https://pubmed.ncbi.nlm.nih.gov/17934890

■■■

"Recently, cannabinoids (CBs) have been shown to possess antitumor properties. Because the psychoactivity of cannabinoid compounds limits their medicinal usage, we undertook the present study to evaluate the in vitro antiproliferative ability of cannabidiol (CBD), a nonpsychoactive cannabinoid compound, on U87 and U373 human glioma cell lines."…

"We also show, for the first time, that the antiproliferative effect of CBD was correlated to induction of apoptosis, as determined by cytofluorimetric analysis and single-strand DNA staining, which was not reverted by cannabinoid antagonists. Finally, CBD, administered s.c. to nude mice at the dose of 0.5 mg/mouse, significantly inhibited the growth of subcutaneously implanted U87 human glioma cells. In conclusion, the nonpsychoactive CBD was able to produce a significant antitumor activity both in vitro and in vivo, thus suggesting a possible application of CBD as an antineoplastic agent."

-Department of Pharmacology, University of Milan, Milan, Italy.

https://pubmed.ncbi.nlm.nih.gov/14617682/

…"While many laboratories have reported that cannabinoids induce apoptosis in various tumor subtypes, including astrocytomas, the requirement for CB1 and CB2 in mediating this therapeutic effect has not yet been demonstrated. This point is especially relevant when considering that many of these studies used high concentrations of cannabinoids known to bypass CB1 and CB2 receptor activation. Here we demonstrate that cannabinoid receptors and ERK1/2 indeed mediate this therapeutic effect, but only when these compounds are applied at submicromolar concentrations and the expression level of these receptors remains low. **Conversely, high concentrations of cannabinoids kill all astrocytoma subclones** independently of CB1, CB2 and AKT, yet still through a mechanisms involving ERK1/2. We also show that increased expression of CB1 and CB2 receptor allows for their coupling to additional kinases, especially AKT, the result of which eliminates the ability of cannabinoids to induce apoptosis even though these receptors still couple to ERK1/2."…

- Department of Pharmacology, University of Washington, Seattle, Washington, USA

- Graduate Program in Neurobiology and Behavior, University of Washington, Seattle, Washington, USA- Department of Neurology, University of Washington, Seattle, Washington, USA

- Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington, USA

-City of Hope National Medical Center, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2806825/

5-Lipoxygenase and anandamide hydrolase (FAAH) mediate the antitumor activity of cannabidiol, a non-psychoactive cannabinoid

"It has been recently reported that cannabidiol (CBD), a non-psychoactive cannabinoid, is able to kill glioma cells, both in vivo and in vitro, independently of cannabinoid receptor stimulation. However, the underlying biochemical mechanisms were not clarified. In the present study, we performed biochemical analysis of the effect of CBD both in vivo, by using glioma tumor tissues excised from nude mice, and in vitro, by using U87 glioma cells. In vivo exposure of tumor tissues to CBD significantly decreased the activity and content of 5-lipoxygenase (LOX, by approximately 40%), and of its end product leukotriene B4 (approximately 25%). In contrast cyclooxygenase (COX)-2 activity and content, and the amount of its end product prostaglandin E2, were not affected by CBD. In addition, in vivo treatment with CBD markedly stimulated (approximately 175%) the activity of fatty acid amide hydrolase (FAAH), the main anandamide-degrading enzyme, while decreasing anandamide content (approximately 30%) and binding to CB1 cannabinoid receptors (approximately 25%). In vitro pre-treatment of U87 glioma cells with MK-886, a specific 5-LOX inhibitor, significantly enhanced the antimitotic effect of CBD, whereas the pre-treatment with indomethacin (pan-COX inhibitor) or celecoxib (COX-2 inhibitor), did not alter

CBD effect. The study of the endocannabinoid system revealed that CBD was able to induce a concentration-dependent increase of FAAH activity in U87 cells. Moreover, a significantly reduced growth rate was observed in FAAH-over-expressing U87 cells, compared to wild-type controls. In conclusion, the present investigation indicates that CBD exerts its antitumoral effects through modulation of the LOX pathway and of the endocannabinoid system, suggesting a possible interaction of these routes in the control of tumor growth."

-Department of Pharmacology, Chemotherapy and Toxicology, University of Milan, Milan, Italy.
https://pubmed.ncbi.nlm.nih.gov/18028339/

Inhibition of glioma growth in vivo by selective activation of the CB(2) cannabinoid receptor

"The development of new therapeutic strategies is essential for the management of gliomas, one of the most malignant forms of cancer. We have shown previously that the growth of the rat glioma C6 cell line is inhibited by psychoactive cannabinoids (I. Galve-Roperh et al., Nat. Med., 6: 313-319, 2000). These compounds act on the brain and some other organs through the widely expressed CB(1) receptor. By contrast, the other cannabinoid receptor subtype, the CB(2) receptor, shows a much more restricted distribution and is absent from normal brain. Here we show that local administration of the selective CB(2) agonist JWH-133 at 50 microg/day to Rag-2(-/-) mice induced a considerable regression of malignant tumors generated by inoculation of C6 glioma cells. The selective involvement of the CB(2) receptor in this action was evidenced by: (a) the prevention by the CB(2) antagonist SR144528 but not the CB(1) antagonist SR141716; (b) the down-regulation of the CB(2) receptor but not the CB(1) receptor in the tumors; and (c) the absence of typical CB(1)-mediated psychotropic side effects. Cannabinoid receptor expression was subsequently examined in biopsies from human astrocytomas. A full 70% (26 of 37) of the human astrocytomas analyzed expressed significant levels of cannabinoid receptors. Of interest, the extent of CB(2) receptor expression was directly related with tumor malignancy. In addition, the growth of grade IV human astrocytoma cells in Rag-2(-/-) mice was completely blocked by JWH-133 administration at 50 microg/day. Experiments carried out with C6 glioma cells in culture evidenced the internalization of the CB(2) but not the CB(1) receptor upon JWH-133 challenge and showed that selective activation of the CB(2) receptor signaled apoptosis via enhanced ceramide synthesis de novo. These results support a therapeutic approach for the treatment of malignant gliomas devoid of psychotropic side effects."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, 28040 Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/11479216/

Cannabinoids inhibit the vascular endothelial growth factor pathway in gliomas

"Cannabinoids inhibit tumor angiogenesis in mice, but the mechanism of their antiangiogenic action is still unknown. Because the vascular endothelial growth factor (VEGF) pathway plays a critical role in tumor angiogenesis, here we studied whether cannabinoids affect it. As a first approach, cDNA array analysis showed that cannabinoid administration to mice bearing s.c. gliomas lowered the expression of various VEGF pathway-related genes. The use of other methods (ELISA, Western blotting, and confocal microscopy) provided additional evidence that cannabinoids depressed the VEGF pathway by decreasing the production of VEGF and the activation of VEGF receptor (VEGFR)-2, the most prominent VEGF receptor, in cultured glioma cells and in mouse gliomas. Cannabinoid-induced inhibition of VEGF production and VEGFR-2 activation was abrogated both in vitro and in vivo by pharmacological blockade of ceramide biosynthesis. These changes in the VEGF pathway were paralleled by changes in tumor size. Moreover, intratumoral administration of the cannabinoid Delta9-tetrahydrocannabinol to two patients with glioblastoma multiforme (grade IV astrocytoma) decreased VEGF levels and VEGFR-2 activation in the tumors. Because blockade of the VEGF pathway constitutes one of the most promising antitumoral approaches currently available, the present findings provide a novel pharmacological target for cannabinoid-based therapies."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/15313899/

Brain Fatty Acid-binding Protein and ω-3/ω-6 Fatty Acids

"Malignant gliomas (MG) are highly infiltrative tumors that consistently recur despite aggressive treatment. Brain fatty acid-binding protein (FABP7), which binds docosahexaenoic acid (DHA) and arachidonic acid (AA), localizes to sites of tumor infiltration and is associated with a poor prognosis in MG. Manipulation of FABP7 expression in MG cell lines affects cell migration, suggesting a role for FABP7 in tumor infiltration and recurrence. Here, we show that DHA inhibits and AA stimulates migration in an FABP7-dependent manner in U87 MG cells. We demonstrate that DHA binds to and sequesters FABP7 to the nucleus, resulting in decreased cell migration. This anti-migratory effect is partially dependent on peroxisome proliferator-activated receptor γ, a DHA-activated transcription factor. Conversely, AA-bound FABP7 stimulates cell migration by activating cyclooxygenase-2 and reducing peroxisome proliferator-activated receptor γ levels. Our data provide mechanistic insight as to why FABP7 is associated with a poor prognosis in MG

and suggest that relative levels of DHA and AA in the tumor environment can make a profound impact on tumor growth properties. We propose that FABP7 and its fatty acid ligands may be key therapeutic targets for controlling the dissemination of MG cells within the brain."…

-Department of Oncology, School of Cancer, Engineering and Imaging Sciences, Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada

-Department of Agriculture, Food and Nutritional Sciences, University of Alberta, Edmonton, Alberta, Canada

https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC2978629

Brain Injury (Head Injury)

…"The endocannabinoid system (ECS) participates in the resolution of brain injuries, decreasing vasoconstriction, gliosis, neuroinflammation and excitotoxicity [14] and plays an essential role during critical neurodevelopmental periods such as adolescence [15]. The blockage of cannabinoid receptors (CB1 and CB2) results in more severe sequelae after TBI [16] and prevents the anti-gliotic actions of estradiol [17] and the neuroprotective effects of minocycline [16]. Astrogliosis is commonly assessed by changes in vimentin expression which is an intermediate filament responsible for maintaining astrocyte cell integrity [18]. Vimentin is overexpressed by astrocytes after central nervous system (CNS) injury or in neurodegenerative diseases [19] and its levels are a reliable indicator of reactive astrogliosis in the TBI model [20]."…

"The ECS participates in TBI sequelae decreasing harmful pathways and promoting the resolution of the injury through CB1 and CB2 receptors [14]. CB1 receptor levels decreased after lesion. This decrease could exacerbate the neurological deficit, since animals with high neurological impairments showed lower CB1 levels. In agreement with this observation, CB1 KO mice [49] and animals treated with a CB1 receptor antagonist [16] showed an impaired recovery after trauma that affected edema and neurological score. "…

"In physiological conditions, CB2 is expressed at very low levels, predominantly in non-neuronal cells [14], although it is also present in neural progenitors, neurons and endothelial cells [57,58]. However, CB2 expression increases under neuroinflammation [59] as observed in our TBI model. High CB2 levels were associated to high neurological impairments, perhaps triggered as a rescue mechanism to reduce brain damage since its pharmacological blockage worsens behavioral deficit after TBI [16]. Moreover, CB2 is commonly related to neuroprotective effects like BBB repair [60] or microglia activation [61] and CB2 agonists induce a better recovery after lesion in behavioral tests [62]. "

-Department of Animal Physiology (II), Biology Faculty, Complutense University of Madrid, Madrid, Spain,

-Instituto Cajal, Consejo Superior de Investigaciones Cientificas (CSIC), Madrid, Spain,

Martin Luther University, GERMANY,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4454518/

Therapeutic use of omega-3 fatty acids [n-3FA] in severe head trauma

"Traumatic brain injury (TBI) has long been recognized as a leading cause of traumatic death and disability1–3. Tremendous advances in surgical and intensive care unit (ICU) management of the primary injury, including maintaining adequate oxygenation, controlling intracranial pressure (ICP), and ensuring proper cerebral perfusion, have resulted in reduced mortality3–4. However, the secondary injury phase of TBI is a prolonged pathogenic process is characterized by neuroinflammation, excitatory amino acids, free radicals, and ion imbalance5. There are no approved therapies to directly address these underlying processes. Here we present a case that was intentionally treated with substantial amounts of omega-3 fatty acids (n-3FA) to provide the nutritional foundation for the brain to begin the healing process following severe TBI."…

DISCUSSION

"We are aware of only one report where n-3FA were used, that being the survivor of the Sago Mine accident in January 2006 suffering from hypoxia and exposure to toxic gases, dehydration, and rhabdomyolysis[6]. To our knowledge, this is the first report of specific use of substantial amounts of n-3FA following severe TBI.

It is well-recognized that n-3FA are important for proper neurodevelopment and function [7–8]. However, average Western dietary intakes result in a deficiency of n-3FA and an over-dominant intake of proinflammatory omega-6s (n-6FA). The ratio of n-3:n-6FA in the Western diet can be as low as 1:50. Such imbalance is reflected directly in the composition of neuron membrane phospholipids favoring inflammatory processes9. Arachidonic Acid, the primary n-6FA in the brain, is metabolized by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes to pro-inflammatory eicosanoids that enhance vascular permeability, increase local blood flow, increase infiltration of leukocytes, and enhance production of proinflammatory cytokines[10]. N-3FA attenuate release of these proinflammatory cytokines, decrease COX activity, inhibit formation of proinflammatory eicosanoids and cytokines, and promote levels of anti-inflammatory decosanoids [10–11]. DHA, in particular, promotes neuronal survival[12–14], neurogenesis[15], neurite development[16–17], neuronal cell migration18, synaptogenesis[17], and modulation of inflammatory cascade [19].

Laboratory animal research shows that n-3FA may help improve clinical outcomes when administered prior to or following TBI[20–22], spinal cord injury (SCI)[23], and brain ischemia[24–25]. N-3FA[26], as well as DHA alone[21], significantly reduces the number of injured axons[20–21]. When DHA

was given within an hour of SCI, neuromotor function was maintained but the effect was lost when treatment was delayed four hours [27]. These findings support the idea that treatment with n-3FA represent a promising therapeutic approach for neurotrauma which would be easy to translate to the emergency patient-care arena considering the well-documented safety and tolerability of these compounds [27].

Early nutritional intervention in TBI is underappreciated. Patients not fed within five and seven days after TBI have a two- and four-fold increased likelihood of death, respectively, and decreasing amount of nutrition in the first five days is related to increased mortality rates [28]. Early enteral nutrition after brain injury can be accomplished by PEG[29] or nasogastric tube, even in the Emergency Department. The American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM), published guidelines and only two Grade A recommendations among 49 total recommendations both state that immune enhancing enteral formulations with n-3FA should be used in critically ill surgical patients (including trauma)[30]."

CONCLUSION

"While further research is needed to establish the true advantage to using n-3FA, our experience suggests that benefits may be possible from aggressively adding substantial amounts of n-3FA to optimize the nutritional foundation of severe TBI patients. An optimal nutritional foundation must be in place if the brain is to be given the best opportunity to repair itself. Administration earlier in the course of treatment, even in the Emergency Department setting, has the potential to improve outcomes from this potentially devastating public health problem."

-Brain Health Education and Research Foundation Arlington, VA

-National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 5625 Fishers Lane, Rockville, MD

https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC3518659/

Breastfeeding

The role of essential fatty acids in neural development: implications for perinatal nutrition

"The brain is 60% structural lipid, which universally uses arachidonic acid [omega-6] (AA; 20:4n6) and docosahexaenoic acid [omega-3] (DHA; 22:6n-3) for growth, function, and integrity. Both acids are consistent components of human milk. Experimental evidence in animals has demonstrated that the effect of essential fatty acid deficiency during early brain development is deleterious and permanent. The risk of neurodevelopmental disorder is highest in the very-low-birth-weight babies. Babies born of low birth weight or prematurely are most likely to have been born to mothers who were inadequately nourished, and the babies tend to be born with AA and

DHA deficits. Because disorders of brain development can be permanent, proper provision should be made to protect the AA and DHA status of both term and preterm infants to ensure optimum conditions for the development of membrane-rich systems such as the brain, nervous, and vascular systems."

-Institute of Brain Chemistry and Human Nutrition, Hackney Hospital, London, UK.
https://pubmed.ncbi.nlm.nih.gov/7682751/

Are deficits of arachidonic and docosahexaenoic acids responsible for the neural and vascular complications of preterm babies?

"We review evidence suggesting that pre- or postnatal deficits of arachidonic acid (AA) and docosahexaenoic acid (DHA) together with underdeveloped antioxidant protection contribute to neurovisual developmental disorders and other complications of premature birth. These two synergistic deficits occur at a time when 70% of energy is focused on brain development and when the brain and blood vessels are growing at high speed. The types of essential fatty acids fed to preterm babies bear no relation to what the infant would have received had it remained a fetus. This failure to meet essential fatty acid requirements exacerbates the AA and DHA deficits seen at birth; furthermore, the immature superoxide defenses remain depressed until the expected date of delivery. Deficits of these systems, which are required for cell membranes, the endothelium, and neural tissue, could provide the biochemical prerequisite for the membrane disorders to which these babies are at high risk: intraventricular hemorrhage, periventricular leucomalacia, retinopathy of prematurity, and bronchopulmonary dysplasia. Although poor vascular development during fetal and neonatal life may be repaired, the structural and antioxidant deficits identified in preterm babies may impair blood vessel development with long-term consequences. The conclusion drawn from this review is that present parenteral and enteral lipid nutrition for preterm babies is flawed and could be pathogenic. Full-term milk composition is the basis for the design of preterm infant foods, but full-term milk is different from the placental product that is rich in AA and DHA. Preterm lipid nutrition should be revised to be more in line with placental lipid transfer to the fetus."

-Academic Department of Paediatrics, St Bartholomews Hospital Medical School, London, United Kingdom.
https://pubmed.ncbi.nlm.nih.gov/9322584/

Placental delivery of arachidonic and docosahexaenoic acids: implications for the lipid nutrition of preterm infants

"Arachidonic (AA) and docosahexaenoic (DHA) acids are major components of cell membranes

and are of special importance to the brain and blood vessels. In utero, the placenta selectively and substantially extracts AA and DHA from the mother and enriches the fetal circulation. Studies indicate that there is little placental conversion of the parent essential fatty acids to AA and DHA. Similarly, analyses of desaturation and reductase activity have shown the placenta to be less functional than the maternal or fetal livers. There appears to be a correlation with placental size and plasma AA and DHA proportions in cord blood; therefore, placental development may be an important variable in determining nutrient transfer to the fetus and, hence, fetal growth itself. In preterm infants, both parenteral and enteral feeding methods are modeled on term breast milk. Consequently, there is a rapid decline of the plasma proportions of AA and DHA to one quarter or one third of the intrauterine amounts that would have been delivered by the placenta. Simultaneously, the proportion of linoleic acid, the precursor for AA, rises in the plasma phosphoglycerides 3-fold. An inadequate supply of AA and DHA during the period of high demand from rapid vascular and brain growth could lead to fragility, leakage, and membrane breakdown. Such breakdown would predictably be followed by peroxidation of free AA, vasoconstriction, inflammation, and ischemia with its biological sequelae. In the brain, cell death would be an extreme consequence."

-Institute of Brain Chemistry and Human Nutrition, University of North London, UK.
https://pubmed.ncbi.nlm.nih.gov/10617983/

The inadequacy of the essential fatty acid content of present preterm feeds

"Arachidonic (AA) and docosahexaenoic (DHA) acids are major components of endothelial, pulmonary and neuro-visual cell membranes. Preterm babies may be born with deficits of both AA and DHA. There is evidence that their endogenous anti-oxidant enzymes defence systems have only reached half the activity expected at term. Yet they are exposed to an oxygen tension greater than physiologically anticipated at this time, and the superoxide dismutase shows no evidence of significant catch-up. After birth, present enteral and parenteral feeds for the preterm baby result in a further drop of AA and DHA plasma proportions to a quarter or third of the intra-uterine expectation. At the same time, the proportion of linoleic acid (LA), the precursor for AA, rises in the plasma phosphoglycerides four-fold, thus denying the preterm infant the provision with which the placenta would have perfused the fetus to meet the very rapid demand for endothelial and neural growth. From the biochemistry it is predictable that this situation could lead to fragile cell membranes, leakage, rupture with peroxidation resulting in the formation of inflammatory and vasoconstrictive agents."

-The Institute of Brain Chemistry and Human Nutrition, University of North London, UK.
https://pubmed.ncbi.nlm.nih.gov/9462903/

Arachidonic and docosahexaenoic acids are strongly associated in maternal and neonatal blood

Background: The red cell membrane fatty acid composition has frequently been used as an index of essential fatty acid (EFA) nutrition. After birth there is a decline in plasma arachidonic acid (AA) and docosahexaenoic (DHA) acids in babies fed on conventional formula which contains only the parent linoleic and alpha-linolenic acids. In human studies, the red cell phosphoglyceride composition appears to be more constant than that of plasma. In infants fed fish oil without AA, the AA proportions fall in the plasma but much less so in the red cells. This result might be considered to mean that there is no need for preformed AA. On the other hand, in a study where the levels of AA fell there was reduction of infant growth. Indeed, where cell membrane composition does change there is often an associated alteration in physiological functions of membranes. We therefore felt it worth investigating the balance between AA and DHA in a physiological situation where plasma levels are known to change, namely in pregnancy.

Purpose: The aim of the study was to investigate a relationship between blood phosphoglyceride AA and DHA in pregnant women and neonates.

Results: AA and DHA correlated in plasma choline phosphoglycerides (CPG) of the British mothers ($r=0.52$ $P<0.0001$). The correlation coefficients and significance were much stronger in the red cell CPG and even more so in the term and preterm infant red cell CPGs ($r=0.75$, 0.80 and 0.88, respectively). Similarly, AA and DHA correlated in red cell CPGs of the Korean women and their term babies. There was also a significant relationship between the two fatty acids in red cell ethanolamine phosphoglycerides in the mothers and their babies. Both linoleic (LA) and alpha-linolenic acids (ALA) were inversely associated with AA and DHA in some of the phosphoglyceride fractions of the mothers and babies.

Conclusions: Although AA and DHA have different primary dietary origins, there were significant relationships between AA and DHA in the phosphoglycerides of the red cell membrane. This finding seems surprising if the red cell composition is determined by diet. These results suggest a physiological mechanism which attempts to maintain an appropriate balance between AA and DHA. It is plausible that there is an optimum balance between AA and DHA for membrane stability, deformability, enzyme and receptor function."

-The Institute of Brain Chemistry and Human Nutrition, The University of North London, London, UK.
https://pubmed.ncbi.nlm.nih.gov/10694772/

The endocannabinoid-CB receptor system: Importance for development and in pediatric disease.

“Endogenous cannabinoids (endocannabinoids) and their cannabinoid CB1 and CB2 receptors, are present from the early stages of gestation and play a number of vital roles for the developing organism. Although most of these data are collected from animal studies, a role for cannabinoid receptors in the developing human brain has been suggested, based on the detection of "atypically" distributed CB1 receptors in several neural pathways of the fetal brain. **In addition, a role for the endocannabinoid system for the human infant is likely, since the endocannabinoid 2-arachidonoyl glycerol** [2-AG] **has been detected in human milk.** Animal research indicates that the Endocannabinoid-CB1 Receptor ('ECBR') system fulfills a number of roles in the developing organism:

1. embryonal implantation (requires a temporary and localized reduction in anandamide);
2. in neural development (by the transient presence of CB1 receptors in white matter areas of the nervous system);
3. as a neuroprotectant (anandamide protects the developing brain from trauma-induced neuronal loss);
4. in the initiation of suckling in the newborn (where activation of the CB1 receptors in the neonatal brain is critical for survival).
5. In addition, subtle but definite deficiencies have been described in memory, motor and addictive behaviors and in higher cognitive ('executive') function in the human offspring as result of prenatal exposure to marihuana.

Therefore, the endocanabinoid-CB1 receptor system may play a role in the development of structures which control these functions, including the nigrostriatal pathway and the prefrontal cortex. From the multitude of roles of the endocannabinoids and their receptors in the developing organism, there are two distinct stages of development, during which proper functioning of the endocannabinoid system seems to be critical for survival: embryonal implantation and neonatal milk sucking. We propose that a dysfunctional Endocannabinoid-CB1 Receptor system in infants with growth failure resulting from an inability to ingest food, may resolve the enigma of "non-organic failure-to-thrive" (NOFTT). Developmental observations suggest further that CB1 receptors develop only gradually during the postnatal period, which correlates with an insensitivity to the psychoactive effects of cannabinoid treatment in the young organism. **Therefore, it is suggested that children may respond positively to medicinal applications of cannabinoids without undesirable central effects. Excellent clinical results have previously been reported in pediatric oncology and in case studies of children with severe neurological disease or brain trauma.** We suggest cannabinoid treatment for children or young adults with cystic fibrosis in order to achieve an improvement of their health condition including

improved food intake and reduced inflammatory exacerbations."

-Department of Behavioral Sciences, College of Judea and Samaria, Ariel 44837, Israel.
https://www.ncbi.nlm.nih.gov/pubmed/15159678

A solid-phase method for the extraction and measurement of anandamide from multiple human biomatrices.

"AEA [anandamide] was detected in serum and plasma from blood isolated from 20 adult women (means+/-standard deviations: 0.68+/-0.29 and 0.64+/-0.28 nM, respectively), from pregnant women at term (1.37+/-0.42 nM), and from umbilical vein (1.26+/-0.33 nM) and umbilical artery (1.14+/-0.35nM), in milk (0.12+/-0.05 nM) and from amniotic (0.03+/-0.02 nM), peritoneal (0.93+/-0.27 nM), follicular (1.17+/-0.51 nM), and ovarian cyst (0.32+/-0.01 nM) fluids. AEA was undetectable in saliva and urine."

Endocannabinoid Research Group, Reproductive Sciences Section, Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, Leicestershire LE27LX, UK.
https://www.ncbi.nlm.nih.gov/pubmed/18823934/

Oxylipins, endocannabinoids, and related compounds in human milk: Levels and effects of storage conditions

"The presence of fatty acid derived oxylipins, endocannabinoids and related compounds in human milk may be of importance to the infant. Presently, clinically relevant protocols for storing and handling human milk that minimize error and variability in oxylipin and endocannabinoid concentrations are lacking. In this study, we compared the individual and combined effects of the following storage conditions on the stability of these fatty acid metabolites in human milk: state (fresh or frozen), storage temperature (4 °C, -20 °C or -80 °C), and duration (1 day, 1 week or 3 months). Thirteen endocannabinoids and related compounds, as well as 37 oxylipins were analyzed simultaneously by liquid chromatography coupled to tandem mass spectrometry. Twelve endocannabinoids and related compounds (2-111 nM) and 31 oxylipins (1.2 pM-1242 nM) were detected, with highest levels being found for 2-arachidonoylglycerol and 17(R)hydroxydocosahexaenoic acid, respectively. The concentrations of most endocannabinoid-related compounds and oxylipins were dependent on storage condition, and especially storage at 4 °C introduced significant variability. Our findings suggest that human milk samples should be analyzed immediately after, or within one day of collection (if stored at 4 °C). Storage at -80 °C is required for long-term preservation, and storage at -20 °C is acceptable for no more than one week. These findings provide a protocol for investigating the oxylipin and

endocannabinoid metabolome in human milk, useful for future milk-related clinical studies."

-Department of Chemistry, Umeå University, Sweden.
-Department of Pharmacology and Clinical Neuroscience, Umeå University, Sweden.
-Department of Clinical Sciences, University, Sweden.
-Department of Nutrition, University of California, Davis, CA, USA
-Foods for Health Institute, University of California, Davis, CA, USA.
https://pubmed.ncbi.nlm.nih.gov/26656029/

Controversial Nutrients That Potentially Affect Preterm Neurodevelopment: Essential Fatty Acids and Iron

"Docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (ARA, 20:4n-6) are required by preterm infants to support growth and development. DHA and ARA are formed from the essential fatty acids, linoleic acid (LA,18:2n-6) and α-linolenic acid (LNA,18:3n-3), respectively, by elongation and desaturation [3] and are the major polyunsaturated fatty acids in fetal plasma. In contrast, LA and LNA are the most abundant n-6 and n-3 fatty acids in human milk, infant formula and IV lipids. Plasma LA increases, while ARA and DHA decrease rapidly with the initiation of feeding. LA and LNA are mutually competitive and their metabolism is inhibited by products of the autologous and opposing fatty acid series [4]. Thus, inappropriately high intakes of one of the n-6 and n-3 fatty acids can have deleterious effects on other n-6 and n-3 fatty acids. DHA and ARA are present in membrane phospholipids where they regulate membrane functions, and from which they are released to act directly or as precursors to molecules that modulate cell growth, inter- and intra-cellular communication and protein function [3]. DHA is selectively accumulated in specific tissues that include the retina and brain grey matter. Depletion of DHA from the brain and retina results in reduced visual function, cognitive and behavioral abnormalities, altered monaminergic neurotransmitter metabolism, and decreased membrane protein and receptor activities [3]. The monoamines dopamine and serotonin are important in many of the cognitive and behavior advances of early childhood; their synthesis is regulated by the iron dependent tyrosine and tryptophan hydroxylase, respectively. ARA is found in membranes throughout the body, fulfills the role of n-6 fatty acids in growth, and is the precursor for eicosanoids and other signal molecules. N-6 and n-3 fatty acids also regulate carbohydrate and lipid metabolism through effects on gene expression involving steroid regulatory element binding proteins and peroxisomal proliferator activated receptors [3,5,6]. The desaturases required for synthesis of ARA and DHA, and delta 9 desaturase required for synthesis of oleic acid [18] (which is the major monoenoic fatty acid in brain white and grey matter), are iron dependent enzymes."

-Michael K Georgieff & Sheila M Innis
-University of Minnesota School of Medicine
-Department of Pediatrics, Nutrition Research ProgramB.C. Research Institute, Professor, University of British Columbia
-Pediatric Research
https://www.nature.com/articles/pr2005138

The endocannabinoid-CB(1) receptor system in pre- and postnatal life

"Recent research suggests that the endogenous cannabinoids ("endocannabinoids") and their cannabinoid receptors have a major influence during pre- and postnatal development. First, high levels of the endocannaboid anandamide and cannabinoid receptors are present in the preimplantation embryo and in the uterus, while a temporary reduction of anandamide levels is essential for embryonal implantation. In women accordingly, an inverse association has been reported between fatty acid amide hydrolase (the anandamide degrading enzyme) in human lymphocytes and miscarriage. Second, CB(1) receptors display a transient presence in white matter areas of the pre- and postnatal nervous system, suggesting a role for CB(1) receptors in brain development. Third, endocannabinoids have been detected in maternal milk and activation of CB(1) receptors appears to be critical for milk sucking by newborn mice, apparently activating oral-motor musculature. Fourth, anandamide has neuroprotectant properties in the developing postnatal brain. Finally, prenatal exposure to the active constituent of marihuana (Delta(9)-tetrahydrocannabinol) or to anandamide affects prefrontal cortical functions, memory and motor and addictive behaviors, suggesting a role for the endocannabinoid CB(1) receptor system in the brain structures which control these functions. Further observations suggest that children may be less prone to psychoactive side effects of Delta(9)-tetrahydrocannabinol or endocannabinoids than adults. The medical implications of these novel developments are far reaching and suggest a promising future for cannabinoids in pediatric medicine for conditions including "non-organic failure-to-thrive" and cystic fibrosis."

-Department of Behavioral Sciences, College of Judea and Samaria, Ariel 44837, Israel.
https://pubmed.ncbi.nlm.nih.gov/15464041

Breast Cancer

Role of dietary fatty acids in mammary gland development and breast cancer

"Breast cancer is the most common cancer among women worldwide. Estimates suggest up to 35% of cases may be preventable through diet and lifestyle modification. Growing research on the role of fats in human health suggests that early exposure in life to specific fatty acids, when

tissues are particularly sensitive to their environment, can have long-term health impacts. The present review examines the role of dietary fat in mammary gland development and breast cancer throughout the lifecycle. Overall, n-3 polyunsaturated fatty acids have promising cancer-preventive effects when introduced early in life, and warrant further research to elucidate the mechanisms of action."

-Department of Human Health and Nutritional Sciences, College of Biological Science, University of Guelph, , Ontario, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3096965/

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"The endocannabinoid system regulates cell proliferation and migration in human breast cancer cells."…

-Institute of Endocrinology and Experimental Oncology, National Research Council, Napoli, Italy
(Istituto di Endocrinologia e Oncologia Sperimentale, Consiglio Nazionale delle Ricerche, Napoli, Italy.)

https://www.ncbi.nlm.nih.gov/pubmed/18676619

Long-chain n-3-to-n-6 polyunsaturated fatty acid ratios in breast adipose tissue from women with and without breast cancer

…"We conclude that total n-6 [omega-6] PUFAs may be contributing to the high risk of breast cancer in the United States and that LC n-3 [omega-3] PUFAs, derived from fish oils, may have a protective effect."

-Division of Hematology-Oncology, Department of Medicine, University of California, Los Angeles School of Medicine, Los Angeles, CA, USA.

https://pubmed.ncbi.nlm.nih.gov/12416257/

Omega-3 fatty acids reduce obesity-induced tumor progression independent of GPR120 [G protein-coupled receptor 120] in a mouse model of postmenopausal breast cancer

"Obesity and inflammation are both risk factors for a variety of cancers including breast cancer in postmenopausal women. Intake of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) decreases the risk of breast cancer, and also reduces obesity-associated inflammation and insulin resistance, but whether the two effects are related is currently unknown."

…"Instead, in vitro studies demonstrated that ω-3 PUFAs act directly on tumor cells to activate JNK, inhibit proliferation and induce apoptosis. Our results show that obesity promotes

mammary tumor progression in this model of postmenopausal breast cancer and that ω-3 PUFAs inhibit mammary tumor progression in obese mice, independent of GPR120. Keywords: obesity, mammary tumors, inflammation, postmenopausal breast cancer,ω-3 PUFAs, GPR120."

-Department of Medicine, Division of Endocrinology and Metabolism University of California, La Jolla, CA
-Biomedical Network Center for the study of Hepatic and Digestive Diseases (CIBERehd), Madrid, Spain
-Department of Pathology University of California, La Jolla, CA
-Moores Cancer Center University of California, La Jolla, CA
-San Diego VA Healthcare System, San Diego, CA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4362785/

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"Breast cancer is one of the most common cancers and is a leading cause of mortality in women."…
"The time course of the mammary tumor incidence pattern was advanced by flaxseed oil compared to the control. At the high dose (0.2 ml) of flaxseed oil, when the omega-6: omega-3 PUFA ratio was closer to 1, there was some delay in the growth of mammary tumors. Melatonin delayed the appearance of palpable tumors and the growth of the tumors with a dose-related statistically significant negative trend for the incidence of tumors. The combination of flaxseed oil and melatonin caused a significant decrease in the number of tumors and tumor weight per mouse compared to the control and to flaxseed oil but not to melatonin alone. Flaxseed oil may delay the growth of mammary tumors if the omega-6:omega-3 PUFA ratio of fat consumed is closer to 1. Melatonin has the potential to markedly delay the appearance of palpable mammary tumors. Studies are in progress with the TG.NK mouse model to understand the histological and molecular changes associated with the dose-response pattern of mammary tumor incidence and growth after treatment with a broad range of doses of melatonin."

-Environmental Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA.
https://www.ncbi.nlm.nih.gov/m/pubmed/11200779/

Anandamide inhibits the Wnt/β-catenin signalling pathway in human breast cancer MDA MB 231 cells.

"We previously showed that methyl-F-anandamide, a stable analogue of the anandamide, inhibited the growth and the progression of cultured human breast cancer cells. As accumulating evidences indicate that the constitutive activation of the canonical Wnt pathway in human breast cancer may highlight a key role for aberrant activation of the β-catenin-TCF cascade and

tumour progression, we studied the anandamide effect on the key elements of Wnt pathway in breast cancer cells. In this study we described that the treatment of human breast cancer cells, MDA MB 231 cells, with methyl-F-anandamide reduced protein levels of β-catenin in the cytoplasmic and nuclear fractions inhibiting the transcriptional activation of T Cell Factor (TCF) responsive element (marker for β-catenin signalling). The anandamide treatment resulted in up-regulation of epithelial markers, like E-cadherin with a concomitant decrease in protein levels of mesenchymal markers, including vimentin and Snail1. We, furthermore, observed that the induction of experimental epithelial-mesenchymal transition by exposure to adriamycin in MCF7 human breast cancer cell line was inhibited by anandamide treatment. In the present study we reported a novel anticancer effect of anandamide involving the inhibition of epithelial-mesenchymal transition, a process triggered during progression of cancer to invasive state."

-Institute of Endocrinology and Experimental Oncology, IEOS CNR, Via Pansini 5, Naples, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/22425263

Carbohydrates and the risk of breast cancer among Mexican women

"In this population, a high percentage of calories from carbohydrate, but not from fat, was associated with increased breast cancer risk. This relation deserves to be investigated further, particularly in populations highly susceptible to insulin resistance."

-National Institute of Public Health, Colonia Santa Maria Ahuacatitlan, Cuernavaca, Mexico.
https://pubmed.ncbi.nlm.nih.gov/15298947

JunD is involved in the antiproliferative effect of Delta9-tetrahydrocannabinol on human breast cancer cells

"It has been recently shown that cannabinoids, the active components of marijuana and their derivatives, inhibit cell cycle progression of human breast cancer cells. Here we studied the mechanism of Delta(9)-tetrahydrocannabinol (THC) antiproliferative action in these cells, and show that it involves the modulation of JunD, a member of the AP-1 transcription factor family. THC activates JunD both by upregulating gene expression and by translocating the protein to the nuclear compartment, and these events are accompanied by a decrease in cell proliferation. Of interest, neither JunD activation nor proliferation inhibition was observed in human non-tumour mammary epithelial cells exposed to THC. We confirmed the importance of JunD in THC action by RNA interference and genetic ablation. Thus, in both JunD-silenced human breast cancer cells and JunD knockout mice-derived immortalized fibroblasts, the antiproliferative effect exerted by

THC was significantly diminished. Gene array and siRNA experiments support that the cyclin-dependent kinase inhibitor p27 and the tumour suppressor gene testin are candidate JunD targets in cannabinoid action. In addition, our data suggest that the stress-regulated protein p8 participates in THC antiproliferative action in a JunD-independent manner. In summary, this is the first report showing not only that cannabinoids regulate JunD but, more generally, that JunD activation reduces the proliferation of cancer cells, which points to a new target to inhibit breast cancer progression."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/18454173

Future Aspects for Cannabinoids in Breast Cancer Therapy

"Cannabinoids (CBs) from Cannabis sativa provide relief for tumor-associated symptoms (including nausea, anorexia, and neuropathic pain) in the palliative treatment of cancer patients. Additionally, they may decelerate tumor progression in breast cancer patients. Indeed, the psychoactive delta-9-tetrahydrocannabinol (THC), non-psychoactive cannabidiol (CBD) and other CBs inhibited disease progression in breast cancer models. The effects of CBs on signaling pathways in cancer cells are conferred via G-protein coupled CB-receptors (CB-Rs), CB1-R and CB2-R, but also via other receptors, and in a receptor-independent way. THC is a partial agonist for CB1-R and CB2-R; CBD is an inverse agonist for both. In breast cancer, CB1-R expression is moderate, but CB2-R expression is high, which is related to tumor aggressiveness. CBs block cell cycle progression and cell growth and induce cancer cell apoptosis by inhibiting constitutive active pro-oncogenic signaling pathways, such as the extracellular-signal-regulated kinase pathway. They reduce angiogenesis and tumor metastasis in animal breast cancer models. CBs are not only active against estrogen receptor-positive, but also against estrogen-resistant breast cancer cells. In human epidermal growth factor receptor 2-positive and triple-negative breast cancer cells, blocking protein kinase B- and cyclooxygenase-2 signaling via CB2-R prevents tumor progression and metastasis. Furthermore, selective estrogen receptor modulators (SERMs), including tamoxifen, bind to CB-Rs; this process may contribute to the growth inhibitory effect of SERMs in cancer cells lacking the estrogen receptor. In summary, CBs are already administered to breast cancer patients at advanced stages of the disease, but they might also be effective at earlier stages to decelerate tumor progression."

-Institute of Biology and Ecology, Faculty of Sciences, University of Pavol Jozef Šafárik in Košice, Košice, Slovakia
-Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria;
-Institute of Chemistry, Faculty of Sciences, University of Pavol Jozef Šafárik in Košice, Slovakia;

-Department of Clinical Pharmacy and Diagnostics, University of Vienna, Vienna, Austria;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6479799/

Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma

"Delta(9)-Tetrahydrocannabinol (THC) exhibits antitumor effects on various cancer cell types, but its use in chemotherapy is limited by its psychotropic activity. We investigated the antitumor activities of other plant cannabinoids, i.e., cannabidiol, cannabigerol, cannabichromene, cannabidiol acid and THC acid, and assessed whether there is any advantage in using Cannabis extracts (enriched in either cannabidiol or THC) over pure cannabinoids. Results obtained in a panel of tumor cell lines clearly indicate that, of the five natural compounds tested, cannabidiol is the most potent inhibitor of cancer cell growth (IC(50) between 6.0 and 10.6 microM), with significantly lower potency in noncancer cells. The cannabidiol-rich extract was equipotent to cannabidiol, whereas cannabigerol and cannabichromene followed in the rank of potency. Both cannabidiol and the cannabidiol-rich extract inhibited the growth of xenograft tumors obtained by s.c. injection into athymic mice of human MDA-MB-231 breast carcinoma or rat v-K-ras-transformed thyroid epithelial cells and reduced lung metastases deriving from intrapaw injection of MDA-MB-231 cells. Judging from several experiments on its possible cellular and molecular mechanisms of action, we propose that cannabidiol lacks a unique mode of action in the cell lines investigated. At least for MDA-MB-231 cells, however, our experiments indicate that cannabidiol effect is due to its capability of inducing apoptosis via: direct or indirect activation of cannabinoid CB(2) and vanilloid transient receptor potential vanilloid type-1 receptors and cannabinoid/vanilloid receptor-independent elevation of intracellular Ca(2+) and reactive oxygen species. Our data support the further testing of cannabidiol and cannabidiol-rich extracts for the potential treatment of cancer."

-Institute of Biomolecular Chemistry, National Research Council Pozzuoli, Italy.
https://pubmed.ncbi.nlm.nih.gov/16728591

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…"In addition to a luminal phenotype and axillary lymph node involvement, low levels of n-3 LC-PUFA in breast adipose tissue may constitute a risk factor that contributes to breast cancer bone metastases formation in premenopausal women. "…

-Department of Gynecology, Centre Hospitalier Régional Universitaire de Tours, Hôpital Bretonneau
-Laboratoire N2C « Nutrition, Croissance et Cancer », Université de Tours,
-Department of Pathology, Centre Hospitalier Régional Universitaire de Tours, Hôpital Bretonneau,

-Boulevard Tonnellé, France
https://www.mdpi.com/2072-6643/12/12/3832/pdf

The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation

"Anandamide was the first brain metabolite shown to act as a ligand of "central" CB1 cannabinoid receptors. Here we report that the endogenous cannabinoid potently and selectively inhibits the proliferation of human breast cancer cells in vitro. Anandamide dose-dependently inhibited the proliferation of MCF-7 and EFM-19 cells with IC50 values between 0.5 and 1.5 microM and 83-92% maximal inhibition at 5-10 microM. The proliferation of several other nonmammary tumoral cell lines was not affected by 10 microM anandamide. The anti-proliferative effect of anandamide was not due to toxicity or to apoptosis of cells but was accompanied by a reduction of cells in the S phase of the cell cycle. A stable analogue of anandamide (R)-methanandamide, another endogenous cannabinoid, 2-arachidonoylglycerol, and the synthetic cannabinoid HU-210 also inhibited EFM-19 cell proliferation, whereas arachidonic acid was much less effective. These cannabimimetic substances displaced the binding of the selective cannabinoid agonist [3H]CP 55, 940 to EFM-19 membranes with an order of potency identical to that observed for the inhibition of EFM-19 cell proliferation. Moreover, anandamide cytostatic effect was inhibited by the selective CB1 receptor antagonist SR 141716A. Cell proliferation was arrested by a prolactin mAb and enhanced by exogenous human prolactin, whose mitogenic action was reverted by very low (0.1-0.5 microM) doses of anandamide. Anandamide suppressed the levels of the long form of the prolactin receptor in both EFM-19 and MCF-7 cells, as well as a typical prolactin-induced response, i.e., the expression of the breast cancer cell susceptibility gene brca1. These data suggest that anandamide blocks human breast cancer cell proliferation through CB1-like receptor-mediated inhibition of endogenous prolactin action at the level of prolactin receptor."

-Institute of Cybernetics, National Research Council), National Research Council, Naples, Italy.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC20983/

Note: Higher consumption of Arachidonic Acid (Omega-6) and lower intake of Omega-3s has been shown to increase tumors in animal studies. See Arachidonic Acid (Omega-6) and Omega Ratio for more information

Breastfeeding

Arachidonic Acid in Human Milk

“Breastfeeding is universally recommended as the optimal choice of infant feeding and consequently human milk has been extensively investigated to unravel its unique nutrient profile. The human milk lipid composition is unique and supplies specifically long-chain polyunsaturated fatty acids (LC-PUFAs), in particular, arachidonic acid (ARA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3). Arachidonic acid (ARA) is the most predominant long-chain polyunsaturated fatty acid in human milk, albeit at low concentrations as compared to other fatty acids. It occurs predominantly in the triglyceride form and to a lesser extent as milk fat globule membrane phospholipids. Human milk ARA levels are modulated by dietary intake as demonstrated by animal and human studies and consequently vary dependent on dietary habits among mothers and regions across the globe. ARA serves as a precursor to eicosanoids and endocannabinoids that also occur in human milk. A review of scientific and clinical studies reveals that ARA plays an important role in physiological development and its related functions during early life nutrition. Therefore, ARA is an important nutrient during infancy and childhood and, as such, appropriate attention is required regarding its nutritional status and presence in the infant diet. Data are emerging indicating considerable genetic variation in encoding for desaturases and other essential fatty acid metabolic enzymes that may influence the ARA level as well as other LC-PUFAs. Human milk from well-nourished mothers has adequate levels of both ARA and DHA to support nutritional and developmental needs of infants. In case breastfeeding is not possible and infant formula is being fed, experts recommend that both ARA and DHA are added at levels present in human milk.”

-Nutrition Science & Advocacy, DSM Nutritional Products; Columbia, MD , USA.
https://pubmed.ncbi.nlm.nih.gov/32121018

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..."Human milk contains n-3 [omega-3] and n-6 [Omega-6] LCPUFA (long chain polyunsaturated fatty acids), which are absent from many infant formulas."...

-Nestle Research Center, Lausanne, Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada.
https://pubmed.ncbi.nlm.nih.gov/16048149

The endocannabinoid-CB receptor system: Importance for development and in pediatric disease

“Endogenous cannabinoids (endocannabinoids) and their cannabinoid CB1 and CB2 receptors, are present from the early stages of gestation and play a number of vital roles for the developing organism. Although most of these data are collected from animal studies, a role for cannabinoid receptors in the developing human brain has been suggested, based on the detection of "atypically" distributed CB1 receptors in several neural pathways of the fetal brain. In addition, a role for the endocannabinoid system for the human infant is likely, since the endocannabinoid 2-arachidonoyl glycerol has been detected in human milk. Animal research indicates that the Endocannabinoid-CB1 Receptor ('ECBR') system fulfills a number of roles in the developing organism: 1. embryonal implantation (requires a temporary and localized reduction in anandamide); 2. in neural development (by the transient presence of CB1 receptors in white matter areas of the nervous system); 3. as a neuroprotectant (anandamide protects the developing brain from trauma-induced neuronal loss); 4. in the initiation of suckling in the newborn (where activation of the CB1 receptors in the neonatal brain is critical for survival). 5. In addition, subtle but definite deficiencies have been described in memory, motor and addictive behaviors and in higher cognitive ('executive') function in the human offspring as result of prenatal exposure to marihuana. Therefore, the endocanabinoid-CB1 receptor system may play a role in the development of structures which control these functions, including the nigrostriatal pathway and the prefrontal cortex. From the multitude of roles of the endocannabinoids and their receptors in the developing organism, there are two distinct stages of development, during which proper functioning of the endocannabinoid system seems to be critical for survival: embryonal implantation and neonatal milk sucking. We propose that a dysfunctional Endocannabinoid-CB1 Receptor system in infants with growth failure resulting from an inability to ingest food, may resolve the enigma of "non-organic failure-to-thrive" (NOFTT). Developmental observations suggest further that CB1 receptors develop only gradually during the postnatal period, which correlates with an insensitivity to the psychoactive effects of cannabinoid treatment in the young organism. Therefore, it is suggested that children may respond positively to medicinal applications of cannabinoids without undesirable central effects. Excellent clinical results have previously been reported in pediatric oncology and in case studies of children with severe neurological disease or brain trauma. We suggest cannabinoid treatment for children or young adults with cystic fibrosis in order to achieve an improvement of their health condition including improved food intake and reduced inflammatory exacerbations.”

-Department of Behavioral Sciences, College of Judea and Samaria, Ariel, Israel.
https://pubmed.ncbi.nlm.nih.gov/15159678/

Breastfeeding provides passive and likely long-lasting active immunity

…"**Results**: Human milk protects against infections in the breastfed offspring mainly via the secretory IgA antibodies, but also most likely via several other factors like the bactericidal lactoferrin. It is striking that the defense factors of human milk function without causing inflammation, some components are even directly anti-inflammatory. Protection against infections has been well evidenced during lactation against, e.g., acute and prolonged diarrhea, respiratory tract infections, otitis media, urinary tract infection, neonatal septicemia, and necrotizing enterocolitis. There is also interesting evidence for an enhanced protection remaining for years after lactation against diarrhea, respiratory tract infections, otitis media, Haemophilus influenzae type b infections, and wheezing illness. In several instances the protection seems to improve with the duration of breastfeeding. Some, but not all studies have shown better vaccine responses among breastfed than non-breastfed infants. A few factors in milk like anti-antibodies (anti-idiotypic antibodies) and T and B lymphocytes have in some experimental models been able to transfer priming of the breastfed offspring. This together with transfer of numerous cytokines and growth factors via milk may add to an active stimulation of the infant's immune system. Consequently, the infant might respond better to both infections and vaccines. Such an enhanced function could also explain why breastfeeding may protect against immunologic diseases like coeliac disease and possibly allergy. Suggestions of protection against autoimmune diseases and tumors have also been published, but need confirmation.

Conclusions: Breastfeeding may, in addition to the well-known passive protection against infections during lactation, have a unique capacity to stimulate the immune system of the offspring possibly with several long-term positive effects."

-Department of Clinical Immunology, Göteborg University, Sweden
https://pubmed.ncbi.nlm.nih.gov/9892025/

Endocannabinoid Metabolome Characterization of Milk from Guatemalan Women Living in the Western Highlands

"**Background:** Recognized as the gold-standard ideal fare, human milk has a unique composition that meets infants' needs throughout development. Endocannabinoids and endocannabinoid-like compounds [endocannabinoid metabolome (ECM)] are endogenous lipid mediators derived from long-chain polyunsaturated fatty acids. Based on animal models, it has been proposed that endocannabinoid arachidonoyl glycerol (AG) plays a role in establishing the suckling response during lactation. In addition, endocannabinoid ethanolamides have been shown to stimulate food intake. The mechanisms of action and the role of the ECM in human milk are not fully

understood.

Objectives: The present study aimed to characterize and quantify the ECM in human milk samples from an underserved population in Guatemala."…

"**Conclusions:** Our study identified the ECM in mature human milk and provides the first report for a population with health disparities within a developing country. The few studies available have been conducted in developed countries. Hypotheses for future studies can be developed based on this study's data to help elucidate specific roles for members of the ECM and how this biological system modulates infant health and development."

-Louisiana State University, Baton Rouge, LA.
-Agricultural Center, Louisiana State University, Baton Rouge, LA.
-Center for Drug Discovery, Northeastern University, Boston, MA.
-Center for Studies of Sensory Impairment, Aging and Metabolism, Guatemala.
-US Department of Agriculture, Agricultural Research Service, Western Human Nutrition Research Center; University of California, Davis, CA.
-Pennington Biomedical Research Center, Baton Rouge, LA.
https://pubmed.ncbi.nlm.nih.gov/31111118/

Breastfeeding protects against illness and infection in infants and children: a review of the evidence

"Nutrition is essential to the health and development of infants and children. Breastfeeding is superior to infant formula feeding because in addition to breastmilk's nutritional advantages, it protects against infections through specific and non-specific immune factors and has long-term consequences for metabolism and disease later in life. The objectives of this paper are to summarise the epidemiological and other scientific evidence in support of breastfeeding, to clarify why breastmilk is a better food for infants than infant formula and to demonstrate support for further breastfeeding initiatives in Australia. There is much epidemiological evidence for the benefits of breastfeeding to the human infant against a wide range of illnesses and infections. Other scientific evidence for breastfeeding has demonstrated specific nutritional components that provide immunologic protection and beneficial effects on intestinal flora. Human milk enhances the immature immunologic system of the neonate and strengthens host defence mechanisms against infective and other foreign agents. Mechanisms to explain active stimulation of the infant's immune system by breastfeeding are through bioactive factors in human milk. Following breastfeeding termination there may be prolonged protection against infections due to influences on the infant immune system mediated via human milk."….

-TVW Telethon Institute for Child Health Research, Western Australia, Australia.
https://pubmed.ncbi.nlm.nih.gov/11550600

Broken Bones

No bones about it: Cannabis may be used to treat fractures

“A new study published in the Journal of Bone and Mineral Research by Tel Aviv University and Hebrew University researchers explores another promising new medical application for marijuana. According to the research, the administration of the non-psychotropic component cannabinoid cannabidiol (CBD) significantly helps heal bone fractures. The study, conducted on rats with mid-femoral fractures, found that CBD -- even when isolated from tetrahydrocannabinol (THC), the major psychoactive component of cannabis -- markedly enhanced the healing process of the femora after just eight weeks.

The research was led jointly by Dr. Yankel Gabet of the Bone Research Laboratory at the Department of Anatomy and Anthropology at TAU's Sackler Faculty of Medicine and the late Prof. Itai Bab of Hebrew University's Bone Laboratory.

Undeniable clinical potential

The same team, in earlier research, discovered that cannabinoid receptors within our bodies stimulated bone formation and inhibited bone loss. This paves the way for the future use of cannabinoid drugs to combat osteoporosis and other bone-related diseases.

"The clinical potential of cannabinoid-related compounds is simply undeniable at this point," said Dr. Gabet. "While there is still a lot of work to be done to develop appropriate therapies, it is clear that it is possible to detach a clinical therapy objective from the psychoactivity of cannabis. CBD, the principal agent in our study, is primarily anti-inflammatory and has no psychoactivity."

According to Dr. Gabet, our bodies are equipped with a cannabinoid system, which regulates both vital and non-vital systems. "We only respond to cannabis because we are built with intrinsic compounds and receptors that can also be activated by compounds in the cannabis plant," he said. The researchers found that the skeleton itself is regulated by cannabinoids. Even the addition of a non-psychogenic compound acting outside of the brain can affect the skeleton.

Separating the components out

"We found that CBD alone makes bones stronger during healing, enhancing the maturation of the collagenous matrix, which provides the basis for new mineralization of bone tissue," said Dr. Gabet. " After being treated with CBD, the healed bone will be harder to break in the future."

The researchers injected one group of rats with CBD alone and another with a combination of CBD and THC. After evaluating the administration of THC and CBD together in the rats, they

found CBD alone provided the necessary therapeutic stimulus.

"We found CBD alone to be sufficiently effective in enhancing fracture healing," said Dr. Gabet. "Other studies have also shown CBD to be a safe agent, which leads us to believe we should continue this line of study in clinical trials to assess its usefulness in improving human fracture healing."“

-ScienceDaily
-Materials provided by American Friends of Tel Aviv University.
https://www.sciencedaily.com/releases/2015/07/150716124359.htm

Bronchospasm

“Bronchospasm (brong´kōspaz’em) involves a contraction of the muscular coat of the bronchial tubes. This results in a narrowing and obstruction of the breathing airways. Bronchospasm is a symptom of asthma.”

- American Academy of Allergy Asthma & Immunology
https://www.aaaai.org/conditions-and-treatments/conditions-dictionary/bronchospasm

Endocannabinoid System in the Airways

…“Giannini et al. demonstrated that the non-selective cannabinoid receptor agonist CP-55,940 can prevent allergen-induced bronchospasm, and reduce cough and leukocyte recruitment in the lung [67]. “…

-Department of Pharmacology, Faculty of Pharmacy, Hacettepe University
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943521/

Burns

Effect of omega 3 polyunsaturated fatty acids derived from fish oil in major burn patients: A prospective randomized controlled pilot trial

“**Background & aims:** The burn patient is the clearest example of prolonged inflammatory response. Various nutrients, particularly omega-3 polyunsaturated fatty acids (ω-3 PUFAs), have been demonstrated as attenuating the inflammatory response, and reduce infectious

complications. In absence of definitive evidence in major burns the study aimed at investigating the effect particularly on infectious complications of enteral nutrition enriched with ω-3 PUFAs.

Intervention: low-fat (18% energy as fat) modular diet (LF-EN) or identical with 50% of fat as fish oil (FO-EN). Study endpoints: infectious and other complications, length of mechanical ventilation time, mortality.

Conclusion: The inclusion of ω-3 PUFAs in a low fat diet in ICU burned patients was associated with significant clinical benefits compared to a conventional low fat diet, with lower rates of severe sepsis, septic shock and pyloric dysfunction."

-Departamento de Nutrición, Centro Nacional de Quemados (CENAQUE), Montevideo, Uruguay.
-Departamento de Medicina Intensiva, Centro Nacional de Quemados (CENAQUE), Facultad de Medicina, Universidad de la República, Montevideo, Uruguay.

https://pubmed.ncbi.nlm.nih.gov/28153504/

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Caffeine

Effects of caffeine on striatal neurotransmission: focus on cannabinoid CB1 receptors.

…"The striatum is in fact a subcortical area involved in sensorimotor, cognitive, and emotional processes, and recent experimental findings showed that chronic caffeine consumption enhances the sensitivity of striatal GABAergic synapses to the stimulation of cannabinoid CB1 receptors. The endocannabinoid system is involved in the psychoactive effects of many compounds, and adenosine A2A receptors (the main receptor target of caffeine) elicit a permissive effect towards CB1 receptors, thus suggesting that A2A-CB1 receptor interaction plays a major role in the generation and maintenance of caffeine reinforcing behavior."

Clinical Neurology, Department of Neurosciences, University Tor Vergata, Rome, Italy
http://www.ncbi.nlm.nih.gov/pubmed/20087854

Caffeine drinking potentiates cannabinoid transmission in the striatum: interaction with stress effects.

…"Our data suggest that the cannabinoid system is implicated in the psychoactive properties of

caffeine and in the ability of caffeine to reduce the pathological consequences of stress."

Clinical Neurology, Department of Neurosciences, University Tor Vergata, Rome, Italy
http://www.ncbi.nlm.nih.gov/pubmed/19027757

Caffeine and cannabinoid receptors modulate impulsive behavior in an animal model of attentional deficit and hyperactivity disorder.

"Attention deficit and hyperactivity disorder (ADHD) is characterized by impaired levels of hyperactivity, impulsivity, and inattention. Adenosine and endocannabinoid systems tightly interact in the modulation of dopamine signaling, involved in the neurobiology of ADHD. In this study, we evaluated the modulating effects of the cannabinoid and adenosine systems in a tolerance to delay of reward task using the most widely used animal model of ADHD. Spontaneous Hypertensive Rats (SHR) and Wistar-Kyoto rats were treated chronically or acutely with caffeine, a non-selective adenosine receptor antagonist, or acutely with a cannabinoid agonist (WIN55212-2, WIN) or antagonist (AM251). Subsequently, animals were tested in the tolerance to delay of reward task, in which they had to choose between a small, but immediate, or a large, but delayed, reward. Treatment with WIN decreased, whereas treatment with AM251 increased the choices of the large reward, selectively in SHR rats, indicating a CB1 receptor-mediated increase in impulsive behavior. An acute pre-treatment with caffeine blocked WIN effects. Conversely, a chronic treatment with caffeine increased the impulsive phenotype and potentiated the WIN effects. The results indicate that both cannabinoid and adenosine receptors modulate impulsive behavior in SHR: the antagonism of cannabinoid receptors might be effective in reducing impulsive symptoms present in ADHD; in addition, caffeine showed the opposite effects on impulsive behavior depending on the length of treatment. These observations are of particular importance to consider when therapeutic manipulation of CB1 receptors is applied to ADHD patients who consume coffee."

-Department of Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.
-CNC-Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal.
-Department of Pharmacology, Universidade Federal de Santa Catarina, Florianópolis, Brazil.
-Institute of Medical Biochemistry Leopoldo de Meis, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.
-Faculty of Medicine, University of Coimbra, Coimbra, Portugal.
-Department of Neurobiology, Universidade Federal Fluminense, Niterói, Brazil.
https://www.ncbi.nlm.nih.gov/pubmed/30667546

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…"In summary, this work highlights two relevant factors influencing cannabinoid CB1 signaling in

the hippocampus: the activity of A1 receptors and the chronic consumption of caffeine. This A1–CB1 receptor interaction therefore points toward the possibility that the pathophysiological or therapeutically relevant actions operated by CB1 receptors can be significantly affected by interference with A1 receptor activity, as is the case of chronic caffeine intake."

-Faculty of Medicine, Institute of Pharmacology and Neurosciences, University of Lisbon, Lisbon, Portugal
-Unit of Neurosciences, Institute of Molecular Medicine, University of Lisbon, Lisbon, Portugal
-Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3055664/

Caloric restriction (CR)

"Caloric restriction (CR), in the absence of malnutrition, delays aging and prevents aging-related diseases through multiple mechanisms. A reduction in chronic inflammation is widely observed in experimental models of caloric restriction.The low inflammation status may contribute to the reduced incidence of osteoporosis, Alzheimer's disease, cardiovascular diseases and cancer in the aging subjects. **The association of caloric restriction with low inflammation suggests a role of energy accumulation in the origin of the chronic inflammation.** This point is enforced by recent advances in obesity research. Abundant literature on obesity suggests that chronic inflammation is a consequence of energy accumulation in the body."

-Pennington Biomedical Research Center, Louisiana State University System
https://www.ncbi.nlm.nih.gov/pubmed/20606248

See also Fasting , Obesity

Cannabinoid Receptors

"The cannabinoid receptors are found in many mammals and in various classes of vertebrates and invertebrates and in all major subdivisions of bilaterians, urochordates, and cephalochordates but not in the nonchordate invertebrate phyla like insects [1–3]."

-School of Optometry, University of Montreal, Montreal, QC, Canada
-Biomedical Sciences, Faculty of Medicine, University of Montreal, Montreal, QC, Canada
-Faculty of Medicine, University of Montreal, Montreal, QC, Canada
-BRAINlab and Neuropsychiatry Laboratory, Department of Neuroscience and Pharmacology, University of Copenhagen
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4761687/

…"The CB1 cannabinoid receptor, the main molecular target of endocannabinoids and cannabis active components, is the most abundant G protein-coupled receptor in the mammalian brain."…

-Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain;

-Department of Biochemistry and Molecular Biology I, Instituto Universitario de Investigación Neuroquímica, Complutense University, Madrid, Spain;

-NeuroCentre Magendie U862, Endocannabinoids and Neuroadaptation, Institut National de la Santé et de la Recherche Médicale, Bordeaux, France;

-NeuroCentre Magendie , University of Bordeaux, 33077 Bordeaux, France;

-Department of Biochemistry and Molecular Biology IV, Complutense University, Madrid, Spain;

-Research Unit, Hospital Universitario Fundación Alcorcón, 28922 Madrid, Spain; and

-Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz, 55099 Mainz, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4050577/

Cannabinoid Receptors: Nomenclature and Pharmacological Principles

"The CB1 and CB2 cannabinoid receptors are members of the G protein-coupled receptor (GPCR) family that are pharmacologically well defined. However, the discovery of additional sites of action for endocannabinoids as well as synthetic cannabinoid compounds suggests the existence of additional cannabinoid receptors. Here we review this evidence, as well as the current nomenclature for classifying a target as a cannabinoid receptor. Basic pharmacological definitions, principles and experimental conditions are discussed in order to place in context the mechanisms underlying cannabinoid receptor activation. Constitutive (agonist-independent) activity is observed with the overexpression of many GPCRs, including cannabinoid receptors. Allosteric modulators can alter the pharmacological responses of cannabinoid receptors. The complex molecular architecture of each of the cannabinoid receptors allows for a single receptor to recognize multiple classes of compounds and produce an array of distinct downstream effects. Natural polymorphisms and alternative splice variants may also contribute to their pharmacological diversity. As our knowledge of the distinct differences grows, we may be able to target select receptor conformations and their corresponding pharmacological responses. Importantly, the basic biology of the endocannabinoid system will continue to be revealed by ongoing investigations."

-Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA

-Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378782/

Endocannabinoids and Their Pharmacological Actions

"The endocannabinoid system consists of G protein-coupled cannabinoid CB(1) and CB(2) receptors, of endogenous compounds known as endocannabinoids that can target these receptors, of enzymes that catalyse endocannabinoid biosynthesis and metabolism, and of processes responsible for the cellular uptake of some endocannabinoids. This review presents in vitro evidence that most or all of the following 13 compounds are probably orthosteric endocannabinoids since they have all been detected in mammalian tissues in one or more investigation, and all been found to bind to cannabinoid receptors, probably to an orthosteric site: anandamide, 2-arachidonoylglycerol, noladin ether, dihomo-γ-linolenoylethanolamide, virodhamine, oleamide, docosahexaenoylethanolamide, eicosapentaenoylethanolamide, sphingosine, docosatetraenoylethanolamide, N-arachidonoyldopamine, N-oleoyldopamine and haemopressin. In addition, this review describes in vitro findings that suggest that the first eight of these compounds can activate CB(1) and sometimes also CB(2) receptors and that another two of these compounds are CB(1) receptor antagonists (sphingosine) or antagonists/inverse agonists (haemopressin). Evidence for the existence of at least three allosteric endocannabinoids is also presented. These endogenous compounds appear to target allosteric sites on cannabinoid receptors in vitro, either as negative allosteric modulators of the CB1 receptor (pepcan-12 and pregnenolone) or as positive allosteric modulators of this receptor (lipoxin A(4)) or of the CB(2) receptor (pepcan-12). Also discussed are current in vitro data that indicate the extent to which some established or putative orthosteric endocannabinoids seem to target non-cannabinoid receptors and ion channels, particularly at concentrations at which they have been found to interact with CB(1) or CB(2) receptors."

-School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK

https://pubmed.ncbi.nlm.nih.gov/26408156/

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…"The receptor CB1 is the most abundant of all receptor types in the brain and other CNS regions involved with pain transmission and modulation, specifically in the spinal dorsal horn and periaqueductal gray.[4,5] CB1 receptors are also located peripherally in both neuron and non-neuronal tissue, while CB2 receptors are mainly found in immune cells and brain glial cells.[4,6] These receptors have been found to have many physiological and patho-physiological functions, including mood alteration, control of feeding and appetite, motor and co-ordination activities, analgesia, immune modulation and gut motility.[1]

Given the ubiquitous expression of CB1 and CB2 receptors, cannabinoids have been shown to produce wide spectrum of effects including induction of proliferation, growth arrest, or apoptosis in a number of cells, including neurons, lymphocytes, and various neural and non neural cells.[7] Alterations in the reproductive system produced by cannabis motivated the studies leading up to the discovery [8] CB1 receptors have been detected in the testis, prostate and vas deferens.[9–11] In addition, expression of functional CB1 receptors on sperm and presence of the archetypal endocannabinoid anandamide in reproductive secretions have also been detected [12] It can be said therefore that discovery of cannabinoid receptors in bladder lagged behind the discovery of these metabotropic receptors in other organs lining the genitourinary tract."…

-Departments of Urology, William Beaumont Hospital, USA,
-University of Pittsburgh, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2878434

Cancer

"Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer. Approximately 70% of deaths from cancer occur in low- and middle-income countries."

- World Health Organization (WHO)
https://www.who.int/news-room/fact-sheets/detail/cancer

…"Cannabinoids appear to kill tumor cells but do not affect their nontransformed counterparts and may even protect them from cell death. "…

-National Cancer Institute
https://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq#section/all
http://bit.do/ncancer

Phyto-, endo- and synthetic cannabinoids: promising chemotherapeutic agents in the treatment of breast and prostate carcinomas

"The term 'cannabinoids' designates a family of compounds with activity upon cannabinoid receptors. Cannabinoids are classified in three groups: phytocannabinoids, endocannabinoids, and the synthetic analogues of both groups. They have become a promising tool in the

treatment of cancer disease, not only as palliative agents, but also as antitumor drugs, due to their ability to inhibit the proliferation, adhesion, migration, invasion, and angiogenesis of tumour cells. Two of the cancers where they have shown high anticancer activity are breast and prostate tumours. Despite this potential clinical interest, several studies have also reported that cannabinoids can stimulate the proliferation of cancer cells at very low concentrations. Areas covered: The aim of this review is to evaluate the promising chemotherapeutic utility of phytocannabinoids, endocannabinoids, and synthetic cannabinoids in breast and prostate cancer. Expert opinion: Cannabinoids, in particular the non-psychoactive CBD, may be promising tools in combination therapy for breast and prostate cancer, due to their direct antitumor effects, their ability to improve the efficacy of conventional antitumor drugs and their usefulness as palliative treatment. Nevertheless, deeper studies to fully establish the mechanisms responsible for their antitumour and pro-tumour properties and their formulation in efficient delivery systems remain to be established."

-Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy , Complutense University of Madrid , Madrid , Spain.
-Institute of Industrial Pharmacy , Complutense University of Madrid , Madrid , Spain.
https://pubmed.ncbi.nlm.nih.gov/27633508/

The Endocannabinoid System: A Target for Cancer Treatment

"In recent years, the endocannabinoid system has received great interest as a potential therapeutic target in numerous pathological conditions. Cannabinoids have shown an anticancer potential by modulating several pathways involved in cell growth, differentiation, migration, and angiogenesis. However, the therapeutic efficacy of cannabinoids is limited to the treatment of chemotherapy-induced symptoms or cancer pain, but their use as anticancer drugs in chemotherapeutic protocols requires further investigation. In this paper, we reviewed the role of cannabinoids in the modulation of signaling mechanisms implicated in tumor progression."

-Institute of Endocrinology and Experimental Oncology, IEOS CNR, Naples, Italy.
-Department of Molecular Medicine and Medical Biotechnology, University of Naples "Federico II", Naples, Italy.
https://pubmed.ncbi.nlm.nih.gov/31979368/

Effects on cell viability

"Cannabinoids are known to control the cell survival/death decision, leading to different outcomes that depend on the nature of the target cell and its proliferative or differentiation status. Cannabinoids induce growth arrest or apoptosis in a number of transformed cells in

culture. They do so by modulating key cell signalling pathways involved in the control of tumour cell fate. The best-characterised example is cannabinoid-induced apoptosis of glioma cells, which occurs via sustained ceramide accumulation, extracellular signal-regulated kinase activation and Akt inhibition. In addition, cannabinoid administration inhibits the angiogenesis and slows the growth of different types of tumours in laboratory animals. By contrast, most of the experimental evidence indicates that cannabinoids protect normal neurons and glial cells from apoptosis as induced by toxic insults such as glutamatergic overstimulation, ischaemia and oxidative damage. It is therefore very likely that cannabinoids regulate cell survival and cell death pathways differently in tumour and non-tumour cells. Regarding immune cells, cannabinoids affect proliferation and survival in a complex and still obscure manner that depends on the experimental setting. The findings reviewed here might set the basis for the use of cannabinoids in the treatment of cancer and neurodegenerative diseases."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain
https://pubmed.ncbi.nlm.nih.gov/16596790/

Anticancer mechanisms of cannabinoids

"In addition to the well-known palliative effects of cannabinoids on some cancer-associated symptoms, a large body of evidence shows that these molecules can decrease tumour growth in animal models of cancer. They do so by modulating key cell signalling pathways involved in the control of cancer cell proliferation and survival. In addition, cannabinoids inhibit angiogenesis and decrease metastasis in various tumour types in laboratory animals. In this review, we discuss the current understanding of cannabinoids as antitumour agents, focusing on recent discoveries about their molecular mechanisms of action, including resistance mechanisms and opportunities for their use in combination therapy. Those observations have already contributed to the foundation for the development of the first clinical studies that will analyze the safety and potential clinical benefit of cannabinoids as anticancer agents."

…"To summarize, cannabinoids induce tumour cell death and inhibit tumour angiogenesis and invasion in animal models of cancer, and there are indications that they act similarly in patients with glioblastoma. Given that cannabinoids show an acceptable safety profile, clinical trials testing them as single drugs or, ideally, in combination therapies in glioblastoma and other types of cancer are both warranted and urgently needed."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, and Instituto Universitario de Investigación Neuroquímica, Madrid, Spain;
-Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Madrid, Spain;
-Instituto de Investigación Sanitaria del Hospital Clínico San Carlos, Madrid, Spain;

-Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain;

-Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain.

-Correspondence to: Guillermo Velasco, Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, c/ José Antonio Novais 12, Madrid, Spain.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791144/

Cannabinoids as therapeutic agents in cancer: current status and future implications

"The pharmacological importance of cannabinoids has been in study for several years. Cannabinoids comprise of (a) the active compounds of the Cannabis sativa plant, (b) endogenous as well as (c) synthetic cannabinoids. Though cannabinoids are clinically used for anti-palliative effects, recent studies open a promising possibility as anti-cancer agents. They have been shown to possess anti-proliferative and anti-angiogenic effects in vitro as well as in vivo in different cancer models. Cannabinoids regulate key cell signaling pathways that are involved in cell survival, invasion, angiogenesis, metastasis, etc."….

- Molecular Medicine and Biotechnology Department, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

- Department of Pathology, The Ohio State University, Columbus, Ohio, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171598/

Omega-3 polyunsaturated fatty acids and cancer.

"While the anticancer effect of omega-3 polyunsaturated fatty acids (omega-3 fatty acids), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been the subject of intense study, our understanding regarding the underlying mechanisms of omega-3 fatty acids against cancer is still limited. Recent studies describing the cancer protective effect of EPA and DHA have sparked a renewed interest in using these fatty acids for cancer prevention and treatment. Here, we summarize the significance of omega- 3 fatty acids in the initiation and progression of cancer, and review the complex mechanisms by which EPA and DHA are thought to have anticancer activities during cancer development. It is concluded that omega-3 fatty acids may exert their anticancer actions by influencing multiple targets implicated in various stages of cancer development, including cell proliferation, cell survival, angiogenesis, inflammation, metastasis and epigenetic abnormalities that are crucial to the onset and progression of cancer."

-Department of Biochemistry, College of Medicine, Chungnam National University, Daejeon, Korea.

https://www.ncbi.nlm.nih.gov/pubmed/23919748

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...”Against this background, the potential of AEA [anandamide] as a natural anti-cancer agent appears very promising, and certainly worth of urgent investigations.”

-Department of Medicine, Campus Bio-Medico University of Rome, Rome, Italy
-European Center for Brain Research, IRCCS Santa Lucia Foundation, Rome, Italy
-Edited by: Ildikó Ràcz, University Hospital Bonn, Germany
-Reviewed by: John J. Woodward, Medical University of South Carolina, United States
-Meliha Karsak, University Medical Center Hamburg-Eppendorf, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5447297/

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“Long-chain n-3 polyunsaturated fatty acids (PUFA) have been shown to provide health benefits in a number of diseases including several forms of cancer. In this chapter we will discuss in detail some of the prominent mechanisms through which n-3 PUFA and its metabolites are believed to function in the prevention of colon tumorigenesis. At the plasma membrane, n-3 PUFA antagonize the production of inflammatory and procarcinogenic n-6 PUFA (i.e.,arachidonic acid)-derived metabolites. Additionally, the highly unsaturated nature of n-3 PUFA impacts cell membrane properties and dynamics thereby altering numerous cellular functions, including intracellular signaling, cell growth, survival, and proliferation. Due to the sterically incompatible relationship between docosahexaenoic acid, sphingolipids, and cholesterol, the major constituents of lipid rafts, n-3 PUFA modulate these crucial membrane microdomains and perturb efficient signal transduction thereby eliciting the same biological effects exploited by some anti-cancer therapies. Moreover, we discuss how alterations in lipid rafts and downstream signaling impact both epithelial cells and the activation of immune cells. This is noteworthy, because chronic inflammation plays a critical role in tumorigenesis. Therefore, we also present an overview regarding the anti-inflammatory and immunomodulatory mechanisms through which n-3 PUFA perturb the tumor microenvironment and downregulate the activation of critical transcription factors and target genes with an established role in cancer development. Finally, we discuss recent evidence suggesting that n-3 PUFA in combination with other dietary bioactive nutrients, such as soluble fiber and curcumin, could be beneficial in cancer prevention. Collectively, we demonstrate that dietary n-3 PUFA have utility in the prevention of cancer development through mechanisms centered at both the molecular, cellular (plasma membrane), and tissue level. ”

-BOOK: Obesity, Inflammation, and Cancer, Edited by Andrew J. Dannenberg & Nathan A. Berger
-Program in Integrative Nutrtion and Complex Diseases and the Center for Environmental Rual Health Texas A&M University, College Station, TX, USA
-Dr. Harmony F. Turk Ph.D

-Dr.Jennifer M. Monk Ph.D
-Tim Y. Hou B.S
-Dr. Robert S. Capkin Ph.D

Cannabinoids and omega-3/6 endocannabinoids as cell death and anticancer modulators.

"Cannabinoids-endocannaboids are possible preventatives of common diseases including cancers. Cannabinoid receptors (CB(½), TRPV1) are central components of the system. Many disease-ameliorating effects of cannabinoids-endocannabinoids are receptor mediated, but many are not, indicating non-CBR signaling pathways. Cannabinoids-endocannabinoids are anti-inflammatory, anti-proliferative, anti-invasive, anti-metastatic and pro-apoptotic in most cancers, in vitro and in vivo in animals. They signal through p38, MAPK, JUN, PI3, AKT, ceramide, caspases, MMPs, PPARs, VEGF, NF-κB, p8, CHOP, TRB3 and pro-apoptotic oncogenes (p53,p21 waf1/cip1) to induce cell cycle arrest, autophagy, apoptosis and tumour inhibition. Paradoxically they are pro-proliferative and anti-apoptotic in some cancers. Differences in receptor expression and concentrations of cannabinoids in cancer and immune cells can elicit anti- or pro-cancer effects through different signal cascades (p38MAPK or PI3/AKT). Similarities between effects of cannabinoids-endocannabinoids, omega-3 LCPUFA and CLAs/CLnAs as anti-inflammatory, antiangiogenic, anti-invasive anti-cancer agents indicate common signaling pathways. Evidence in vivo and in vitro shows EPA and DHA can form endocannabinoids that: (i) are ligands for CB(½) receptors and possibly TRPV-1, (ii) have non-receptor mediated bioactivity, (iii) induce cell cycle arrest, (iii) increase autophagy and apoptosis, and (iv) augment chemotherapeutic actions in vitro. They can also form bioactive, eicosanoid-like products that appear to be non-CBR ligands but have effects on PPARs and NF-kB transcription factors. The use of cannabinoids in cancer treatment is currently limited to chemo- and radio-therapy-associated nausea and cancer-associated pain apart from one trial on brain tumours in patients. Further clinical studies are urgently required to determine the true potential of these intriguing, low toxicity compounds in cancer therapy. Particularly in view of their synergistic effects with chemotherapeutic agents similar to that observed for n-3 LCPUFA."

-University of Aberdeen, School of Medicine and Dentistry, Cancer Medicine Research Group, Aberdeen, United Kingdom.
https://www.ncbi.nlm.nih.gov/pubmed/23103355

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…"Cannabinoids are a class of bioactive lipids[1, 2, 3] that have a range of interesting activities, including the ability to reduce the growth of tumours such as glioma,[4] breast cancer,[5] prostate

cancer,[6] and colon cancer[7] in different animal models. They impair tumour progression at different levels, with the most prevalent effects being the inhibition of cell proliferation by apoptosis,[8] cell cycle arrest,[9] and autophagy.[10] Cannabinoids induce autophagy in various types of cancer cell lines, and pharmacological or genetic inhibition of autophagy prevents their antiproliferative action, thus demonstrating that autophagy is important for cannabinoid antineoplastic activity.[11] Autophagy is an evolutionarily conserved process in eukaryotes by which cytoplasmic cargo sequestered inside double-membrane vesicles are delivered to the lysosome for degradation.[12] This process has the role to rid the cell of intracellular misfolded or long-lived proteins, superfluous or damaged organelles, and invading microorganisms, and also is an adaptive response to provide nutrients and energy on exposure to various stresses.[13]"…

-Department of Life and Reproduction Sciences, Biochemistry Section, University of Verona, Verona, Italy
-Department of Ecological and Biological Sciences, University of Tuscia, Viterbo, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3698539

Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients

"Epidemiologic studies have indicated that high intake of saturated fat and/or animal fat increases the risk of colon and breast cancer. Omega-3 PUFAs in fish oil (FO) can inhibit the growth of human cancer cells in vitro and in vivo. These effects are related to the uptake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into the cellular substrate pool and their competitive metabolism with arachidonic acid (AA) at the cyclooxygenase and 5-lipoxygenase levels. The metabolites of EPA [omega-3] and DHA [omega-3] have less inflammatory and immunosuppressant potency than the substances derived from AA. Based on previous experimental data, we hypothesized that FO supplementation after major abdominal cancer surgery would improve hepatic and pancreatic function."…

"Moreover, patients with increased risk of sepsis (IL-6/IL-10 ratio >8) showed a tendency to shorter ICU stay (18 hr) under omega-3 PUFA treatment. Weight loss as encountered after the SO emulsion of 1.1 +/- 2.2 kg was absent in the FO group. After major abdominal tumor surgery, FO supplementation improved liver and pancreas function, which might have contributed to the faster recovery of patients."

-Department of Anesthesiology and Critical Care Medicine, University Hospital Carl Gustav Carus, University of Technology, Dresden, Germany.
https://pubmed.ncbi.nlm.nih.gov/15239141

…"Cannabinoids have been previously implicated in inducing autophagy in various cancer cell types: glioma [171] hepatocellular carcinoma [172], pancreatic adenocarcinoma [173], and these effects are at least, in part, dependent on the CB1 receptor. "…

-Andras Bilkei-Gorzo
-Institute of Molecular Psychiatry, University of Bonn, Bonn 53127, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481530

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"Inflammation can be induced by chronic infection, inflammatory diseases and physicochemical factors. Chronic inflammation is estimated to contribute to approximately 25% of human cancers. Under inflammatory conditions, inflammatory and epithelial cells release reactive oxygen (ROS) and nitrogen species (RNS), which are capable of causing DNA damage, including the formation of 8-oxo-7,8-dihydro-2′-deoxyguanosine and 8-nitroguanine. We reported that 8-nitroguanine was clearly formed at the sites of cancer induced by infectious agents including Helicobacter pylori, inflammatory diseases including Barrett's esophagus, and physicochemical factors including asbestos. DNA damage can lead to mutations and genomic instability if not properly repaired. Moreover, DNA damage response can also induce high mobility group box 1-generating inflammatory microenvironment, which is characterized by hypoxia. Hypoxia induces hypoxia-inducible factor and inducible nitric oxide synthase (iNOS), which increases the levels of intracellular RNS and ROS, resulting DNA damage in progression with poor prognosis. Furthermore, tumor-producing inflammation can induce nuclear factor-κB, resulting in iNOS-dependent DNA damage. Therefore, crosstalk between DNA damage and inflammation may play important roles in cancer development. A proposed mechanism for the crosstalk may explain why aspirin decreases the long-term risk of cancer mortality."

-Faculty of Pharmaceutical Sciences, Suzuka University of Medical Science, Suzuka, Mie 513-8670, Japan;
-Division of Health Science, Graduate School of Health Science, Suzuka University of Medical Science, Suzuka, Mie 513-8670, Japan;
-Department of Environmental and Molecular Medicine, Mie University Graduate School of Medicine, Japan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5578195

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…"Cannabinoids, the active components of Cannabis sativa linnaeus (marijuana) and their derivatives, exert a wide array of effects on the CNS as well as on peripheral sites such as the immune, cardiovascular, digestive, reproductive, and ocular systems [13–15]. Nowadays, it is widely accepted that most of these effects are mediated by the activation of specific G protein–coupled receptors that are normally bound by a family of endogenous ligands — the endocannabinoids [14,

[16, 17]. Two different cannabinoid receptors have been characterized and cloned from mammalian tissues: the "central" CB1 receptor, mostly expressed in brain and responsible for cannabinoid psychoactivity [18], and the "peripheral" CB2 receptor, mostly expressed in the immune system and unrelated to cannabinoid psychoactivity [19]. Marijuana and its derivatives have been used in medicine for many centuries, and currently there is a renaissance in the study of the therapeutic effects of cannabinoids, which constitutes a widely debated issue with ample scientific and social relevance. Ongoing research is determining whether cannabinoid ligands may be effective agents in the treatment of, for example, pain and inflammation, neurodegenerative disorders such as multiple sclerosis and Parkinson's disease, and the wasting and emesis associated with AIDS and cancer chemotherapy [13–15]. In addition, cannabinoids may be potential antitumoral agents owing to their ability to induce the regression of various types of tumors, including lung adenocarcinoma [20], glioma [21, 22], and thyroid epithelioma [23] in animal models. Although cannabinoids directly induce apoptosis or cell cycle arrest in different transformed cells in vitro [24], the involvement of this and other potential mechanisms (e.g., inhibition of tumor angiogenesis) in their antitumoral action in vivo is as yet unknown."…

-Project on Cellular and Molecular Biology and Gene Therapy, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas, Madrid, Spain

- Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain

-Department of Pathology, Hospital General de Móstoles, Madrid, Spain- Department of Chemistry, Clemson University, Clemson, South Carolina, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC151833

Cannabinoids in the treatment of cancer

"Cannabinoids, the active components of the hemp plant Cannabis sativa, along with their endogenous counterparts and synthetic derivatives, have elicited anti-cancer effects in many different in vitro and in vivo models of cancer. While the various cannabinoids have been examined in a variety of cancer models, recent studies have focused on the role of cannabinoid receptor agonists (both CB(1) and CB(2)) in the treatment of estrogen receptor-negative breast cancer. This review will summarize the anti-cancer properties of the cannabinoids, discuss their potential mechanisms of action, as well as explore controversies surrounding the results."

-Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand.

https://pubmed.ncbi.nlm.nih.gov/19442435/

Endocannabinoids as emerging suppressors of angiogenesis and tumor invasion (review)

“The medicinal properties of extracts from the hemp plant Cannabis sativa have been known for centuries but only in the 90s membrane receptors for the Cannabis major principle were discovered in mammalian cells. Later on the endogenous ligands for the cannabinoid receptors were identified and the term 'endocannabinoid system' was coined to indicate the complex signaling system of cannabinoid receptors, endogenous ligands and the enzymes responsible for their biosynthesis and inactivation. The 'endocannabinoid system' is involved in a broad range of functions and in a growing number of pathological conditions. There is increasing evidence that endocannabinoids are able to inhibit cancer cell growth in culture as well as in animal models. Most work has focused on the role of endocannabinoids in regulating tumor cell growth and apoptosis and ongoing research is addressed to further dissect the precise mechanisms of cannabinoid antitumor action. However, endocannabinoids are now emerging as suppressors of angiogenesis and tumor spreading since they have been reported to inhibit angiogenesis, cell migration and metastasis in different types of cancer, pointing to a potential role of the endocannabinoid system as a target for a therapeutic approach of such malignant diseases. The potential use of cannabinoids to retard tumor growth and spreading is even more appealing considering that they show a good safety profile, regarding toxicity, and are already used in cancer patients as palliatives to stimulate appetite and to prevent devastating effects such as nausea, vomiting and pain.”

-Department of Pharmaceutical Sciences, University of Salerno, Italy
https://pubmed.ncbi.nlm.nih.gov/17342320/

The endocannabinoid system in cancer-potential therapeutic target?

“Endogenous arachidonic acid metabolites with properties similar to compounds of Cannabis sativa Linnaeus, the so-called endocannabinoids, have effects on various types of cancer. Although endocannabinoids and synthetic cannabinoids may have pro-proliferative effects, predominantly inhibitory effects on tumor growth, angiogenesis, migration and metastasis have been described. Remarkably, these effects may be selective for the cancer cells, while normal cells and tissues are spared. Such apparent tumor cell selectivity makes the endocannabinoid system an attractive potential target for cancer therapy. In this review we discuss various means by which the endocannabinoid system may be targeted in cancer and the current knowledge considering the regulation of the endocannabinoid system in malignancy.”

-Department of Laboratory Medicine, Divison of Pathology, Karolinska Institutet and Karolinska University Hospital Huddinge, Stockholm, Sweden.

https://pubmed.ncbi.nlm.nih.gov/18249558/

Cannabinoids for cancer treatment: progress and promise

"Cannabinoids are a class of pharmacologic compounds that offer potential applications as antitumor drugs, based on the ability of some members of this class to limit inflammation, cell proliferation, and cell survival. In particular, emerging evidence suggests that agonists of cannabinoid receptors expressed by tumor cells may offer a novel strategy to treat cancer. Here, we review recent work that raises interest in the development and exploration of potent, nontoxic, and nonhabit forming cannabinoids for cancer therapy."

-Chemoprevention Program, Paul P. Carbone Comprehensive Cancer Center and Department of Dermatology, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin USA.

https://pubmed.ncbi.nlm.nih.gov/18199524/

The endocannabinoid system as a target for the development of new drugs for cancer therapy

"Studies on the main bioactive components of Cannabis sativa, the cannabinoids, and particularly delta 9-tetrahydrocannabinol (THC), led to the discovery of a new endogenous signalling system that controls several physiological and pathological conditions: the endocannabinoid system. This comprises the cannabinlid receptors, their endogenous agonists--the endocannabinoids--and proteins for endocannabinoid biosynthesis and inactivation. Recently, evidence has accumulated indicating that stimulation of cannabinoid receptors by either THC or the endocannabinoids influence the intracellular events controlling the proliferation and apoptosis of numerous types of cancer cells, thereby leading to anti-tumour effects both in vitro and in vivo. This evidence is reviewed here and suggests that future anti-cancer therapy might be developed from our knowledge of how the endocannabinoid system controls the growth and metastasis of malignant cells."

-Department of Pharmaceutical Sciences, University of Salerno, Institute of Endocrinology and Experimental Oncology of the CNR, Department of Biology and Cellular and Molecular Pathology, Federico II University, Naples.

https://pubmed.ncbi.nlm.nih.gov/12723496/

Cannabinoids and cancer

"Marijuana has been used in medicine for millennia, but it was not until 1964 that delta9-tetrahydrocannabinol (delta9-THC), its major psychoactive component, was isolated in pure form

and its structure was elucidated. Shortly thereafter it was synthesized and became readily available. However, it took another decade until the first report on its antineoplastic activity appeared. In 1975, Munson discovered that cannabinoids suppress Lewis lung carcinoma cell growth. The mechanism of this action was shown to be inhibition of DNA synthesis. Antiproliferative action on some other cancer cells was also found. In spite of the promising results from these early studies, further investigations in this area were not reported until a few years ago, when almost simultaneously two groups initiated research on the antiproliferative effects of cannabinoids on cancer cells: Di Marzo's group found that cannabinoids inhibit breast cancer cell proliferation, and Guzman's group found that cannabinoids inhibit the growth of C6 glioma cell. Other groups also started work in this field, and today, a wide array of cancer cell lines that are affected is known, and some mechanisms involved have been elucidated."

-Hebrew University, Pharmacy School, Department of Medicinal Chemistry and Natural Products, Israel
https://pubmed.ncbi.nlm.nih.gov/16250836/

Cannabinoids in cancer treatment: Therapeutic potential and legislation

"The plant Cannabis sativa L. has been used as an herbal remedy for centuries and is the most important source of phytocannabinoids. The endocannabinoid system (ECS) consists of receptors, endogenous ligands (endocannabinoids) and metabolizing enzymes, and plays an important role in different physiological and pathological processes. Phytocannabinoids and synthetic cannabinoids can interact with the components of ECS or other cellular pathways and thus affect the development/progression of diseases, including cancer. In cancer patients, cannabinoids have primarily been used as a part of palliative care to alleviate pain, relieve nausea and stimulate appetite. In addition, numerous cell culture and animal studies showed antitumor effects of cannabinoids in various cancer types. Here we reviewed the literature on anticancer effects of plant-derived and synthetic cannabinoids, to better understand their mechanisms of action and role in cancer treatment. We also reviewed the current legislative updates on the use of cannabinoids for medical and therapeutic purposes, primarily in the EU countries. In vitro and in vivo cancer models show that cannabinoids can effectively modulate tumor growth, however, the antitumor effects appear to be largely dependent on cancer type and drug dose/concentration. Understanding how cannabinoids are able to regulate essential cellular processes involved in tumorigenesis, such as progression through the cell cycle, cell proliferation and cell death, as well as the interactions between cannabinoids and the immune system, are crucial for improving existing and developing new therapeutic approaches for cancer patients.

TABLE 1 -- Expression of cannabinoid (CB) receptors in selected human cancer types

Cancer cell type	Regulation of CB_1/CB_2	Mechanisms and other relevant circumstances	Reference
Breast cancer	Elevated CB_2 receptor expression in HER2+breast tumors.	HER2 induces CB_2 expression activating ELK1 (ERK/MAPK cascade); activated pro-oncogenic signaling through tyrosine kinase c-Src.	[28,29]
	Presence of TRPV1 in human breast adenocarcinoma cell line (MCF-7).	TRPV1 agonists/antagonists induce significant inhibition of MCF-7 cell growth.	[30]
	Elevated CB_1 receptor expression.	Activation of Akt signaling pathway was proposed. Increased CB_1 and FAAH levels correlate with severity of the disease.	[31-34] [35,36]
Prostate cancer	Expression of CB_1 and CB_2 receptor significantly higher in human prostate cancer.	Additionally: Presence of TRPV1 and TRPA1 in all prostate cancer cells (except LNCaP cells), TRPV2 in DU-145 and PC-3 cells only, TRPM8 in AR-dependent prostate cell lines (e.g., LNCaP).	[37-39]
	Expression of CB_1 and CB_2 receptor significantly higher in human prostate cancer.	Expression of GPR55 in PC-3 and DU-145 cell lines has been reported, mediating effects of LPI.	[40]
Chemically induced hepatocellular carcinoma	Upregulation of CB_1 receptors.	Diethylnitrosamine induced liver cancer.	[41]
Hepatocellular carcinoma	Overexpression of CB_1 and CB_2 receptors.	Overexpression of CB_1 and CB_2 receptors is associated with improved prognosis.	[42]
Non-small cell lung cancer	Overexpression of CB_1 and CB_2 receptors.	Activation of Akt signaling pathway, MMP9 expression and activity.	[43]
Chronic lymphocytic leukemia	Overexpression of CB_1 and CB_2 receptors.	CB_1 receptor expression correlated with high-risk markers.	[44]
Pancreatic cancer	CB1 and CB_2 receptors expressed in normal and pancreatic cancer cells (higher expression of CB_1).	Cannabinoids induced apoptosis via CB_2 receptor (ceramide dependent pathway).	[45-47]
Melanoma	CB_2 is overexpressed in human melanoma tissues and cell lines.	Not reported.	[48]

HER2: Human epidermal growth factor receptor 2; ELK1: ETS domain-containing protein; c-Src: Tyrosine-protein kinase Src; ERK: Extracellular-signal-regulated kinase; MAPK: Mitogen-activated protein kinase; TRPV1: Transient receptor potential vanilloid receptor 1; Akt: Protein Kinase B; FAAH: Fatty acid amide hydrolase; TRPA1: Transient receptor potential ankyrin 1; GPR55: Orphan G-protein coupled receptor 55; AR: Androgen receptor; LPI: Lysophosphatidylinositol; MMP9: Matrix metallopeptidase 9

The national legislation of the EU Member States defines the legal boundaries of permissible use of cannabinoids for medical and therapeutic purposes, however, these legislative guidelines may not be aligned with the current scientific knowledge."…

"Subsequent studies demonstrated the important role of the ECS and endocannabinoids in different physiological and pathological processes, such the regulation of excitatory and inhibitory synaptic transmission in the central nervous system (CNS), food intake, nociceptive signaling, analgesia, immunomodulation, inflammation, and cancer cell signaling [17-19].

In cancer patients, cannabinoids have primarily been used as a part of palliative care to alleviate pain, relieve nausea and stimulate appetite [8,20]. In addition, numerous cell culture and animal studies showed antitumor effects of cannabinoids and suggested new therapeutic opportunities for cancer patients [20]. However, recent research also emphasizes the importance of safety measures when using cannabinoids, since these compounds can potentially impair cognitive functions, especially in adolescents [21]."…

"It is important to note that cannabinoids may also exert their antitumor effects independent of the CB receptors, for example as demonstrated in human pancreatic cancer cell line MIA PaCa-2 [27]. The biological role of the ECS in cancer pathophysiology is not completely clear [20] but most

studies suggest that CB receptors and their endogenous ligands are upregulated in tumor tissue [28,29,31,34-39,41,48] and that the overexpression of ECS components (i.e., receptors, ligands, and enzymes) correlates with tumor aggressiveness [49-51]. However, a tumor-suppressive role of ECS was also indicated by some studies, e.g., the upregulation of endocannabinoid-degrading enzymes was observed in aggressive human cancers and cancer cell lines [51]. Moreover, experimental studies showed that the activation of CB receptors by cannabinoids is antitumorigenic in most cases, i.e., it inhibits tumor cell proliferation, induces apoptosis in vitro, and blocks angiogenesis and tumor invasion/metastasis in vivo [35,46,51,52]. The effects of CB receptor (over)expression in selected human tumor cell lines are described in more detail in Table 1."…"By targeting the ECS, cannabinoids affect many essential cellular processes and signaling pathways which are crucial for tumor development [51,53,54]. For example, they can induce cell cycle arrest, promote apoptosis, and inhibit proliferation, migration and angiogenesis in tumor cells (Figure 1) [53,54]. In addition to CB receptor-mediated (CB1 and CB2 receptors) cannabinoid effects, it appears that these processes can also be CB receptor-independent (e.g., through TRPV1, 5-hydroxytryptamine [5-HT]3, or nicotinic acetylcholine receptor [nAChR] among others) [53], suggesting that molecular mechanisms underlying the antitumor activity of cannabinoids are even more complex than originally thought. Moreover, it is expected that future studies will discover novel molecular targets of cannabinoids [53]."….

"The ability of plant-derived and synthetic cannabinoids to control cancer cell growth, invasion, and death has been demonstrated in numerous experimental studies using cancer cell lines and genetically engineered mouse models. Also, different types of cannabinoids may have different modes of action. For example, a phytocannabinoid THC promotes apoptosis in a CB-receptor dependent manner, while CBD exerts this effect independently of CB1/CB2 receptors and possibly includes the activation of TRPV2 receptor, at least in some cancer types. Also, some CB receptor agonists are less efficient in promoting cancer cell death although they demonstrate higher affinity for CB receptors than THC, such as synthetic CB receptor agonist WIN-55,212-2. Better understanding of homo- or hetero-oligomerization of CB receptors, their interactions with lipid rafts for example, and mechanisms of selective G-protein coupling may clarify these differences [54]. Finally, because molecular changes are tumor-specific in most cases (i.e., the presence of intra- and inter-tumor heterogeneity), CB-receptor mediated antitumor effects largely depend on the type of cancer that is being investigated and characteristics of derived tumor cell line, including the donor characteristics, tumor site of origin and hormonal responsiveness [53-55]."

-Department of Cell Biology, Institute of Biomedical Sciences, Faculty of Medicine, University of Maribor, Maribor, Slovenia

-Department of Labour Law, Faculty of Law, University of Maribor, Maribor, Slovenia

-Laboratory for Separation Processes and Product Design, Faculty of Chemistry and Chemical Engineering, University of Maribor, Maribor, Slovenia

-Institute for Biostatistics and Medical Informatics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6387667/

Cannabinoids and cancer

"Marijuana has been used in medicine for millennia, but it was not until 1964 that delta9-tetrahydrocannabinol (delta9-THC), its major psychoactive component, was isolated in pure form and its structure was elucidated. Shortly thereafter it was synthesized and became readily available. However, it took another decade until the first report on its antineoplastic activity appeared. In 1975, Munson discovered that cannabinoids suppress Lewis lung carcinoma cell growth. The mechanism of this action was shown to be inhibition of DNA synthesis. Antiproliferative action on some other cancer cells was also found. In spite of the promising results from these early studies, further investigations in this area were not reported until a few years ago, when almost simultaneously two groups initiated research on the antiproliferative effects of cannabinoids on cancer cells: Di Marzo's group found that cannabinoids inhibit breast cancer cell proliferation, and Guzman's group found that cannabinoids inhibit the growth of C6 glioma cell. Other groups also started work in this field, and today, a wide array of cancer cell lines that are affected is known, and some mechanisms involved have been elucidated."

-Hebrew University, Pharmacy School, Department of Medicinal Chemistry and Natural Products, Israel.
https://pubmed.ncbi.nlm.nih.gov/16250836/

Endocannabinoids and cancer

…"Recent applications of cannabinoids have included their potential use as anti-tumor agents [79,80] which relies on their ability to inhibit tumor angiogenesis [81,82] or directly induce apoptosis or cell cycle arrest in neoplastic cells [83–86]. Studies from our laboratory demonstrated that AEA can induce apoptosis in malignant immune cells [87]. Molt-4 human tumor cells when cultured for 4 h in the presence of various concentrations of anandamide (5, 10, 20, and 40 μM) were found to undergo significant levels of apoptosis as quantified using the TUNEL assay at concentrations of 20 μM or greater. Also, murine EL-4 tumor T cells were found to be more sensitive to AEA as much as exposure to 5 and 10 μM AEA was sufficient to trigger significant levels of apoptosis [87]. Role of the endocannabinoids as potential endogenous tumor growth inhibitors has been suggested in a study where it was observed that levels of both AEA and 2-AG were higher in precancerous polyps than in fully developed carcinoma in colon [88]. Recent in vivo studies

proposed that selective targeting of CB2 receptor resulted in colorectal tumor growth inhibition via apoptosis which was mediated through the stimulation of ceramide [89]. In a xenograft model of thyroid cancer, substances that block endocannabinoid degradation increased levels of AEA and 2-AG in tissues and reduced tumor growth [90]. Various attempts have been made to inactivate cannabinoid degrading enzymes thus increasing the local concentration of endocannabinoids at the tumor cell surface leading to anti-tumor effects of CB-receptor signaling in various types of cancer including thyroid, brain and prostate cancers [90–93].

Although majority of the effects of cannabinoids are mediated through CB receptors, AEA has been shown to induce its effects on cancerous cells by interacting with TRPV1 receptor [94,95] or cholesterol rich lipid rafts [96]. Furthermore, it has been reported that signaling pathways are differentially regulated by cannabinoids in normal cells versus cancer cells. In malignancies, such as thyroid cancer, lymphoma, melanoma, pancreas and breast cancer, the levels of cannabinoid receptors are often higher in the tumors when compared to normal cells, resulting in increased sensitivity to cannabinoids in malignant cells [67,83,97–99]. Moreover, many animal studies have reported anti-proliferative and pro-apoptotic effects of cannabinoids on tumor cells but not on normal tissue [79,83,85,97]. Thus the role of the endocannabinoid system in cancer indicates that this system is involved in regulating many of the functions that are essential in cancer development."…

-Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, United State

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044336

Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells

"Autophagy can promote cell survival or cell death, but the molecular basis underlying its dual role in cancer remains obscure. Here we demonstrate that Δ9-tetrahydrocannabinol (THC), the main active component of marijuana, induces human glioma cell death through stimulation of autophagy. Our data indicate that THC induced ceramide accumulation and eukaryotic translation initiation factor 2α (eIF2α) phosphorylation and thereby activated an ER stress response that promoted autophagy via tribbles homolog 3–dependent (TRB3-dependent) inhibition of the Akt/mammalian target of rapamycin complex 1 (mTORC1) axis. We also showed that autophagy is upstream of apoptosis in cannabinoid-induced human and mouse cancer cell death and that activation of this pathway was necessary for the antitumor action of cannabinoids in vivo. These findings describe a mechanism by which THC can promote the autophagic death of human and mouse cancer cells and provide evidence that cannabinoid

administration may be an effective therapeutic strategy for targeting human cancers."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.

-Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain.

-3D Lab (Development, Differentiation, and Degeneration), Department of Cellular and Molecular Physiopathology, Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain.

-INSERM U624, Campus de Luminy, Marseille, France.

-National Institute for Infectious Diseases, IRCCS "L. Spallanzani," Rome, Italy.

-Laboratory of Molecular Neuroembryology, IRCCS Fondazione Santa Lucia and Department of Biology, University of Rome "Tor Vergata," Rome, Italy.

-Cancer Genetics Program, Beth Israel Deaconess Cancer Center and Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

-Department of Neurosurgery, University Hospital, Tenerife, Spain.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2673842/

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…"A growing body of literature exists surrounding n-3 PUFA and cancers of the breast and prostate. Animal studies suggest a beneficial effect, however the relationship in humans is more complex. Many human studies fail to differentiate between ALA, EPA, and DHA when reporting effects of n-3 PUFA on cancer risk, or a fish oil blend is used, preventing evaluation of individual effects of EPA and DHA. Despite these challenges, important mechanistic insights are continually being identified that will eventually help elucidate the individual effects of n-3 PUFA in two of the most common forms of cancer worldwide."…

-Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3224740

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…"In contrast to ALA [alpha-linolenic acid / omega-3], there is some evidence suggesting a protective role for EPA [eicosapentaenoic acid / omega-3] and DHA [docosahexaenoic acid / omega-3] in prostate cancer. In vitro studies have identified dose-dependent inhibition of human cancer cell growth [73] and repression of PSA [74] in PC-3, DU 145, and LNCaP prostate cancer cell lines. "…

-Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3224740

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…"Emerging evidence has demonstrated promising effects of cannabinoids on inhibition of tumor cell growth by modulating different cell signaling pathways in diverse cancer cells, such as

lymphoma, hepatocellular carcinoma cells, breast cancer, pancreatic cancer, and skin cancer cells [1–7]. Natural and synthetic cannabinoids act by interacting with two distinctive G protein-coupled cannabinoid receptors, subtype 1 (CB1) and 2 (CB2) [8,9]. CB1 is expressed abundantly in central nervous system and certain peripheral nerve terminal sites, whereas CB2 is expressed dominantly in the immune system, especially on plasma cells [10,11]. "…

-Department of Pharmaceutical Sciences and Drug Discovery Institute, University of Pittsburgh, Pittsburgh, PA

-Department of Computational Biology, Joint Pitt/CMU Computational Biology Program, University of Pittsburgh, Pittsburgh, PA

-Division of Hematology/Oncology, Columbia University, NY

-Hematology/Oncology, Department of Medicine, Indiana University, Indianapolis, IN

-Hisun Institute, Zhejiang Hisun Pharmaceutical Co. Ltd., Taizhou, Zhejiang, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504841/

The dual effects of delta(9)-tetrahydrocannabinol on cholangiocarcinoma cells: anti-invasion activity at low concentration and apoptosis induction at high concentration

"Currently, only gemcitabine plus platinum demonstrates the considerable activity for cholangiocarcinoma. The anticancer effect of Delta (9)-tetrahydrocannabinol (THC), the principal active component of cannabinoids has been demonstrated in various kinds of cancers. We therefore evaluate the antitumor effects of THC on cholangiocarcinoma cells. Both cholangiocarcinoma cell lines and surgical specimens from cholangiocarcinoma patients expressed cannabinoid receptors. THC inhibited cell proliferation, migration and invasion, and induced cell apoptosis. THC also decreased actin polymerization and reduced tumor cell survival in anoikis assay. pMEK1/2 and pAkt demonstrated the lower extent than untreated cells. Consequently, THC is potentially used to retard cholangiocarcinoma cell growth and metastasis."

-Faculty of Pharmacy, Rangsit University, Patumthani, Thailand.

https://pubmed.ncbi.nlm.nih.gov/19916793/

Omega-3 fatty acids and their lipid mediators: towards an understanding of resolvin and protectin formation

"Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have long been associated with decreased inflammation and are also implicated in the prevention of tumorigenesis. Conventional thinking attributed this mainly to a suppressive effect of these fatty acids on the formation of arachidonic acid-derived prostaglandins and leukotrienes. Recent years have seen the discovery of a new

class of inflammation-dampening and resolution-promoting n-3 PUFA-derived lipid mediators called resolvins and protectins. Chemically, these compounds are hydroxylated derivatives of the parent n-3 PUFA eicosapentaenoic acid (EPA) for the E-resolvins, and docosahexaenoic acid (DHA) for the D-resolvins and protectin D1. "…

-Department of Gastroenterology, Hepatology and Endocrinology, Charité University Medicine, Rudolf-Virchow-Hospital, Berlin, Germany

https://pubmed.ncbi.nlm.nih.gov/22326554/

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…"Based on the ability of CBs [cannabinoids] to inhibit inflammation and block cancer cell proliferation, plant-derived and synthetic CBs have been investigated for their applications as antitumor drugs. Indeed, a growing number of reports on the role of receptors for CBs in tumor cells suggest that CBs with different properties that can block or activate CB-receptors (CB-Rs) may be useful in cancer treatment [7,8]."…

-Institute of Biology and Ecology, Faculty of Sciences, University of Pavol Jozef Šafárik in Košice, Košice, Slovakia

-Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria;

-Institute of Chemistry, Faculty of Sciences, University of Pavol Jozef Šafárik in Košice, Slovakia;

-Department of Clinical Pharmacy and Diagnostics, University of Vienna, Vienna, Austria;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6479799/

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…"Within the World Cancer Research Foundation report, red meat was among the top 10 factors associated with incidence and progression of carcinomas in all populations [(11)]."…

-Departments of Medicine Pathology and Cellular and Molecular Medicine, Glycobiology Research and Training Center, University of California, San Diego, La Jolla, CA

-Edited by Stuart A. Kornfeld, Washington University School of Medicine

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4299224/

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…"Studies have long shown that people who took marijuana extracts in clinical trials tended to need less pain medicine.

More recently, scientists reported that THC and other cannabinoids such as CBD slow growth and/or cause death in certain types of cancer cells growing in lab dishes. Some animal studies also suggest certain cannabinoids may slow growth and reduce spread of some forms of cancer."…

- *American Cancer Society*
https://www.cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/marijuana-and-cancer.html

Antineoplastic and apoptotic effects of cannabinoids. N-acylethanolamines: protectors or killers?

"The proapoptotic and antineoplastic properties of cannabinoids with emphasis on effects of N-acylethanolamines were analyzed. Cannabinoids enhanced apoptotic and necrotic processes in many types of tumour cells and tissues. Involvement of different types of receptors and signaling pathways in mediating the proapoptotic effects of cannabinoids are discussed. The evidences in favour of both proapoptotic, pronecrotic and protective, antiapoptotic effects of cannabinoids and, especially N-acylethanolamines, are evaluated. The hypothesis is suggested that N-acylethanolamines, formed in some tissues under strong stress conditions, can be not a consequence of tissue damage but cause such damage. The conclusion is made on promising of cannabinoids as potential anticancer agents."

-Institute of Endocrinology and Metabolism, AMS of Ukraine, Kyiv, Ukraine.
https://pubmed.ncbi.nlm.nih.gov/18438336/

See also Zinc

Cancer Cachexia

"Cancer cachexia is a wasting syndrome characterized by weight loss, anorexia, asthenia and anemia. The pathogenicity of this syndrome is multifactorial, due to a complex interaction of tumor and host factors. The signs and symptoms of cachexia are considered as the prognostic parameters in cancer patients."

-Department of Oral Pathology, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227249

See also Ceramide , Omega-3s & Cancer , Skeletal Muscle

Cancer-induced Bone Disease (CIBD)

The Endocannabinoid/Endovanilloid System in Bone: From Osteoporosis to Osteosarcoma

"Patients with primary bone cancer, like OS, and bone metastases commonly acquire cancer-induced bone disease (CIBD), presenting several troubles such as bone pain, restricted mobility, high rate of fractures, nerve compression, and hypercalcemia. It has been observed that pharmacological and genetic manipulation of CB2 reduces the progression of CIBD [107]. In particular, its activation with specific ligands acts directly on tumor-inducing apoptosis or necrosis in malignant cells, but also on osteoclasts, inhibiting their formation and differentiation. CB2 activation is also associated with a reduction in tumor angiogenesis, maybe due to an autocrine inhibition in vascular endothelial growth factor (VEGF) production by the tumor itself. In 2013, Lozano-Ondoua et al. were the first ones who, using the CB2-selective agonist JWH015, observed a reduction in the number of breast cancer cell line 66.1 in the intramedullary cavity of mice after an injection that mimicked a bone metastasis condition [108]."

-Department of Women, Child, and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy;

-Department of Experimental Medicine, University of Campania Luigi Vanvitelli, Naples, Italy;

-Department of Gynecology, Obstetrics and Reproductive Sciences, University of Campania Luigi Vanvitelli, Naples, Italy;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6514542/

Emerging therapeutic targets in cancer induced bone disease: A focus on the peripheral type 2 cannabinoid receptor.

"Skeletal complications are a common cause of morbidity in patients with primary bone cancer and bone metastases. The type 2 cannabinoid (Cnr2) receptor is implicated in cancer, bone metabolism and pain perception. Emerging data have uncovered the role of Cnr2 in the regulation of tumour-bone cell interactions and suggest that agents that target Cnr2 in the skeleton have potential efficacy in the reduction of skeletal complications associated with cancer. This review aims to provide an overview of findings relating to the role of Cnr2 receptor in the regulation of skeletal tumour growth, osteolysis and bone pain, and highlights the many unanswered questions and unmet needs. This review argues that development and testing of peripherally-acting, tumour-, Cnr2-selective ligands in preclinical models of metastatic cancer will pave the way for future research that will advance our knowledge about the basic mechanism(s) by which the endocannabinoid system regulate cancer metastasis, stimulate the

development of a safer cannabis-based therapy for the treatment of cancer and provide policy makers with powerful tools to assess the science and therapeutic potential of cannabinoid-based therapy. Thus, offering the prospect of identifying selective Cnr2 ligands, as novel, alternative to cannabis herbal extracts for the treatment of advanced cancer patients."

-Department of Oncology and Metabolism, University of Sheffield, Medical School, Beech Hill Road, Sheffield, UK.
-Department of Oncology and Metabolism, University of Sheffield, Medical School, Beech Hill Road, Sheffield, UK.
https://www.ncbi.nlm.nih.gov/pubmed/28274851

Cancer & Inflammation

"Aging is considered the major risk factor for cancer, one of the most important mortality causes in the western world. Inflammaging, a state of chronic, low-level systemic inflammation, is a pervasive feature of human aging. Chronic inflammation increases cancer risk and affects all cancer stages, triggering the initial genetic mutation or epigenetic mechanism, promoting cancer initiation, progression and metastatic diffusion. Thus, inflammaging is a strong candidate to connect age and cancer. **A corollary of this hypothesis is that interventions aiming to decrease inflammaging should protect against cancer, as well as most/all age-related diseases.** Epidemiological data are concordant in suggesting that the Mediterranean Diet (MD) decreases the risk of a variety of cancers but the underpinning mechanism(s) is (are) still unclear. Here we review data indicating that the MD (as a whole diet or single bioactive nutrients typical of the MD) modulates multiple interconnected processes involved in carcinogenesis and inflammatory response such as free radical production, NF-κB activation and expression of inflammatory mediators, and the eicosanoids pathway. Particular attention is devoted to the capability of MD to affect the balance between pro- and anti-inflammaging as well as to emerging topics such as maintenance of gut microbiota (GM) homeostasis and epigenetic modulation of oncogenesis through specific microRNAs."…

"Human aging is a complex, extremely heterogeneous and dynamic trait determined by a number of environmental, genetic, epigenetic, and stochastic factors [1]. A pervasive feature of human aging and probably one of its major causes, is represented by the chronic, low-level state of systemic and sterile (in the absence of overt infection) inflammation called "inflammaging" [2,3]. Indeed, inflammation has been recently included among the seven pillars of aging [4]. It can be beneficial as an acute, transient immune response to harmful conditions, facilitating the repair, turnover and adaptation of many tissues. However, during aging, inflammatory response tends to become chronic and of low grade, leading to tissue degeneration.

Indeed, inflammaging is characterized by a general increase in plasma levels and cell capability to produce pro-inflammatory cytokines such as Interleukin-6 (IL-6), Interleukin-1 (IL-1) and Tumour Necrosis Factor-α (TNF-α) and by a subsequent increase of the main inflammatory markers, such as C-reactive protein (CRP) and serum amyloid A (A-SAA) [2,5]. This generalized pro-inflammatory status, interacting with the genetic background and environmental factors, potentially triggers the onset of the most important age-related diseases, such as cardiovascular diseases, atherosclerosis, metabolic syndrome, type 2 diabetes, obesity, neurodegeneration, arthrosis and arthritis, osteoporosis and osteoarthritis, sarcopenia, major depression, frailty and cancer [6,7].

The hypothesis of a possible correlation between cancer and inflammation was firstly formulated by the Greek physician Galenus [8,9]. In 1863 Rudolph Virchow, a pioneer of cellular pathology, noted inflammatory cells within tumor mass and that tumors arise at sites of chronic inflammation [10,11]. A functional framework developed by Hanahan and Weinberg (2000) characterizes cancer by six biological hallmarks, able to regulate the conversion of normal cells in cancer cells: self-sufficiency in growth signals, insensitivity to growth inhibitory signals, limitless replicative potential, the ability to evade programmed cell-death (apoptosis), the ability to sustain angiogenesis, the ability to invade tissues and metastasize [12]. Studies have also supported the important role of inflammatory cells and cytokines in the tumor microenvironment [13,14,15]. In 2011, Weinberg and Hanahan proposed four additional new cancer hallmarks: ability to evade the immune system, presence of inflammation, tendency towards genomic instability and dysregulated metabolism [16]. The correlation between chronic inflammation and cancer has been supported by epidemiological and experimental studies on humans and animal models [13,15,17] along with the observation that preventive treatments with anti-inflammatory drugs such as aspirin or cyclooxygenase-2 (COX-2) inhibitors reduce the risk of developing colorectal and breast cancer and even mortality [15,18,19]. Chronic inflammation affects all cancer stages, increasing the onset risk, supporting the initial genetic mutation or epigenetic mechanism leading to cancer initiation [20,21,22], promoting tumor progression, and supporting metastatic diffusion [9,22,23,24,25].”

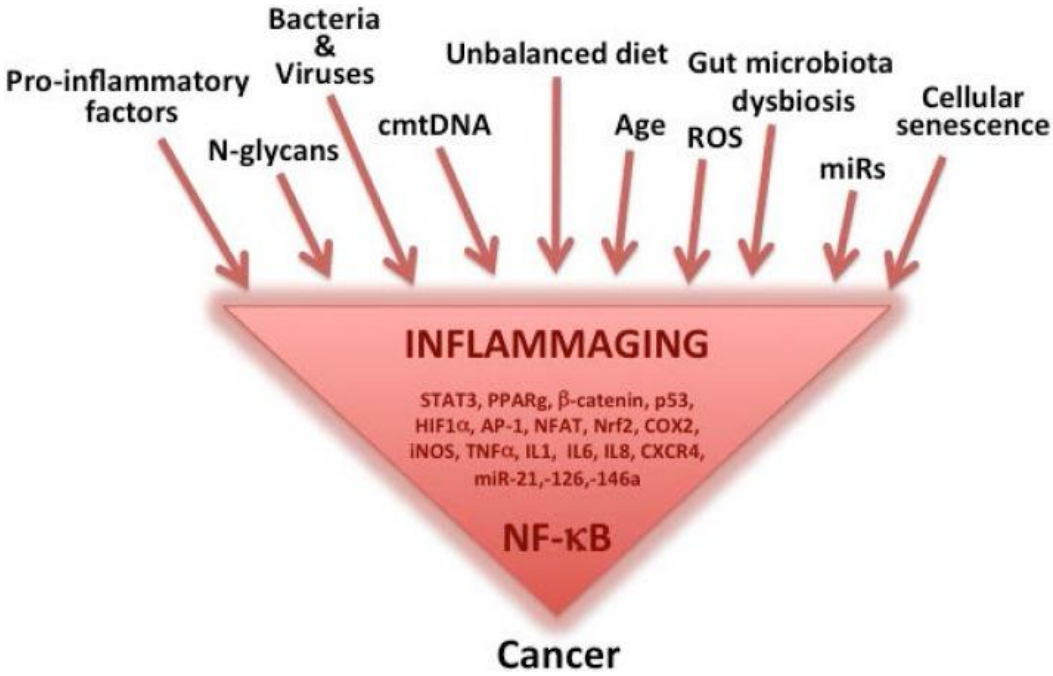
Inflammatory Sources for Cancer Development

“Apart from inflammaging, viruses, bacteria and parasite infections as well as the exposure to chemical or physical agents can support chronic inflammation and have been linked to several cancer types [36,37,38]. Similarly, unresolved inflammation unrelated to infections can also contribute to carcinogenesis as observed in Barrett’s metaplasia, chronic pancreatitis or esophagitis [21,38,39,40,41,42,43] or in autoimmune diseases [21].

Obesity plays a central role in carcinogenesis since adipose tissue has been recognized as an endocrine source of mediators (hormones, acute-phase proteins, cytokines, adipokines and

growth factors, [44]) able to sustain a chronic low-grade inflammation. During the last fifteen years, obesity has been associated with several types of tumors such as breast, endometrium, prostate, kidney, esophagus, stomach, colon, pancreas, gallbladder, and liver [45,46,47,48,49] and also with an increased cancer aggressiveness, risk of relapse and mortality [49].”…

“The MD is characterized by a high content of “good fats”, monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids, present in marine fish, vegetable oils (especially olive oil) **[See note below regarding cooking oils]**, in nuts and seeds, and by a low intake of saturated fatty acids and hydrogenated oils (trans fats). In particular, the MD provides an optimal dietary fat profile characterized by a low intake of saturated and ω-6 fatty acids and a moderate intake of ω-3 fatty acids [78]. The ratio between ω-6 and ω-3 PUFAs plays an important role in the modulation of inflammation and blood coagulation [79] and is one of the most powerful anti-inflammatory features of this diet.”…



-Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Italy;
-Interdepartmental Centre “L. Galvani” (CIG) University of Bologna, Bologna, Italy;
-IRCCS, Institute of Neurological Sciences, Italy
-National Research Council of Italy, CNR, Institute for Organic Synthesis and Photoreactivity (ISOF), Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425163

Note: While olive oil does contains some healthy ingredients, it has been reported by some doctors that it is still not healthy due to the omega ratio of olive oil being high in omega-6s. See Cooking Oils for more research quotes.

Chronic Inflammation in Skin Malignancies

"Chronic inflammation is linked to the development and progression of multiple cancers, including those of the lung, stomach, liver, colon, breast and skin. Inflammation not only drives the oncogenic transformation of epithelial cells under the stress of chronic infection and autoimmune diseases, but also promotes the growth, progression and metastatic spread of cancers. Tumor-infiltrating inflammatory cells are comprised of a diverse population of myeloid and immune cell types, including monocytes, macrophages, dendritic cells, T and B cells, and others. Different myeloid and lymphoid cells within tumor microenvironment exert diverse, often contradicting, effects during skin cancer development and progression. The nature of tumor-immune interaction determines the rate of cancer progression and the outcome of cancer treatment. Inflammatory environment within skin tumor also inhibits naturally occurring anti-tumor immunity and limits the efficacy of cancer immunotherapy. In this article we aim to give an overview on the mechanism by which inflammation interferes with the development and therapeutic intervention of cancers, especially those of the skin."

-Department of Dermatology, 303 Hospital of People's Liberation Army, Nanning, Guangxi Province, China

-Department of Immunology, School of Medicine, University of Connecticut Health Center, Farmington, Connecticut, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911907/

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…"Omega-3 (ω-3) and omega-6 (ω-6) polyunsaturated fatty acids (PUFAs) are essential fatty acids that have been shown to play an important role in several chronic illnesses [1]. Epidemiologic data suggest that changes in total fat intake and the shifted ratio favoring ω-6 over ω-3 PUFAs in the Western diet, have paralleled the rise of cardiovascular disease, obesity, diabetes, and other chronic diseases as leading contributors to morbidity and mortality rates [2]. Of its many clinical consequences, obesity is a well known risk factor for the development of several epithelial malignancies, and it is becoming increasingly apparent that inflammation may be a key mediator of this obesity-cancer link [3]. Partly for this reason, manipulating fatty acid composition has garnered increasing scientific attention as an attractive potential cancer prevention and adjunctive treatment strategy."…

-Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center; New York, NY

-Department of Medicine, Weill Cornell Medical College; New York, NY

-The Rockefeller University; New York, NY

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3780443/

Significance of long chain polyunsaturated fatty acids in human health

..."Recent findings reviewed in the present study highlight that the omega-6 fatty acid ARA appears increased, and omega-3 EPA and DHA decreased in most cancer tissues compared to normal ones, and that increments in omega-3 LC-PUFAs consumption and an omega-6/omega-3 ratio of 2–4:1, are associated with a reduced risk of breast, prostate, colon and renal cancers. Along with their lipid-lowering properties, omega-3 LC-PUFAs also exert cardioprotective functions, such as reducing platelet aggregation and inflammation, and controlling the presence of DHA in our body, especially in our liver and brain, which is crucial for optimal brain functionality. Considering that DHA is the principal omega-3 FA in cortical gray matter, the importance of DHA intake and its derived lipid mediators have been recently reported in patients with major depressive and bipolar disorders, Alzheimer disease, Parkinson's disease, and amyotrophic lateral sclerosis. The present study reviews the relationships between major diseases occurring today in the Western world and LC-PUFAs. More specifically this review focuses on the dietary omega-3 LC-PUFAs and the omega-6/omega-3 balance, in a wide range of inflammation disorders, including autoimmune diseases. This review suggests that the current recommendations of consumption and/or supplementation of omega-3 FAs are specific to particular groups of age and physiological status, and still need more fine tuning for overall human health and well being."

-Canary Islands Cancer Research Institute (ICIC), Ave. La Trinidad 61, Torre A. Arévalo, 7th floor, 38204 La Laguna, Tenerife Spain

-Centre Algatech, Institute of Microbiology, Academy of Sciences of the Czech Republic, Třeboň, Czech Republic

-Department of Nutrition and Preventive Medicine, Norwich Medical School, University of East Anglia, Norwich, NR4 7UQ UK

-Department of Animal Biology, Soil Science and Geology (Animal Physiology Unit), Faculty of Sciences, Universidad de La Laguna, Ave. Astrofísico Francisco Sánchez s/n, 38206 La Laguna, Tenerife Spain

-Institute of Biomedical Technologies (ITB), Universidad de La Laguna, Campus de Ofra, 38071 La Laguna, Tenerife Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5532176

bit.do/longchain

Chronic inflammation and oxidative stress in human carcinogenesis

"A wide array of chronic inflammatory conditions predispose susceptible cells to neoplastic transformation. In general, the longer the inflammation persists, the higher the risk of cancer. A mutated cell is a sine qua non for carcinogenesis. Inflammatory processes may induce DNA mutations in cells via oxidative/nitrosative stress. This condition occurs when the generation of free radicals and active intermediates in a system exceeds the system's ability to neutralize and eliminate them. Inflammatory cells and cancer cells themselves produce free radicals and soluble

mediators such as metabolites of arachidonic acid, cytokines and chemokines, which act by further producing reactive species. These, in turn, strongly recruit inflammatory cells in a vicious circle. Reactive intermediates of oxygen and nitrogen may directly oxidize DNA, or may interfere with mechanisms of DNA repair. These reactive substances may also rapidly react with proteins, carbohydrates and lipids, and the derivative products may induce a high perturbation in the intracellular and intercellular homeostasis, until DNA mutation. The main substances that link inflammation to cancer via oxidative/nitrosative stress are prostaglandins and cytokines. The effectors are represented by an imbalance between pro-oxidant and antioxidant enzyme activities (lipoxygenase, cyclooxygenase and phospholipid hydroperoxide glutathione-peroxidase), hydroperoxides and lipoperoxides, aldehydes and peroxinitrite. This review focalizes some of these intricate events by discussing the relationships occurring among oxidative/nitrosative/metabolic stress, inflammation and cancer."

-Division of Gastroenterology, "F. Magrassi and A. Lanzara" Medical-Surgical Department, Second University of Naples, Naples, Italy.

https://pubmed.ncbi.nlm.nih.gov/17893868/

Inflammation-Induced Cell Proliferation Potentiates DNA Damage-Induced Mutations In Vivo

"Mutations are a critical driver of cancer initiation. While extensive studies have focused on exposure-induced mutations, few studies have explored the importance of tissue physiology as a modulator of mutation susceptibility in vivo. Of particular interest is inflammation, a known cancer risk factor relevant to chronic inflammatory diseases and pathogen-induced inflammation. Here, we used the fluorescent yellow direct repeat (FYDR) mice that harbor a reporter to detect misalignments during homologous recombination (HR), an important class of mutations. FYDR mice were exposed to cerulein, a potent inducer of pancreatic inflammation. We show that inflammation induces DSBs (γH2AX foci) and that several days later there is an increase in cell proliferation. While isolated bouts of inflammation did not induce HR, overlap between inflammation-induced DNA damage and inflammation-induced cell proliferation induced HR significantly. To study exogenously-induced DNA damage, animals were exposed to methylnitrosourea, a model alkylating agent that creates DNA lesions relevant to both environmental exposures and cancer chemotherapy. We found that exposure to alkylation damage induces HR, and importantly, that inflammation-induced cell proliferation and alkylation induce HR in a synergistic fashion. Taken together, these results show that, during an acute bout of inflammation, there is a kinetic barrier separating DNA damage from cell proliferation that protects against mutations, and that inflammation-induced cell proliferation greatly potentiates

exposure-induced mutations. These studies demonstrate a fundamental mechanism by which inflammation can act synergistically with DNA damage to induce mutations that drive cancer and cancer recurrence."

…"People with chronic inflammatory conditions have a markedly increased risk for cancer. In addition, many cancers have an inflammatory microenvironment that promotes tumor growth. Here, we show that inflammatory infiltration synergizes with tissue regeneration to induce DNA sequence rearrangements in vivo. Chronically inflamed issues that are continuously regenerating are thus at an increased risk for mutagenesis and malignant transformation. Further, rapidly dividing tumor cells in an inflammatory microenvironment can also acquire mutations, which have been shown to contribute to drug resistance and disease recurrence. Finally, inflammation-induced tissue regeneration sensitizes tissues to DNA damaging environmental exposures and chemotherapeutics. The work described here thus increases our understanding of how inflammation leads to genetic changes that drive cancer formation and recurrence."…

"Effective strategies for preventing and treating cancer depend not only upon understanding genetic and exposure-induced factors, but also physiological factors that drive disease. DNA damage, caused by endogenous metabolites and exogenous agents, promotes mutations, a key driver of phenotypic changes that potentiate metastasis and enable recurrence after treatment [1]. While significant progress has been made in terms of understanding how genes and exposures modulate the risk of mutations, relatively little is known about the potential role of tissue physiology in modulating the risk of mutations in vivo. Of particular interest is the inflammatory state, a critical cancer risk factor that is associated with sweeping changes in tissue architecture due to immune cell infiltration and associated changes in the levels of cytokines and reactive oxygen and nitrogen species (RONS) [2–4]. Inflammation is a well-established tumor promoter that contributes to cancer growth, angiogenesis, and resistance to apoptosis [2,5]. In addition to the role of inflammation in cancer progression, it is increasingly recognized that inflammation-induced DNA damage may also drive mutations that contribute to both initiation and progression [3,6]. With recent advances that enable analysis of key factors that impact the risk of mutation [7], here, we set out to determine how interactions between DNA damage and inflammation-induced physiological changes impact the risk of mutations in vivo.

It has long been thought that it is the convergence of conditions that induce DNA damage and cell division simultaneously that is a key driver of inflammation-induced mutations [8–11]."

- *Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA*
- *Singapore–MIT Alliance for Research and Technology, Singapore,*
-Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA-University of Washington, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4372043/

…"COX-2 inhibitors have shown potential in esophageal cancer. Several studies have demonstrated that both selective and nonselective COX-2 inhibitors suppress inflammation and cell growth while inducing apoptosis in BE and EAC [esophageal adenocarcinoma] [94–96]. Furthermore, chronic intake of NSAIDs is associated with a decreased incidence of EAC, suggesting a role in prevention as well 96. In ESCC [esophageal squamous cell carcinoma], COX-2 inhibition leads to decreased cell proliferation, PGE2 production and overall tumor progression in vitro and in vivo [92]."…

-Division of Gastroenterology, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
-Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania
-Department of Medical Oncology, Dana Farber Cancer Institute
-Department of Genetics, University of Pennsylvania, Philadelphia, Pennsylvania
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5003768/

NSAIDs affect the production of prostaglandins and endocannabinoids. These medications have been linked to acute liver failure, and Interstitial Nephritis, caution use should be used when taking over the counter anti-inflammatory medications.

Role of Inflammation in Cancer

"The mammalian immune system recognizes and eliminates cells with non-native DNA, including transformed cells [103–108]. During cancer progression, however, tumor cells can escape elimination by the immune system by being selected for low immunogenicity or by being able to inhibit immune cell activation and induce an immunosuppressive microenvironment [104, 109–111]. Some of these pathways can be targeted for cancer immunotherapies [108, 112–114].

In contrast to this immunosurveillance function, inflammation and associated activation of the immune system can also promote cancer progression [115–117]. Chronic inflammation due to infectious and non-infectious agents such as auto-inflammatory diseases and diet-induced metabolic syndrome is an important etiology for the development of cancer [116–118]. In this regard, epidemiological analyses have confirmed that interference with inflammation using non-steroidal anti-inflammatory drugs including aspirin are protective for the development of inflammation-induced cancers such as colorectal carcinomas [119, 120]. Aspirin use has also been associated with reduced incidence of other cancers including those of the esophagus and stomach [121].

Inflammation not only works as promoter during carcinogenesis (inflammation-induced cancer), but growing tumors that escaped immunosurveillance also induce an inflammatory response that can support cancer progression (cancer-related inflammation) [115, 122]. In particular, cells

from the myeloid lineage such as neutrophils and monocytes/macrophages support cancer progression [110, 123–125]. Thus, while the immune system exerts considerable immunosurveillance to eliminate tumor cells, inflammatory pathways can be co-opted by tumor cells to promote cancer progression. Moreover, inflammation can also act as an oncogenic promoter during tumorigenesis, inducing DNA damage via reactive oxygen species."

-Departments of Medicine, Pathology and Cellular and Molecular Medicine, Glycobiology Research and Training Center, University of California San Diego, La Jolla, CA, USA

https://www.frontiersin.org/articles/10.3389/fonc.2014.00033/full

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…"Inflammation has long been associated with the development of cancer."…

-Yale University School of Medicine

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1994795/

Immunity, Inflammation, and Cancer

"Inflammatory responses play decisive roles at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis. Inflammation also affects immune surveillance and responses to therapy. Immune cells that infiltrate tumors engage in an extensive and dynamic crosstalk with cancer cells and some of the molecular events that mediate this dialog have been revealed. This review outlines the principal mechanisms that govern the effects of inflammation and immunity on tumor development and discusses attractive new targets for cancer therapy and prevention."

-Laboratory of Gene Regulation and Signal Transduction, Departments of Pharmacology and Pathology, School of Medicine, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA, USA.

-2nd Department of Medicine, Klinikum rechts der Isar, Technical University Munich, Munich, Germany.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2866629/

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…"Recent data have expanded the concept that inflammation is a critical component of tumour progression. "..

-Cancer Research Institute, University of California

-Department of Pathology, University of California

-Department of Anatomy, University of California

-UCSF Comprehensive Cancer Center, University of California

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2803035/

Cannabis-derived substances in cancer therapy--an emerging anti-inflammatory role for the cannabinoids

“Cannabinoids, the active components of the cannabis plant, have some clinical merit both as an anti-emetic and appetite stimulant in cachexic patients. Recently, interest in developing cannabinoids as therapies has increased following reports that they possess anti-tumour properties. Research into cannabinoids as anti-cancer agents is in its infancy, and has mainly focussed on the pro-apoptotic effects of this class of agent. Impressive anti-cancer activities have been reported; actions that are mediated in large part by disruptions to ubiquitous signalling pathways such as ERK and PI3-K. However, recent developments have highlighted a putative role for cannabinoids as anti-inflammatory agents. Chronic inflammation has been associated with neoplasia for sometime, and as a consequence, reducing inflammation as a way of impacting cancer presents a new role for these compounds. This article reviews the ever-changing relationship between cannabinoids and cancer, and updates our understanding of this class of agent. Furthermore, the relationship between chronic inflammation and cancer, and how cannabinoids can impact this relationship will be described.”

-Division of Cellular and Molecular Medicine (Oncology), St George's University of London, London, UK.
https://pubmed.ncbi.nlm.nih.gov/20925645/

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“It is well admitted that the link between chronic inflammation and cancer involves cytokines and mediators of inflammatory pathways, which act during the different steps of tumorigenesis.“…

“Several diseases are associated to chronic inflammation, such as osteoarthritis, Crohn's disease, and cancer [2]. Although the first evidence of a connection between inflammation and cancer dates back to more than a century ago [3], only recently, this link has been further investigated, thus evidencing that the incidence of several cancers is tightly associated to inflammation such as colon, breast, and prostate cancers [4–6]. This hypothesis is supported by the findings that the tumor microenvironment is characterized by the infiltration with different types of immune cells (i.e., dendritic cells, lymphocytes, and macrophages) responsible for the release of cytokines [1]. The role of these cytokines in tumor incidence has been established in many studies. “…

“A body of evidence indicates a role for inflammation in the development/modulation of different steps of cancer progression. Inflammation may play a role in tumor initiation by triggering the production of reactive oxygen species (ROS), responsible for DNA damage, thus

increasing the rate of mutations [12]. It may also be implicated in tumor promotion, where inflammation triggers the secretion of growth factors, such as the epithelial (EGF) and fibroblast growth factors (FGF). These, in turn, favor the proliferation of initiated tumor cells by determining an imbalance between cell proliferation and cell death stimuli [6], due to the activation of different cell survival pathways [7]."…

"A constitutive activation of such proinflammatory factors has been frequently found in many cancers, such as hepatocellular carcinoma [17], prostate cancer [18], as well as chronic and acute myeloid leukemia [19], where it is frequently associated with a bad prognosis. In these instances, the modulation of Bcl-2 anti-apoptotic family members has been frequently shown [13–15, 20]."

-Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, Luxembourg, Luxembourg
-Dipartimento di Biologia, Università di Roma di Roma Tor Vergata, Via Ricerca Scientifica snc, Rome, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2841246

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…"Because the availability of free AA is a rate-limiting step in the synthesis of PG, modulating AA availability could serve as a means of altering PG synthesis and prevent/inhibit the pathological effects of 2-series PG. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are ω-3 PUFA found primarily in fish oils. EPA and DHA compete with AA both at the level of incorporation into cell membrane phospholipids (15) as well as at the level of substrate for COX pathway (16) generating the 3-series of PG, e.g., PGE3 (Fig. (Fig.11A). Dietary supplements of fish oils rich in ω-3 PUFA are used as preventive measures against a number of illnesses, including arthritis and cancer (17)."…

-Divisions of Hematology–Oncology and †Gynecologic Oncology, Department of Obstetrics and Gynecology, Division of Cardiology, Department of Medicine, and Department of Molecular and Medical Pharmacology, University of California, Los Angeles, CA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC149905/

Protective Effects of Omega-3 Fatty Acids in Cancer-Related Complications

"Omega-3 polyunsaturated fatty acids (PUFAs) are considered immunonutrients and are commonly used in the nutritional therapy of cancer patients due to their ample biological effects. Omega-3 PUFAs play essential roles in cell signaling and in the cell structure and fluidity of membranes. They participate in the resolution of inflammation and have anti-inflammatory and antinociceptive effects. Additionally, they can act as agonists of G protein-coupled receptors, namely, GPR40/FFA1 and GPR120/FFA4. Cancer patients undergo complications, such as

anorexia-cachexia syndrome, pain, depression, and paraneoplastic syndromes. Interestingly, the 2017 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for cancer patients only discuss the use of omega-3 PUFAs for cancer-cachexia treatment, leaving aside other cancer-related complications that could potentially be managed by omega-3 PUFA supplementation. This critical review aimed to discuss the effects and the possible underlying mechanisms of omega-3 PUFA supplementation in cancer-related complications. Data compilation in this critical review indicates that further investigation is still required to assess the factual benefits of omega-3 PUFA supplementation in cancer-associated illnesses. Nevertheless, preclinical evidence reveals that omega-3 PUFAs and their metabolites might modulate pivotal pathways underlying complications secondary to cancer, indicating that this is a promising field of knowledge to be explored."

…"Omega-3 PUFAs are essential fatty acids, containing between 18 and 22 carbons, with the first double bond on the third carbon, counting from the omega end. Omega-3 PUFAs comprise three different active molecules: (i) α-linolenic acid (ALA; 18:3n-3), (ii) eicosapentaenoic acid (EPA; 20:5n-3), and (iii) docosahexaenoic acid (DHA; 22:6n-3). ALA is synthesized in plants and can be found in seeds, nuts, and plant oils. EPA and DHA are not synthesized by the organism and can only be found in the flesh of cold-water fish [30]. Interestingly, ALA can be converted to EPA and DHA by several reactions of elongation and desaturation, but these conversions produce small amounts of EPA and DHA in the organism [31].

The omega-6 arachidonic acid (AA; 20:4n-6) and linoleic acid (LA; 18:2n-6) are also essential fatty acids. Notably, both became major components of the cell membrane due to the increase of Western diets, rich in cereals and vegetable oils, containing excessive omega-6 PUFAs and leading to an undesired omega-6/omega-3 ratio of 20:1 [32]. The metabolic pathways of AA and LA share the same enzymes that convert ALA to EPA and DHA, indicating that there is competition between the pathways. In inflammatory processes, membrane phospholipids are cleaved by phospholipase A2 (PLA2) to release AA to the cytoplasm and initiate the production of highly inflammatory eicosanoids (such as prostaglandin E2 and leukotriene B4) by the action of cyclooxygenases and lipoxygenases. The membrane lipid composition modification from an omega-6 PUFA to omega-3 PUFA profile is very important because it increases the production of omega-3-derived mediators, such as thromboxane A3 and prostacyclin I3, which are weaker inducers of inflammation [33]. Supporting this mechanism, a systematic review and meta-analysis demonstrated that omega-3 PUFAs were able to reduce thromboxane B2 blood levels in subjects with a high risk of cardiovascular diseases, along with a decrease of leukotriene B4 in the neutrophils of unhealthy patients [34]. Regarding lymphocyte membranes, an in vitro and pilot clinical study evaluated the fatty acid composition of CD4+T cell membranes after EPA and DHA

supplementation. The in vitro analysis showed that EPA or DHA incubation increased the membrane contents of omega-3 PUFAs. Additionally, the pilot clinical study from the same article evaluated the membrane composition of lymphocytes in elderly individuals after six weeks of omega-3 PUFA supplementation and observed a similar omega-3 PUFA-rich membrane [35]. Additionally, a review article demonstrated that EPA and DHA supplementation are often employed in the nutritional therapy of cancer patients and promotes beneficial effects during cancer treatment due to a membrane modulation [36]. On the other hand, an analysis of the fatty acid composition of the red blood cells of cancer patients showed that there was no difference between the omega-3 PUFAs contents in the membrane of cancer patients and healthy subjects, irrespective of their diet. Interestingly, the same cancer patients showed higher omega-6 PUFA contents and an increased desaturation activity, demonstrating a higher inflammatory profile [37].

The notion that an omega-3 PUFA-enriched membrane could be favorable for disease management was corroborated by the discovery of pro-resolution mediators of inflammation, derived from omega-3 PUFAs. Over the past decade, the identification of resolvins, protectins/neuroprotectins, and maresins was a milestone—currently, it is well-recognized that solving, rather than inhibiting, inflammation is quite an interesting approach for the treatment of a series of chronic illnesses such as cancer."....

-Toxicology and Pharmacology Research Center, School of Health Sciences, PUCRS, Brazil;
-Postgraduate Program in Medicine and Health Sciences, School of Medicine, PUCRS, Porto Alegre, Brazil
- Postgraduate Program in Dentistry, School of Health Sciences, PUCRS, Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6566772

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"The IL-6/STAT3 signaling pathway is upregulated in several cancers [43], including esophageal [44]. IL-6 is a cytokine that signals via association of its receptor (IL-6Rα) with gp130, which triggers downstream recruitment and activation of several molecules (SHP2, Ras-MAPK, and PI3K) and notably the STAT1 and STAT3 transcription factors [45]. In normal physiology, the IL-6/STAT3 pathway allows normal cells to survive in highly toxic inflammatory environments created by the immune system to kill pathogens; however, in carcinogenesis, this pathway is hijacked by neoplastic cells to promote growth, survival, angiogenesis, and metastasis [46]. Interestingly, STAT3 signaling is often constitutively activated in cancer, a phenomenon that not only suppresses apoptosis but also inhibits anti-tumor immunity [47]."...

-Division of Gastroenterology, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
-Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania
-Department of Medical Oncology, Dana Farber Cancer Institute
-Department of Genetics, University of Pennsylvania, Philadelphia, Pennsylvania

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5003768/

The interplay between pathogen-associated and danger-associated molecular patterns: an inflammatory code in cancer?

“There is increasing evidence of a close link between inflammation and cancer, and at the core of inflammation there are both pathogen-associated molecular patterns (PAMPs) and danger (or damage)-associated molecular patterns (DAMPs). Microorganisms harbor molecules structurally conserved within groups called PAMPs that are recognized by specific receptors present on immune cells, such as monocytes and dendritic cells (DCs); these are the pattern recognition receptors (PRRs). Activation through different PRRs leads to production of pro-inflammatory cytokines. A robust immune response also requires the presence of endogenous molecules that pose 'danger' to self-tissues and are produced by damaged or stressed cells; these are the DAMPs, which act also as inducers of inflammation. PAMPs and DAMPs are each recognized by a limited set of receptors that in number probably do not exceed 100. PAMPs and DAMPs interact with each other, and a single PRR can bind to a PAMP as well as a DAMP. Within this framework, we propose that PAMPs and DAMPs act in synchrony, modifying the activation threshold of one another. Thus, the range of PAMP-DAMP partnerships defines the course of inflammation, in a predictable manner, in an 'inflammatory code'. The definition of relevant PAMP-DAMP complexes is important for the understanding of inflammatory disorders in general, and of cancer in particular. Here, we review relevant findings that support the notion of a PAMP-DAMP-based inflammatory code, with emphasis on cancer immunology and immunotherapy.”

-Department of Immunology, National School of Biological Sciences, National Polytechnic Institute, Carpio and Plan de Ayala, Col. Santo Tomás, México D.F., Mexico.
https://pubmed.ncbi.nlm.nih.gov/24100386

Targeting cancer-promoting inflammation - have anti-inflammatory therapies come of age?

“The immune system has crucial roles in cancer development and treatment. Whereas adaptive immunity can prevent or constrain cancer through immunosurveillance, innate immunity and inflammation often promote tumorigenesis and malignant progression of nascent cancer. The past decade has witnessed the translation of knowledge derived from preclinical studies of antitumour immunity into clinically effective, approved immunotherapies for cancer. By contrast, the successful implementation of treatments that target cancer-associated inflammation is still awaited. Anti-inflammatory agents have the potential to not only prevent or delay cancer onset

but also to improve the efficacy of conventional therapeutics and next-generation immunotherapies. Herein, we review the current clinical advances and experimental findings supporting the utility of an anti-inflammatory approach to the treatment of solid malignancies. Gaining a better mechanistic understanding of the mode of action of anti-inflammatory agents and designing more effective treatment combinations would advance the clinical application of this therapeutic approach."

-Department of Hepatobiliary Surgery, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

-Department of Liver Surgery, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China.

-Laboratory of Gene Regulation and Signal Transduction, Departments of Pharmacology and Pathology, University of California San Diego School of Medicine, La Jolla, CA, USA.

-Department of Hepatobiliary Surgery, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

https://pubmed.ncbi.nlm.nih.gov/33469195/

See also Damage-associated molecular patterns (DAMPs) , Skin Cancer

Candida

"Candida organisms commonly colonize the human gastrointestinal tract as a component of the resident microbiota. Their presence is generally benign. Recent studies, however, show that high level Candida colonization is associated with several diseases of the gastrointestinal tract. Further, results from animal models argue that Candida colonization delays healing of inflammatory lesions and that inflammation promotes colonization. These effects may create a vicious cycle in which low-level inflammation promotes fungal colonization and fungal colonization promotes further inflammation. Both inflammatory bowel disease and gastrointestinal Candida colonization are associated with elevated levels of the pro-inflammatory cytokine IL-17. Therefore, effects on IL-17 levels may underlie the ability of Candida colonization to enhance inflammation. Because Candida is a frequent colonizer, these effects have the potential to impact many people."…

-Carol A. Kumamoto, Department of Molecular Biology and Microbiology, Tufts University, 136 Harrison Ave., Boston, MA 02111 USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3163673/

Effects of Fresh Garlic Extract [FGE] on Candida albicans Biofilms

…"These results appear promising and merit further investigation for determination of the antifungal activity of FGE [Fresh Garlic Extract] against C. albicans biofilms."

-Mayo Clinic College of Medicine, Department of Medicine, Division of Infectious Diseases
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC538912/

Mechanisms, clinically curative effects, and antifungal activities of cinnamon oil and pogostemon oil complex against three species of Candida.

..."Thus, the cinnamon oil and pogostemon oil complexes had strong anti-fungus effects against Candida albicans, Candida tropicalis, and Candida krusei. They impacted the morphology and sub-micro structures of the fungus within 48 - 72 h, and eventually denatured and killed the cells. The complexes have also shown considerable curative effects to intestinal Candida infections."

-Department of Fungus, Second Hospital of Hebei Medical University, Hepingxilu 215, Shijiazhuang, Hebei, China
https://www.ncbi.nlm.nih.gov/pubmed/22594097

Antifungal activity of four honeys of different types from Algeria against pathogenic yeast: Candida albicans and Rhodotorula sp.

"This study demonstrates that, in vitro, these natural products have clearly an antifungal activity against Rhodotorula sp. and C. albicans."

-Institute of Veterinary Sciences University, Ibn-khaldoun Tiaret (14000), Algeria
-Department of Biology, Faculty of Sciences, Mostaganem University, Algeria
-Laboratory Science and Technology Environment and Development, Mostaganem University, Algeria
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609343/

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…"Classic antibiotic approaches attempt to kill or suppress growth of bacteria by targeting essential cell functions such as cell wall biosynthesis, protein synthesis, DNA replication, RNA polymerase, or metabolic pathways. These conventional therapies run a high risk of toxicity since many of these cell functions are also essential to mammalian cells and require fine molecular distinction between the microbial target and the host cell counterpart(s). Second, the repetitive use of the same targets means that when a bacterium evolves resistance to a particular antibiotic agent during therapy, it can become simultaneously cross resistant to other agents acting on the same target, even though the bacterium has never been exposed to the other agents. Third, conventional therapies exert a "life-or-death" challenge upon the bacterium, and

thus a strong selective pressure to evolve resistance to the antimicrobial agent. Finally, many current antibiotics have very broad spectrums of activity, with the side effect of eradicating many components of the normal flora, leading to undesired complications such as Clostridium difficile colitis or secondary fungal infections (e.g. Candida).”…

US Patent Current Assignee :
-University of California
-US Department of Veterans Office of General Counsel (OGC)
https://patents.google.com/patent/US10085997B2

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“Invasive candidiasis caused by Candida albicans and non-albicans Candida (NAC) present a serious disease threat. “…

“Invasive candidiasis, including candidemia, is a serious fungal infection caused by Candida albicans and non-albicans Candida (NAC) species that can lead to mortality rates as high as 70%, depending on the population sampled [1]. The most common form of invasive candidiasis is blood infection, or candidemia, leading to disseminated candidiasis that can result in the infection of various tissues as well, resulting in infection of bone and liver, endocarditis, meningitis, pulmonary and splenic abscesses and endophthalmitis [2].”

-Department of Oral Biology, University of Florida College of Dentistry, 1600 SW Archer Road, Gainesville, FL, USA;
-Division of Infectious Diseases and Global Medicine, Department of Medicine, University of Florida College of Medicine, Gainesville, FL, USA;
-Fox Chase Chemical Diversity Center, Inc., Pennsylvania Biotechnology Center, Doylestown, PA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5872333/

An immunological link between Candida albicans colonization and Crohn's disease

“The etiology of Crohn's Disease (CD), an autoimmune, inflammatory bowel disease (IBD) which affects approximately one million people in Europe, is still unclear. Nevertheless, it is widely accepted that CD could result from an inappropriate inflammatory response to intestinal microorganisms in a genetically susceptible host. Most studies to date have concerned the involvement of bacteria in disease progression. In addition to bacteria, there appears to be a possible link between the commensal yeast Candida albicans and disease development. In this review, in an attempt to link the gut colonization process and the development of CD, we describe the different pathways that are involved in the progression of CD and in the host response to C. albicans, making the yeast a possible initiator of the inflammatory process observed in this IBD.”

-Université Lille Nord de France , France .
https://pubmed.ncbi.nlm.nih.gov/23855357/

Gut colonization by Candida albicans aggravates inflammation in the gut and extra-gut tissues in mice.

…"These findings suggest that C. albicans gut colonization in mice aggravates inflammation in allergic and autoimmune diseases, not only in the gut but also in the extra-gut tissues and underscores the necessity of investigating the pathogenic role of C. albicans gut colonization in immune diseases in humans."

-Research Faculty of Agriculture, Hokkaido University, Sapporo, Hokkaido, Japan.
https://www.ncbi.nlm.nih.gov/pubmed/20807027

Cannabidiol (CBD)

"CBD is the most abundant non-psychoactive cannabinoid of C. sativa and hence has been extensively studied for its anti-inflammatory properties. CBD is currently undergoing clinical trials for its effectiveness in schizophrenia [57], refractory epileptic encephalopathy [58], and tuberous sclerosis [59, 60]. In addition to CB1, CB2, TRPV1, and adenosine receptors, the activation of GPR55, inhibition of fatty acid amide hydrolase (FAAH), stimulation of peroxisome proliferator-activated receptor-gamma (PPAR-γ), and heterodimerization of CB2/5HT1A are also involved in mediating the anti-inflammatory effects of CBD [20, 61, 62]. Subsequently, CBD was also found to extensively inhibit the production of pro-inflammatory cytokines, such as IL-1α, IL-1β, IL-6, and tissue necrosis factor α (TNF-α), etc., in pre-clinical in vitro and in vivo models of inflammation and cancer [20]. The anti-inflammatory activity of CBD was paralleled by the modulation of downstream gene expression, reduction in lipid peroxidation, Ca2+ homeostasis, and reduction of oxidative stress [61, 63, 64]. However, Δ9-THC mediates its anti-inflammatory actions mainly via CB2 receptor activation, decreased production of cytokines, inhibition of Th-1, promotion of Th-2 cells, induction of apoptosis, and downregulation of cell proliferation [35, 52]. Cannabichromene (CBC) has been reported to inhibit the expression and activity of TRPV1-4 channels [65]. Cannabigerol (CBG) has exhibited protective properties in a murine model of inflammatory bowel disease (IBD) by regulating cytokine (IL-1β, IL-10, and interferon-γ) levels and inhibiting inducible nitric oxide synthase (iNOS) expression [66]. Cannabinol (CBN), like CBD and THC, is shown to inhibit pro-inflammatory cytokine production [67]. Cannabidiolic acid (CBDA) has been

demonstrated to be a selective inhibitor of cyclooxygenase-2 (COX-2), and it likely plays an essential role in the reduction of inflammation [68]. Data on other minor cannabinoids are limited at this point."

-Department of Biological Sciences, University of Lethbridge, Lethbridge, AB, Canada

-Edited by: Kuo-Feng Hua, National Ilan University, Taiwan

-Reviewed by: George Kunos, National Institutes of Health (NIH), United States; Antonella Naldini, University of Siena, Italy; Liying Li, Capital Medical University, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7876066/

Decreased glial reactivity could be involved in the antipsychotic-like effect of cannabidiol

"NMDA receptor hypofunction could be involved, in addition to the positive, also to the negative symptoms and cognitive deficits found in schizophrenia patients. An increasing number of data has linked schizophrenia with neuroinflammatory conditions and glial cells, such as microglia and astrocytes, have been related to the pathogenesis of schizophrenia. Cannabidiol (CBD), a major non-psychotomimetic constituent of Cannabis sativa with anti-inflammatory and neuroprotective properties induces antipsychotic-like effects. The present study evaluated if repeated treatment with CBD (30 and 60 mg/kg) would attenuate the behavioral and glial changes observed in an animal model of schizophrenia based on the NMDA receptor hypofunction (chronic administration of MK-801, an NMDA receptor antagonist, for 28 days). The behavioral alterations were evaluated in the social interaction and novel object recognition (NOR) tests. These tests have been widely used to study changes related to negative symptoms and cognitive deficits of schizophrenia, respectively. We also evaluated changes in NeuN (a neuronal marker), Iba-1 (a microglia marker) and GFAP (an astrocyte marker) expression in the medial prefrontal cortex (mPFC), dorsal striatum, nucleus accumbens core and shell, and dorsal hippocampus by immunohistochemistry. CBD effects were compared to those induced by the atypical antipsychotic clozapine. Repeated MK-801 administration impaired performance in the social interaction and NOR tests. It also increased the number of GFAP-positive astrocytes in the mPFC and the percentage of Iba-1-positive microglia cells with a reactive phenotype in the mPFC and dorsal hippocampus without changing the number of Iba-1-positive cells. No change in the number of NeuN-positive cells was observed. Both the behavioral disruptions and the changes in expression of glial markers induced by MK-801 treatment were attenuated by repeated treatment with CBD or clozapine. These data reinforces the proposal that CBD may induce antipsychotic-like effects. Although the possible mechanism of action of these effects is still

unknown, it may involve CBD anti-inflammatory and neuroprotective properties. Furthermore, our data support the view that inhibition of microglial activation may improve schizophrenia symptoms."

-Department of Pharmacology, Medical School of Ribeirão Preto, University of São Paulo, Brazil; Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Brazil.

-Department of Physiology, Faculty of Medicine, Complutense University of Madrid, Spain.

-Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Brazil; Department of Physiology, Faculty of Odontology of Ribeirão Preto, University of São Paulo, Brazil.

-Department of Physiology (Animal Physiology II), Faculty of Biology, Complutense University of Madrid, Spain.

-Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Brazil.

https://pubmed.ncbi.nlm.nih.gov/25680767

Analysis of endocannabinoid signaling elements and related proteins in lymphocytes of patients with Dravet syndrome

"Cannabidiol (CBD) reduces seizures in childhood epilepsy syndromes including Dravet syndrome (DS). A formulation of CBD has obtained orphan drug designation for these syndromes and clinical trials are currently underway. The mechanism responsible for CBD effects is not known, although it could involve targets sensitive to CBD in other neurological disorders. We believe of interest to investigate whether these potential targets are altered in DS, in particular whether the endocannabinoid system is dysregulated. To this end, lymphocytes from patients and controls were used for analysis of gene expression of transmitter receptors and transporters, ion channels, and enzymes associated with CBD effects, as well as endocannabinoid genes. Plasma endocannabinoid levels were also analyzed. There were no differences between DS patients and controls in most of the CBD targets analyzed, except an increase in the voltage-dependent calcium channel α-1h subunit. We also found that cannabinoid type-2 (CB 2) receptor gene expression was elevated in DS patients, with no changes in other endocannabinoid-related receptors and enzymes, as well as in plasma levels of endocannabinoids. Such elevation was paralleled by an increase in CD70, a marker of lymphocyte activation, and certain trends in inflammation-related proteins (e.g., peroxisome proliferator-activated receptor-γ receptors, cytokines). In conclusion, together with changes in the voltage-dependent calcium channel α-1h subunit, we found an upregulation of CB 2 receptors, associated with an activation of lymphocytes and changes in inflammation-related genes, in DS patients. Such changes were also reported in inflammatory disorders and may indirectly support the occurrence of a potential dysregulation of the endocannabinoid system in the brain."…

-Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Instituto Universitario de Investigación en Neuroquímica, Universidad Complutense, Madrid, Spain

-Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

-Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain

-Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Pozzuoli, Naples, Italy

-Instituto de Genética Médica y Molecular (INGEMM), Hospital Universitario La Paz, Universidad Autónoma de Madrid, IdiPAZ, Madrid, Spain

-Centro de Investigación Biomédica en Red sobre Enfermedades Raras (CIBERER), Instituto de Salud Carlos III, Madrid, Spain

-Dravet Syndrome Foundation, Madrid, Spain

-Departamento de Biología Celular, Facultad de Biología, Universidad de Barcelona, Barcelona, Spain

-Servicio Navarro de Salud Osasunbidea, Estella, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4804326

…"This review discusses recent studies suggesting that cannabidiol [CBD] may have utility in treating a number of human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types 1 and 2 diabetes, atherosclerosis, Alzheimer disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain."

Department of Pharmacology and Toxicology, School of Medicine, and Center for Excellence in Cardiovascular-Renal Research, University of Mississippi Medical Center, Jackson, MS 39216, USA.

https://www.ncbi.nlm.nih.gov/pubmed/21238581

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"A phytocannabinoid derived from Cannabis species, which is devoid of psychoactive activity, with analgesic, anti-inflammatory, antineoplastic and chemopreventive activities. Upon administration, cannabidiol (CBD) exerts its anti-proliferative, anti-angiogenic and pro-apoptotic activity through various mechanisms, which likely do not involve signaling by cannabinoid receptor 1 (CB1), CB2, or vanilloid receptor 1. CBD stimulates endoplasmic reticulum (ER) stress and inhibits AKT/mTOR signaling, thereby activating autophagy and promoting apoptosis. In addition, CBD enhances the generation of reactive oxygen species (ROS), which further enhances apoptosis. This agent also upregulates the expression of intercellular adhesion molecule 1 (ICAM-1) and tissue inhibitor of matrix metalloproteinases-1 (TIMP1) and decreases the expression of inhibitor of DNA binding 1 (ID-1). This inhibits cancer cell invasiveness and metastasis. CBD may also activate the transient receptor potential vanilloid type 2 (TRPV2), which may increase the uptake of various cytotoxic agents in cancer cells. The analgesic effect of

CBD is mediated through the binding of this agent to and activation of CB1."

-National Cancer Institute Thesaurus
https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI%20Thesaurus&code=C118452

Cannabidiol is a powerful new antibiotic

"Given cannabidiol's documented anti-inflammatory effects, existing safety data in humans, and potential for varied delivery routes, it is a promising new antibiotic worth further investigation."…"The combination of inherent antimicrobial activity and potential to reduce damage caused by the inflammatory response to infections is particularly attractive."

- Dr. Blaskovich
https://www.sciencedaily.com/releases/2019/06/190623143055.htm

■■■

…"Cannabidiol (CBD^) has been shown to have many beneficial properties, including anti-inflammatory action. "…

-Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, NC
^removed 'figure 5' footnote, for readability

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340993/

■■■

"Cannabidiol (CBD) is a phytocannabinoid with therapeutic properties for numerous disorders exerted through molecular mechanisms that are yet to be completely identified. CBD acts in some experimental models as an anti-inflammatory, anticonvulsant, anti-oxidant, anti-emetic, anxiolytic and antipsychotic agent, and is therefore a potential medicine for the treatment of neuroinflammation, epilepsy, oxidative injury, vomiting and nausea, anxiety and schizophrenia, respectively. The neuroprotective potential of CBD, based on the combination of its anti-inflammatory and anti-oxidant properties, is of particular interest and is presently under intense preclinical research in numerous neurodegenerative disorders. In fact, CBD combined with Δ9-tetrahydrocannabinol is already under clinical evaluation in patients with Huntington's disease to determine its potential as a disease-modifying therapy. The neuroprotective properties of CBD do not appear to be exerted by the activation of key targets within the endocannabinoid system for plant-derived cannabinoids like Δ9-tetrahydrocannabinol, i.e. CB1 and CB2 receptors, as CBD has negligible activity at these cannabinoid receptors, although certain activity at the CB2 receptor has been documented in specific pathological conditions (i.e. damage of immature

brain) [Synthetic cannabinoids?]. Within the endocannabinoid system, CBD has been shown to have an inhibitory effect on the inactivation of endocannabinoids (i.e. inhibition of FAAH enzyme), thereby enhancing the action of these endogenous molecules on cannabinoid receptors, which is also noted in certain pathological conditions. CBD acts not only through the endocannabinoid system, but also causes direct or indirect activation of metabotropic receptors for serotonin or adenosine, and can target nuclear receptors of the PPAR family and also ion channels."

-Departamento de Bioquímica y Biología Molecular III, Instituto Universitario de Investigación en Neuroquímica, Facultad de Medicina, Universidad Complutense, 28040-Madrid

-Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), 28222-Majadahonda, Madrid, Spain

-Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), 28222-Majadahonda, Madrid, Spain

-Unidad Experimental, Fundación para la Investigación Biomédica, Hospital Universitario Puerta de Hierro, 28222-Majadahonda, Madrid, Spain

-School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK

-Institute for Drug Research, Medical Faculty, Hebrew University, Jerusalem 91120, Israel

-Servicio de Neonatología, Departamento de Pediatría, Hospital Universitario Puerta de Hierro, 28222-Majadahonda, Madrid, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3579248/

■■■

…"These data indicate that topical CBD application has therapeutic potential for relief of arthritis pain-related behaviours and inflammation without evident side-effects."..

-Department of Pharmaceutical Sciences, University of Kentucky College of Pharmacy, Lexington, KY, USA

-Department of Physiology, University of Kentucky College of Medicine, Lexington, KY, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7023045/

A comparative study on cannabidiol-induced apoptosis in murine thymocytes and EL-4 thymoma cells

"It has been shown that leukemia and glioma cells are sensitive to cannabidiol (CBD)-induced apoptosis, whereas primary monocytes and glia cells are relatively insensitive. In the current study, the cellular events and sensitivity to CBD-induced apoptosis between murine thymocytes and EL-4 thymoma cells were compared. Cannabidiol markedly induced apoptosis in a time- and concentration-related manner in both cells. The efficacy of CBD to induce apoptosis was comparable between the 2 types of T cells, whereas CBD induced apoptosis in thymocytes with a slightly greater potency than in EL4 cells. Time-course analyses revealed CBD-mediated apoptosis occurred earlier in EL-4 cells than that in thymocytes. An increased level of cellular

reactive oxygen species (ROS) was detected in both cells with the peak response at 2 h post CBD treatment. Concordantly, CBD triggered a gradual diminishment in the cellular thiols. The presence of N-acetyl-L-cysteine (NAC), a precursor of glutathione, markedly attenuated the induction of apoptosis, and restored the diminished levels of cellular thiols. The results demonstrated that both thymocytes and EL-4 thymoma cells were susceptible to CBD-induced apoptosis and that ROS played a critical role in the apoptosis induction."

-Department of Veterinary Medicine, National Taiwan University, Taipei, Taiwan.
https://pubmed.ncbi.nlm.nih.gov/18387516/

Cannabinoids

*Cannabinoids are fat like lipids which can be in synthetic form, plant form "**phyto**cannabinoids", and endogenous form known as "**endo**cannabinoids"*

"Cannabis sativa L. is an important herbaceous species originating from Central Asia, which has been used in folk medicine and as a source of textile fiber since the dawn of times. This fast-growing plant has recently seen a resurgence of interest because of its multi-purpose applications: it is indeed a treasure trove of phytochemicals and a rich source of both cellulosic and woody fibers. Equally highly interested in this plant are the pharmaceutical and construction sectors, since its metabolites show potent bioactivities on human health and its outer and inner stem tissues can be used to make bioplastics and concrete-like material, respectively. In this review, the rich spectrum of hemp phytochemicals is discussed by putting a special emphasis on molecules of industrial interest, including cannabinoids, terpenes and phenolic compounds, and their biosynthetic routes. **Cannabinoids represent the most studied group of compounds, mainly due to their wide range of pharmaceutical effects in humans, including psychotropic activities.** The therapeutic and commercial interests of some terpenes and phenolic compounds, and in particular stilbenoids and lignans, are also highlighted in view of the most recent literature data."….

"Most of the biological properties related to cannabinoids rely on their interactions with the endocannabinoid system in humans. The endocannabinoid system includes two G protein-coupled cannabinoid receptors, CB1 and CB2, as well as two endogenous ligands, anandamide and 2-arachidonylglycerol. Endocannabinoids are thought to modulate or play a regulatory role in a variety of physiological processing including appetite, pain-sensation, mood, memory, inflammation, insulin, sensitivity and fat and energy metabolism (De Petrocellis et al., 2011; Di Marzo and Piscitelli,

2015). The psychoactive decarboxylated form of THCA, THC, is a partial agonist of both CB1 and CB2 receptors, but has higher affinity for the CB1 receptor, which appears to mediate its psychoactive properties. In addition to being present in the central nervous system and throughout the brain, CB1 receptors are also found in the immune cells and the gastrointestinal, reproductive, adrenal, heart, lung and bladder tissues, where cannabinoids can therefore also exert their activities. CB2 receptors are thought to have immunomodulatory effects and to regulate cytokine activity. But THC has actually more molecular targets than just CB1 and CB2 receptors, and exhibit potent anti-inflammatory, anti-cancer, analgesic, muscle relaxant, neuro-antioxidative (De Petrocellis et al., 2011), and anti-spasmodic activities (Pacher et al., 2006)."....

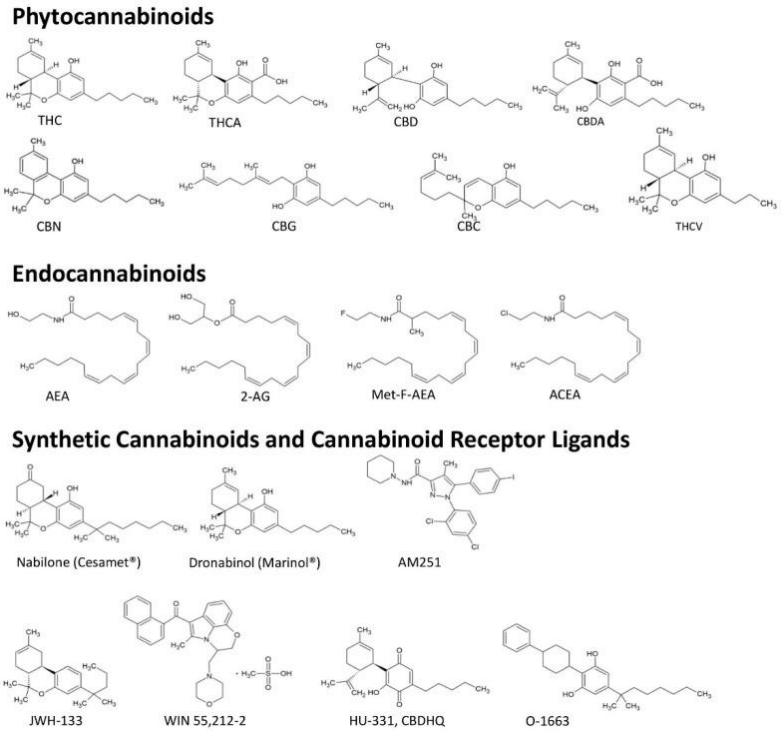
-Environmental Research and Innovation, Luxembourg Institute of Science and Technology, Esch-sur-Alzette, Luxembourg

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740396/

Introduction: Cannabis sativa and Cannabinoids

..."Cannabis sativa (C. sativa) was known among ancient Asian, African, and European agricultural societies. Due to its hallucinogenic effects, Cannabis sativa was applied in religious ceremonies, but it was also widely used in fiber manufacturing, nutrition and medicine. However, in the early part of the last century, C. sativa lost its importance in industry and medicine [1,2]. At present, application of C. sativa in industry and medicine is experiencing a revival. Since 1990, C. sativa became important as a source of compounds to treat cancer and life-threating diseases. The C. sativa plant contains >500 chemical and biologically active compounds [3]. So far, 60 structures have been identified as belonging to the family of cannabinoids (CBs). CBs share a lipid structure featuring alkylresorcinol and monoterpene moieties (terpenophenols) [2,4].

Two CBs have been intensively investigated for their pharmacological properties: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD); THC, but not CBD, exerts potent psychotropic effects (Figure 1). A high THC/CBD ratio is responsible for the euphoric, relaxing, and anxiolytic effects of medical cannabis (marijuana), whereas, a high CBD/THC ratio has a rather sedating effect [5]."...



-Institute of Biology and Ecology, Faculty of Sciences, University of Pavol Jozef Šafárik in Košice, Košice, Slovakia
-Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria;
-Institute of Chemistry, Faculty of Sciences, University of Pavol Jozef Šafárik in Košice, Slovakia;
-Department of Clinical Pharmacy and Diagnostics, University of Vienna, Vienna, Austria;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6479799/

■■■

…"Cannabinoids can be divided to various classes: 'phytocannabinoids' occuring in the cannabis plant; 'endogenous cannabinoids' produced in the body; and 'synthetic cannabinoids' chemically synthesized in a laboratory to target cannabinoid receptors and/or enzymes involved in the production or metabolism of endocannabinoids."…

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ, USA
-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck, Germany
-School of Translational Medicine, University of Manchester, Manchester, UK
-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression

"Cannabinoids are a group of compounds present in Cannabis plant (Cannabis sativa L.). They mediate their physiological and behavioral effects by activating specific cannabinoid receptors. With the recent discovery of the cannabinoid receptors (CB1 and CB2) and the endocannabinoid system, research in this field has expanded exponentially. Cannabinoids have been shown to act as potent immunosuppressive and anti-inflammatory agents and have been shown to mediate beneficial effects in a wide range of immune-mediated diseases such as multiple sclerosis, diabetes, septic shock, rheumatoid arthritis, and allergic asthma. Cannabinoid receptor 1 (CB1) is mainly expressed on the cells of the central nervous system as well as in the periphery. In contrast, cannabinoid receptor 2 (CB2) is predominantly expressed on immune cells. The precise mechanisms through which cannabinoids mediate immunosuppression is only now beginning to be understood and can be broadly categorized into four pathways: apoptosis, inhibition of proliferation, suppression of cytokine and chemokine production and induction of T regulatory cells (T regs). Studies from our laboratory have focused on mechanisms of apoptosis induction by natural and synthetic cannabinoids through activation of CB2 receptors. In this review, we will focus on apoptotic mechanisms of immunosuppression mediated by cannabinoids on different immune cell populations and discuss how activation of CB2 provides a novel therapeutic modality against inflammatory and autoimmune diseases as well as malignancies of the immune system, without exerting the untoward psychotropic effects."…

-Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3005548/

Cannabinoid Receptors (CB1/CB2)

Also know has Cannabinoid Receptors type 1 (CB1) and type 2 (CB2)

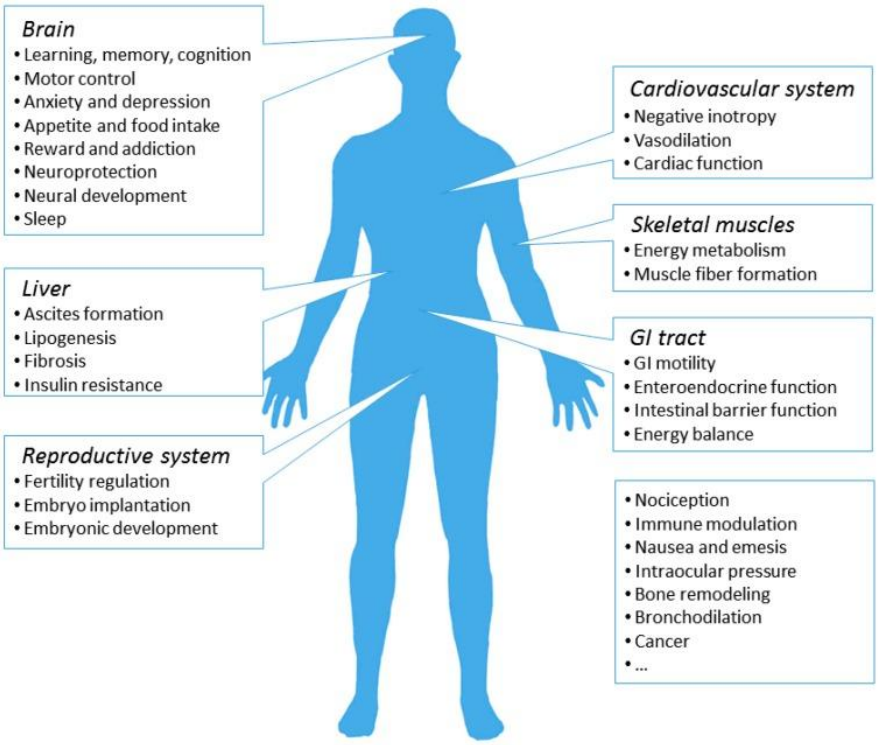
"Cannabinoid receptors type 1 (CB1) and type 2 (CB2) are promising targets for a number of diseases, including obesity, neuropathic pain, and multiple sclerosis, among others. "…

-Laboratory of Toxicology, Dept. of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Belgium.
-The Lambert Initiative for Cannabinoid Therapeutics, Brain and Mind Centre, The University of Sydney, Australia
-School of Chemistry, Faculty of Science, The University of Sydney, Sydney, Australia.
-Laboratory of Toxicology, Dept. of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Belgium.
https://www.ncbi.nlm.nih.gov/pubmed/31472128

Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System

"CB1R was first discovered in the brain. Later, by using autoradiography, in situ hybridization, and immunohistochemistry, CB1R was proven to be the most widely-expressed receptor protein from the GPCR family in the brain [9,59]. The brain regions with highest levels of CB1R expression include olfactory bulb, hippocampus, basal ganglia, and cerebellum [59]. Moderate CB1R expression is found in the cerebral cortex, septum, amygdala, hypothalamus, and parts of the brainstem and the dorsal horn of spinal cord [59]. Whereas regions like the thalamus and the ventral horn of spinal cord have low CB1R expression [59]. Several previous studies have suggested a highly concentrated expression of CB1R on presynaptic terminals, where it mediates retrograde signaling of endocannabinoids [60,61]. However, this does not preclude the existence of CB1Rs at postsynaptic sites, as functional studies demonstrate self-inhibition in neocortical neurons by endocannabinoids [33,47,49,62]. In addition to neurons, the CB1R is expressed, although to a much lower extent, in astrocytes, oligodendrocytes and microglia, where it has been shown to mediate synaptic transmission [33,54].

The CB1R is also abundantly expressed in the peripheral nervous system (PNS) as well as in the peripheral tissues in a region-specific manner [59,63,64,65] (Figure 2). In PNS, the CB1R is mostly expressed in sympathetic nerve terminals [64]. Also, the CB1R is observed in trigeminal ganglion,



dorsal root ganglion, and dermic nerve endings of primary sensory neurons, where it regulates nociception from afferent nerve fibers [65,66,67]. In the gastrointestinal (GI) tract, the CB1R is enriched in both the enteric nervous system and in non-neuronal cells in the intestinal mucosa, including enteroendocrine cells, immune cells, and enterocytes [68]. Through neuronal and non-neuronal routes, the CB1R modulates the mobility of GI tract, the secretion of gastric acids, fluids, neurotransmitter and hormones, as well as the permeability of the intestinal epithelium [68]. Therefore, CB1R could control appetite from the hypothalamus in the CNS and regulate the energy balance and food intake from the GI tract as well. Intriguingly, hepatic CB1R also participates in the regulation of energy balance and metabolism, but in an unusual way. Normally, the expression of CB1R in the liver is very low [69]. However, under pathological conditions, the expression of CB1R in several types of hepatic cells is remarkably increased, where the CB1R actively contributes to hepatic insulin resistance, fibrosis, and lipogenesis [63]. Similarly, the CB1R is upregulated in the cardiovascular system under pathological conditions, which in turn, promotes disease progression and cardiac dysfunction [70]. Oxidative stress, inflammation and fibrosis have been observed as a result of CB1R activation in cardiomyocytes, vascular endothelial cells, and smooth muscle cells [70]. In addition to the aforementioned tissues, the expression of the CB1R has also been reported in adipose tissue, skeletal muscle, bone, skin, eye, reproductive system, and several types of cancer cells [63].”

Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, Canada;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5877694/

■■■

“Cannabinoid receptor 1 (CB1) is the principal target of Δ9-tetrahydrocannabinol (THC), a psychoactive chemical from Cannabis sativa with a wide range of therapeutic applications and a long history of recreational use. CB1 is activated by endocannabinoids, and is a promising therapeutic target for pain management, inflammation, obesity and substance abuse disorders.”…

-iHuman Institute, ShanghaiTech University, Pudong New District, Shanghai, China

-National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

-Center for Drug Discovery, Department of Pharmaceutical Sciences; Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA, USA

-Departments of Biological Sciences and Chemistry, Bridge Institute, University of Southern California, Los Angeles, CA, USA

-Departments of Molecular Therapeutics and Neuroscience, The Scripps Research Institute, Jupiter, FL, USA

-University of California, San Diego, La Jolla, CA , USA

-Shanghai Institute of Materia Medica, Shanghai 201210, China

-GPCR Consortium, San Marcos, CA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5322940

■■■

"Although the active component of cannabis Delta9-THC was isolated by our group 35 years ago, until recently its mode of action remained obscure. In the last decade it was established that Delta9-THC acts through specific receptors - CB1 and CB2 - and mimics the physiological activity of endogenous cannabinoids of two types, the best known representatives being arachidonoylethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG). THC is officially used against vomiting caused by cancer chemotherapy and for enhancing appetite, particularly in AIDS patients. Illegally, usually by smoking marijuana, it is used for ameliorating the symptoms of multiple sclerosis, against pain, and in a variety of other diseases. A synthetic cannabinoid, HU-211, is in advanced clinical tests against brain damage caused by closed head injury. It may prove to be valuable against stroke and other neurological diseases."

-R Mechoulam, Hebrew University, Medical Faculty, Jerusalem, Israel.
https://pubmed.ncbi.nlm.nih.gov/10575284/

The CB2 receptor and its role as a regulator of inflammation

"The CB2 receptor is the peripheral receptor for cannabinoids. It is mainly expressed in immune tissues, highlighting the possibility that the endocannabinoid system has an immunomodulatory role. In this respect, the CB2 receptor was shown to modulate immune cell functions, both in cellulo and in animal models of inflammatory diseases. In this regard, numerous studies have reported that mice lacking the CB2 receptor have an exacerbated inflammatory phenotype. This suggests that therapeutic strategies aiming at modulating CB2 signaling could be promising for the treatment of various inflammatory conditions. Herein, we review the pharmacology of the CB2 receptor, its expression pattern, and the signaling pathways induced by its activation. We next examine the regulation of immune cell functions by the CB2 receptor and the evidence obtained from primary human cells, immortalized cell lines, and animal models of inflammation. Finally, we discuss the possible therapies targeting the CB2 receptor and the questions that remain to be addressed to determine whether this receptor could be a potential target to treat inflammatory disease."

-Quebec University Institute of Cardiology and Pulmonology Research Center, Department of Medicine, Faculty of Medicine, Laval University, Quebec, QC
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5075023

Cannabinoid Overdose

Cannabinoid receptor localization in brain.

…"Sparse densities in lower brainstem areas controlling cardiovascular and respiratory functions may explain why high doses of delta 9-tetrahydrocannabinol are not lethal."

-Unit on Functional Neuroanatomy, National Institute of Mental Health

https://www.ncbi.nlm.nih.gov/pubmed/2308954

What are its overdose effects?

"No deaths from overdose of marijuana have been reported."

-Drug Enforcement Agency (DEA)

https://www.dea.gov/sites/default/files/2018-06/drug_of_abuse.pdf

Cannabis

"Cannabis sativa L. preparations have been used in medicine for millenia. However, concern over the dangers of abuse led to the banning of the medicinal use of marijuana in most countries in the 1930s. Only recently, marijuana and individual natural and synthetic cannabinoid receptor agonists and antagonists, as well as chemically related compounds, whose mechanism of action is still obscure, have come back to being considered of therapeutic value. However, their use is highly restricted. Despite the mild addiction to cannabis and the possible enhancement of addiction to other substances of abuse, when combined with cannabis, **the therapeutic value of cannabinoids is too high to be put aside. Numerous diseases, such as anorexia, emesis, pain, inflammation, multiple sclerosis, neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, obesity, and metabolic syndrome-related disorders, to name just a few, are being treated or have the potential to be treated by cannabinoid agonists/antagonists/cannabinoid-related compounds. In view of the very low toxicity and the generally benign side effects of this group of compounds, neglecting or denying their clinical potential is unacceptable** - instead, we need to work on the development of more selective cannabinoid receptor agonists/antagonists and related compounds, as well as on novel drugs of this family with better selectivity, distribution patterns, and pharmacokinetics, and - in cases where it is impossible to separate the desired clinical action and the psychoactivity - just to monitor these side effects carefully."

-Natalya M. Kogan MSc, Medicinal Chemistry and Natural Products Dept, Pharmacy School, Ein-Kerem Medical Campus, the Hebrew University of Jerusalem, Israel;

-Raphael Mechoulam PhD, Medicinal Chemistry and Natural Products Dept, Pharmacy School, Ein-Kerem Medical Campus, the Hebrew University of Jerusalem, Israel;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202504/

Cannabis & Opioids

Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010.

"Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Further investigation is required to determine how medical cannabis laws may interact with policies aimed at preventing opioid analgesic overdose."

-Center for Health Equity Research and Promotion, Philadelphia Veterans Affairs Medical Center, Philadelphia, USA

-Robert Wood Johnson Foundation Clinical Scholars Program, University of Pennsylvania, Philadelphia

-Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia4Robert Wood Johnson Health and Society Scholars Program, University of Pennsylvania, Philadelphia.

-Division of General Internal Medicine, Montefiore Medical Center/Albert Einstein College of Medicine, USA

-Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia6Department of Health Policy and Management, the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

http://www.ncbi.nlm.nih.gov/pubmed/25154332

Capsaicin

(active component of chili peppers)

Cannabinoid Ligands Targeting TRP Channels

"Many endogenous and exogeneous compounds activate receptors found in the TRP superfamily. Natural, pungent compounds like capsaicin and allicin, from **chili peppers** and garlic respectively, can activate and gate specific TRP channels. In addition to these pungent compounds, the six TRP channels that make up the ionotropic cannabinoid receptors can also be modulated by endogenous, phytogenic, and synthetic cannabinoids."

-Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, NC, USA

-Edited by: Eric Murillo-Rodriguez, Anahuac Mayab University, Mexico

-Reviewed by: Chiayu Chiu, Universidad de Valparaíso, Chile; Jeong Hee Hong, Gachon University, South Korea

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340993/

■■■

…"Transient receptor potential vanilloids 1 (TRPV1) channels are activated by vanilloids such as capsaicin as well as by heat, protons, and various lipids, including endocannabinoids, anandamide, and N-arachidonoyl dopamine [79]…

-Department of Life Science, School of Natural Science, Hanyang University, Seoul, Korea;
-BK21 PLUS Life Science for BioDefense Research (BDR) Team, Hanyang University, Seoul , Korea
-The Research Institute for Natural Science, Hanyang University, Seoul. Korea
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516922/

Cardioprotective

Omega-3 Fatty Acids for Cardioprotection

"The most compelling evidence for the cardiovascular benefit provided by omega-3 fatty acids comes from 3 large controlled trials of 32,000 participants randomized to receive omega-3 fatty acid supplements containing docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) or to act as controls. These trials showed reductions in cardiovascular events of 19% to 45%. These findings suggest that intake of omega-3 fatty acids, whether from dietary sources or fish oil supplements, should be increased, especially in those with or at risk for coronary artery disease. Patients should consume both DHA and EPA. The target DHA and EPA consumption levels are about 1 g/d for those with known coronary artery disease and at least 500 mg/d for those without disease. Patients with hypertriglyceridemia benefit from treatment with 3 to 4 g/d of DHA and EPA, a dosage that lowers triglyceride levels by 20% to 50%. Although 2 meals of oily fish per week can provide 400 to 500 mg/d of DHA and EPA, secondary prevention patients and those with hypertriglyceridemia must use fish oil supplements if they are to reach 1 g/d and 3 to 4 g/d of DHA and EPA, respectively. "…

-Mid America Heart Institute and University of Missouri-Kansas City, Italy
-Ochsner Medical Center, New Orleans, LA
-Laboratory of Clinical Epidemiology of Cardiovascular Disease, Italy
-Nutrition and Metabolic Disease Research Center, Sanford Research/USD and Sanford School of Medicine of the University of South Dakota, Sioux Falls
https://www.mayoclinicproceedings.org/article/S0025-6196(11)60866-5/fulltext

Cardioprotective mechanism of omega-3 polyunsaturated fatty acids.

"Omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid and docosahexaenoic acid, are widely regarded as cardioprotective. Several large-scale, randomized clinical trials have shown that dietary intake of omega-3 PUFAs improves the prognosis of patients with symptomatic heart failure or recent myocardial infarction. Therefore, dietary consumption of omega-3 PUFA is recommended in international guidelines for the general population to prevent the occurrence of cardiovascular diseases (CVDs). However, the precise mechanisms underlying the cardioprotective effects of omega-3 PUFAs are not fully understood. Omega-3 PUFAs can be incorporated into the phospholipid bilayer of cell membranes and can affect membrane fluidity, lipid microdomain formation, and signaling across membranes. Omega-3 PUFAs also modulate the function of membrane ion channels, such as Na and L-type Ca channels, to prevent lethal arrhythmias. **Moreover, omega-3 PUFAs also prevent the conversion of arachidonic acid** [omega-6] **into pro-inflammatory eicosanoids** by serving as an alternative substrate for cyclooxygenase or lipoxygenase, resulting in the production of less potent products. In addition, a number of enzymatically oxygenated metabolites derived from omega-3 PUFAs were recently identified as anti-inflammatory mediators. These omega-3 metabolites may contribute to the beneficial effects against CVDs that are attributed to omega-3 PUFAs."

-Department of Cardiology, Keio University School of Medicine, Tokyo, Japan.

-Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan; -Graduate School of Medical Life Science, Yokohama City University, Kanagawa, Japan.

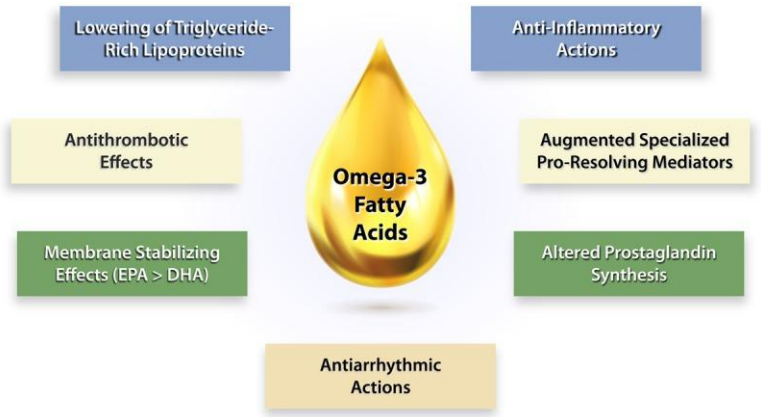
https://www.ncbi.nlm.nih.gov/pubmed/26359712

Omega-3 fatty acids from fish oils and cardiovascular disease

…"Controlled intervention trials with fish oil supplements enriched in EPA/DHA have shown their potential to reduce mortality in post-myocardial infarction patients with a substantial reduction in the risk of sudden cardiac death. The cardioprotective effects of EPA/DHA are widespread, appear to act independently of blood cholesterol reduction, and are mediated by diverse mechanisms. Their overall effects include anti-arrhythmic, blood triglyceride-lowering, anti-thrombotic, anti-inflammatory, endothelial relaxation, plus others. Current dietary intakes of EPA/DHA in North America and elsewhere are well below those recommended by the American Heart Association for the management of patients with coronary heart disease."

-Department of Psychiatry and Behavioural Neurosciences, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada.

https://pubmed.ncbi.nlm.nih.gov/15524182



"Potential mechanisms of cardioprotection for omega-3 fatty acids. Omega-3 fatty acids may lessen risk of cardiovascular events through a number of mechanisms that contribute to their overall protective actions. Lowering of TGRL (triglyceride-rich lipoprotein) may account for some but certainly not all of the observed benefits (Figure (Figure2).2). By boosting the production of anti-aggregatory and vasodilatory prostanoids, such as prostacyclin, omega-3 fatty acids may combat thrombosis as well as vasospasm. Omega-3 fatty acids can incorporate into plasma membranes and those of the mitochondria potentially stabilizing them to resist oxidation and confer protection against arrhythmias. Omega-3 fatty acids and certain prostanoids produced from them can exert anti-inflammatory actions. In addition, the omega-3 fatty acids can provide precursors for the synthesis of specialized proresolving mediators that can combat inflammation, perhaps causing less interference with his defenses than direct anti-inflammatory therapies. A combination of these various mechanisms may contribute to the cardiovascular protection associated with omega-3 fatty acid consumption. DHA indicates docosahexaenoic acid; and EPA, eicosapentaenoic acid."

-From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (R.P.M., P.L., D.L.B.)

-Elucida Research LLC, Beverly, MA (R.P.M.).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7176343/

Activation of Endocannabinoid Receptor 2 as a Mechanism of Propofol Pretreatment-Induced Cardioprotection against Ischemia-Reperfusion Injury in Rats

…"We concluded that enhancing endogenous endocannabinoid release and subsequent activation of CB2 [cannabinoid receptor 2] receptor signaling represent a major mechanism whereby propofol conditioning confers antioxidative and cardioprotective effects against

myocardial I/R injury."…

-Department of Anesthesiology, Changzheng Hospital Affiliated to Second Military Medical University, No. 415 Fengyang Road, Shanghai 200003, China

-Department of Neurology, PLA Rocket Force General Hospital, No. 16 Xinjiekouwai Street, Beijing 100088, China

-Department of Anesthesiology, PLA Rocket Force General Hospital, No. 16 Xinjiekouwai Street, Beijing 100088, China

-Nursing School of Shanghai Jiguang Polytechnic College, No. 2859 Shuichan Road, Shanghai 201901, China

-Hebei North University School of Medicine, Zhangjiakou, Hebei 075000, China

-School of Pharmacy, Second Military Medical University, No. 325 Guohe Road, Shanghai 200433, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5549482/

The endogenous cardiac cannabinoid system: a new protective mechanism against myocardial ischemia

"The pharmacological (and recreational) effects of cannabis have been known for centuries. However, it is only recently that one has identified two subtypes of G-protein-coupled receptors, namely CB1 and CB2-receptors, which mediate the numerous effects of delta9-tetrahydrocannabinol and other cannabinoids. Logically, the existence of cannabinoid-receptors implies that endogenous ligands for these receptors (endocannabinoids) exist and exert a physiological role. Hence, arachidonoylethanolamide (anandamide) and sn-2 arachidonoylglycerol, the first two endocannabinoids identified, are formed from plasma membrane phospholipids and act as CB1 and/or CB2 agonists. The presence of both CB1 and CB2-receptors in the rat heart is noteworthy. This endogenous cardiac cannabinoid system is involved in several phenomena associated with cardioprotective effects. The reduction in infarct size following myocardial ischemia, observed in rats exposed to either LPS or heat stress 24 hours before, is abolished in the presence of a CB2-receptor antagonist. Endocannabinoids and synthetic cannabinoids, the latter through either CB1 or CB2-receptors, exert direct cardioprotective effects in rat isolated hearts. The ability of cannabinoids to reduce infarct size has been confirmed in vivo in anesthetized mice and rats. This latter effect appears to be mediated through CB2-receptors. Thus, the endogenous cardiac cannabinoid system, through activation of CB2-receptors, appears to be an important mechanism of protection against myocardial ischemia."

-Faculty of Pharmacy, University of Montreal, QC, Canada.

https://pubmed.ncbi.nlm.nih.gov/16618028

Cardiovascular Disease

Endocannabinoids and the Cardiovascular System in Health and Disease

"The endocannabinoid system is widely distributed throughout the cardiovascular system. Endocannabinoids play a minimal role in the regulation of cardiovascular function in normal conditions, but are altered in most cardiovascular disorders. In shock, endocannabinoids released within blood mediate the associated hypotension through CB(1) activation. In hypertension, there is evidence for changes in the expression of CB(1), and CB(1) antagonism reduces blood pressure in obese hypertensive and diabetic patients. The endocannabinoid system is also upregulated in cardiac pathologies. This is likely to be cardioprotective, via CB(2) and CB(1) (lesser extent). In the vasculature, endocannabinoids cause vasorelaxation through activation of multiple target sites, inhibition of calcium channels, activation of potassium channels, NO production and the release of vasoactive substances. Changes in the expression or function of any of these pathways alter the vascular effect of endocannabinoids. Endocannabinoids have positive (CB(2)) and negative effects (CB(1)) on the progression of atherosclerosis. However, any negative effects of CB(1) may not be consequential, as chronic CB(1) antagonism in large scale human trials was not associated with significant reductions in atheroma. In neurovascular disorders such as stroke, endocannabinoids are upregulated and protective, involving activation of CB(1), CB(2), TRPV1 and PPARα. Although most of this evidence is from preclinical studies, it seems likely that cannabinoid-based therapies could be beneficial in a range of cardiovascular disorders."

-Faculty of Medicine and Health Sciences, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital Centre, University of Nottingham

https://pubmed.ncbi.nlm.nih.gov/26408169/

Anandamide and endocannabinoid system: an attractive therapeutic approach for cardiovascular disease

"Hypertension, one of the most frequent cardiovascular diseases, remains the most important risk factor for the development of associated cardiovascular pathologies and it affects millions of people around the world. Although there are a large number of antihypertensive therapies, these are insufficient to properly control blood pressure. The failures and disadvantages of conventional therapies have stimulated the research for the development of new types of antihypertensive alternatives. These new agents would possess distinct mechanisms of action that would allow a better blood pressure control and more effective prevention of

cardiovascular disease, and others related, such as myocardial infarction and stroke.[1]

Cannabinoids (CBs) and their endogenous and synthetic analogs induce important hypotensive effects by complex mechanisms. It has been found recently that the endogenous CB system is involved in the mechanism of hypotension associated with hemorrhagic, endotoxic, and cardiogenic shock, as well as with advanced liver cirrhosis. In this sense, it has also been proposed that the pharmacological manipulation of the endocannabinoid system (ECS) may offer a new approach to antihypertensive therapy.[2] For this reason, we decided to focus our review on the cardiovascular effects of endocannabinoids (eCBs) and its action on blood pressure."…

"Other research groups have shown that the ECS is not only involved in the modulation of responses during hypertensive pathology but also has a number of beneficial effects in other types of cardiovascular diseases.[15,16] Moreover, it has been shown that the action on CB2 receptors is implicated in the adhesion, migration, proliferation, and function of immune cells during the process of atherosclerotic plaque formation.[11]"…

-Virna Margarita Martín Giménez, Faculty of Chemical and Technological Sciences, Universidad Católica de Cuyo, San Juan Campus, Argentina;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6009078

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"Our findings reveal previously unknown associations between circulating ECs [endocannabinoids] and EC-related molecules with markers of lipid metabolism and CVD [cardiovascular disease] risk after HFCS [high-fructose corn syrup] consumption."

-Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, Davis, California
-Department of Nutrition, School of Veterinary Medicine, University of California, Davis, Davis, California
-Division of Gastroenterology and Hepatology, School of Medicine, University of California, Davis, Davis, California
-Department of Pediatrics, School of Medicine, University of California, Davis, Davis, California
-U.S. Department of Agriculture, Western Human Nutrition Research Center, Davis, California
-Division of Biomedical Sciences, School of Medicine, University of California, Riverside, Riverside, California
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6335011/

Diabetic Cardiovascular Disease Induced by Oxidative Stress

..."Another promising avenue is the omega-3 polyunsaturated fatty acids (omega-3 PUFAs). PUFAs have been linked to considerable cardiovascular benefits in diabetics and heart failure patients [177,178,179]. Consistent with the above, a rat model of diabetes shows that PUFAs alter favorably the lipid metabolism in diabetic rats themselves and on the oxidation level of their offspring [180]. This fatty acid acts as an indirect anti-oxidant in vascular endothelial cells and

reduced inflammation and levels of adhesion molecules, in turn diminish the risk of atherosclerosis and cardiovascular disease [181].Targeting oxidative stress and mitochondrial dysfunction simultaneously would seem to be a logical alternative approach. "....

Conclusions

"Several lines of evidence indicate that oxidative stress plays a pivotal role in the development of diabetic-induced cardiovascular disease. Hyperglycemia and metabolic abnormalities of diabetes cause the production of ROS in vascular cells and in cardiomyocytes. Diabetic oxidative stress occurs by multiple mechanisms, with prominent roles of mitochondrial dysfunction and NOX enzymes, and in cardiac and vascular dysfunction including chronic inflammation, fibrosis, apoptosis, VSMC proliferation and arterial stiffness. As such, therapeutic strategies to reduce ROS production or enhance ROS degradation should have protective effects against diabetes-induced cardiovascular disease. Up to this point, however, randomized clinical trials have yet to provide convincing evidence that antioxidant treatment has beneficial effects in human diabetic cardiovascular disease. However, this may not necessarily be regarded as a general failure of the ROS hypothesis but may simply reflect the numerous open questions regarding antioxidant treatment. Further study to understand the initiation of oxidative stress as well as its downstream effects on cellular function will likely add more insight into the underlying mechanisms of diabetes-induced cardiovascular disease and identify more specific targeted therapies."

-Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford University, Stanford, CA 94305, USA

-Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, USA

-Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, 3-25-8 Nishi-Shinbashi, Minatoku, Tokyo 105-0003, Japan;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632800

■■■

…"The omega-3 (n–3) fatty acids derived from fish, eicosapentaenoic acid (EPA; 20:5n–3) and docosahexaenoic acid (DHA; 22:6n–3), are associated with a reduced risk of cardiovascular disease and other chronic diseases (1–3). EPA and DHA promote an antiinflammatory state (4) and regulate the expression of genes involved in fatty acid metabolism (5–7). However, our ability to detect associations between EPA and DHA intake, gene variants, and disease is limited by the validity and feasibility of dietary assessment. Both plasma and red blood cell (RBC) fatty acid composition are valid biomarkers of EPA and DHA intake (8–13), but their measurement requires technically challenging, expensive, and time-consuming assays that are impractical in large-scale studies. Simpler and less expensive biomarkers of EPA and DHA intake are clearly

needed."…

-The Center for Alaska Native Health Research, Institute of Arctic Biology, University of Alaska Fairbanks, Fairbanks, AK (DMO, MAJ, MJW, AB, and BL)

-The Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (ARK).

-Supported by a Centers of Biomedical Research Excellence grant from the NIH NCRR (P20 RR16430) and undergraduate research awards to MJW and MAJ from Alaska EPSCOR (NSF 0346770), Alaska INBRE (NIH NCRR RR016466), and the UAF Center for Research Services.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2646803/

Associations With Eicosapentaenoic Acid to Arachidonic Acid Ratio and Mortality in Hospitalized Heart Failure Patients

"Background: Intake of n-3 polyunsaturated fatty acids (n-3 PUFAs) lowers the risk of atherosclerotic cardiovascular events, particularly ischemic heart disease. In addition, the ratio of eicosapentaenoic acid (EPA; n-3 PUFA) to arachidonic acid (AA; n-6 PUFA) has recently been recognized as a risk marker of cardiovascular disease. In contrast, the prognostic impact of the EPA/AA ratio on patients with heart failure (HF) remains unclear."…

"Conclusion: The EPA/AA ratio was an independent predictor of cardiac mortality in patients with HF; therefore, the prognosis of patients with HF may be improved by taking appropriate management to control the EPA/AA balance."

-Department of Cardiovascular Medicine, Fukushima Medical University, Fukushima, Japan.

- Department of Advanced Cardiac Therapeutics, Fukushima Medical University, Fukushima, Japan.

https://pubmed.ncbi.nlm.nih.gov/27138463/

Eicosapentaenoic acid to arachidonic acid (EPA/AA) ratio as an associated factor of high risk plaque on coronary computed tomography in patients without coronary artery disease

…"Low EPA/AA was an associated factor of HRP on CCTA in patients without CAD [coronary artery disease]. In addition to conventional coronary risk factors and CACS [coronary artery calcification score], EPA/AA and CCTA [Coronary computed tomography angiography] might be useful for risk stratification of CAD."…

-Department of Cardiology, Fujita Health University, Kutsukake-cho, Toyoake, Aichi, Japan.

-Department of Radiology, Fujita Health University, Kutsukake-cho, Toyoake, Aichi, Japan.

https://pubmed.ncbi.nlm.nih.gov/27175609/

Beneficial effect(s) of n-3 fatty acids in cardiovascular diseases: but, why and how?

“Low rates of coronary heart disease was found in Greenland Eskimos and Japanese who are exposed to a diet rich in fish oil. Suggested mechanisms for this cardio-protective effect focused on the effects of n-3 fatty acids on eicosanoid metabolism, inflammation, beta oxidation, endothelial dysfunction, cytokine growth factors, and gene expression of adhesion molecules; But, none of these mechanisms could adequately explain the beneficial actions of n-3 fatty acids. One attractive suggestion is a direct cardiac effect of n-3 fatty acids on arrhythmogenesis. N-3 fatty acids can modify Na+ channels by directly binding to the channel proteins and thus, prevent ischemia-induced ventricular fibrillation and sudden cardiac death. Though this is an attractive explanation, there could be other actions as well. N-3 fatty acids can inhibit the synthesis and release of pro-inflammatory cytokines such as tumor necrosis factoralpha (TNFalpha) and interleukin-1 (IL-1) and IL-2 that are released during the early course of ischemic heart disease. These cytokines decrease myocardial contractility and induce myocardial damage, enhance the production of free radicals, which can also suppress myocardial function. Further, n-3 fatty acids can increase parasympathetic tone leading to an increase in heart rate variability and thus, protect the myocardium against ventricular arrhythmias. Increased parasympathetic tone and acetylcholine, the principle vagal neurotransmitter, significantly attenuate the release of TNF, IL-1beta, IL-6 and IL-18. Exercise enhances parasympathetic tone, and the production of anti-inflammatory cytokine IL-10 which may explain the beneficial action of exercise in the prevention of cardiovascular diseases and diabetes mellitus. TNFalpha has neurotoxic actions, where as n-3 fatty acids are potent neuroprotectors and brain is rich in these fatty acids. Based on this, it is suggested that the principle mechanism of cardioprotective and neuroprotective action(s) of n-3 fatty acids can be due to the suppression of TNFalpha and IL synthesis and release, modulation of hypothalamic-pituitary-adrenal anti-inflammatory responses, and an increase in acetylcholine release, the vagal neurotransmitter. Thus, there appears to be a close interaction between the central nervous system, endocrine organs, cytokines, exercise, and dietary n-3 fatty acids. This may explain why these fatty acids could be of benefit in the management of conditions such as septicemia and septic shock, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, diabetes mellitus, essential hypertension and atherosclerosis.”

-EFA Sciences LLC, 1420 Providence Highway, Norwood, MA
https://pubmed.ncbi.nlm.nih.gov/11133172/

Basic mechanisms behind the effects of n-3 fatty acids on cardiovascular disease

"The epidemiological association between high intakes of n-3 fatty acids (FA) and decreased morbidity and mortality from cardiovascular disease (CVD) can be explained by two main basic mechanisms: (a) an effect on atherothrombosis, and (b) an effect on cardiac arrhythmias. These mechanisms probably reflect different beneficial influences of n-3 FA on cardiovascular biology. Effects on atherothrombosis include the modulation of the expression of pro-atherogenic genes (e.g., endothelial leukocyte adhesion molecules, inflammatory cytokines and cyclooxygenase (COX)-2) and the hepatic synthesis of very low density lipoproteins (VLDL), and are slow in onset, requiring incorporation into cell membrane phospholipids, and usually doses in humans in the order of 3g/day or higher. Effects on cardiac arrhythmias include complex interactions with ion channels (sodium, potassium and calcium channels), typically requiring the presence of free FA in extracellular fluids and usually occurring with lower doses (around 1g/day) of nutritional or pharmacological intake. We have focused most of our research effort in unraveling the pathophysiological background of protection by n-3 FA from atherothrombosis. As the result of incorporation of n-3 FA in the sn-2 position predominantly of the phosphatidyl ethanolamine pool in the inner leaflet of the plasma membrane, n-3 FA appear on the one hand to increase the production of bioactive lipid mediators (protectins and resolvins) affecting cytokine-induced signal transduction; and on the other hand to directly interfere with the generation of reactive oxygen species (mostly hydrogen peroxide), directly responsible for the activation of the transcription factor nuclear factor (NF)-kappaB, which controls the expression of a variety of pro-inflammatory and pro-atherogenic genes, including those encoding for interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF)alpha, vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and COX-2. The upstream-direct or indirect-inhibition of cytokine- and other atherogenic trigger-induced signaling pathway may involve interference with the activation of protein kinase (PK) C isoforms and NADP(H) oxidase. Such interference may also explain the blunt anti-inflammatory effect of n-3 FA in many experimental models and clinical conditions of inflammation. All together, these mechanisms may provide an integrated view of how n-3 FA may affect CVD."

-C.N.R. Institute of Clinical Physiology, Pisa and Lecce, Italy; University of Lecce, Ecotekne, Lecce, Italy.
https://pubmed.ncbi.nlm.nih.gov/18951002/

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…"The evidence of cardioprotection in published studies is derived from many sources, including epidemiological studies analyzing populations with high dietary ω-3 [omega-3] PUFAs intake.[77] "…

-Department of Pharmacology, University of Michigan, Ann Arbor, MI
-Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6242736

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…"The relationship between omega-3 fatty acids and cardiovascular disease is well studied, and has appeared inconsistent at times (Harris et al., 2006; Kromhout et al., 2010; Rizos et al., 2012). Still, it is important to consider that there is strong mechanistic evidence supporting a protective effect of omega-3 fatty acids on cardiovascular disease. In this review, I will provide an overview of the evidence for the heart rate-lowering effects of omega-3 fatty acids both in animals and humans, and explain how findings from our in vitro work provide a likely mechanism by which omega-3 fatty acids act on cardiac myocytes to reduce heart rate."…

-Laboratory for Lipid Medicine and Technology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3483717

Docosahexaenoic acid (DHA) and cardiovascular disease risk factors

"Numerous epidemiological and controlled interventional trials have supported the health benefits of long-chain omega-3 fatty acids in the form of docosahexaenoic acid (DHA, 22:6n-3) plus eicosapentaenoic acid (EPA, 20:5n-3) from fish and fish oils as well as from algal sources. The beneficial effects on cardiovascular disease and related mortality including various risk factors for cardiovascular disease (particularly lowering circulating triglyceride levels and the triglyceride:HDL-cholesterol ratio) have been observed in the absence of any concomitant blood cholesterol lowering. With appropriate dosages, consistent reductions in both fasting and postprandial triglyceride levels and moderate increases in fasting HDL-cholesterol levels have been observed with algal DHA in the majority of trials. These results are similar to findings for fish oils containing DHA and EPA. Related to greater fish intake, higher levels of DHA in circulating blood biomarkers (such as serum phospholipid) have been associated with reduced risks for the progression of coronary atherosclerosis and lowered risk from sudden cardiac death. Controlled clinical trials have also indicated the potential for algal DHA supplementation to have moderate beneficial effects on other cardiovascular disease risk factors including blood pressures and resting heart rates. Recommended intakes of DHA+EPA from numerous international groups for the prevention and management of cardiovascular disease have been forthcoming, although most have not offered specific recommendations for the optimal individual intake of DHA and EPA."

-Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada
https://pubmed.ncbi.nlm.nih.gov/19545988

Cardiovascular Disease and Atherosclerosis

..."Atherosclerosis is now considered a "systemic disease" characterised by low-grade arterial inflammatory lesions that can mature along with disease progression [109]. It is the underlying cause of coronary heart disease (CHD), and abnormalities in the metabolism of essential fatty acids that are characteristic of the associated risk factors [110]. Under normal physiological conditions, healthy endothelial cells synthesise and release adequate amounts of NO, PGI2, and PGE1, maintaining a downstream balance between pro- and anti-inflammatory molecules. However, in atherosclerosis, this balance becomes disrupted, leaning towards an increase in the production of proinflammatory cytokines such as IL-1, IL-2, IL-6 and TNF-α, resulting in the further progression of the disease [110]. These proinflammatory cytokines can induce oxidative stress by enhancing the production of ROS by monocytes, macrophages, and leukocytes. Since PUFA and their eicosanoid derivatives modulate inflammation, they play a significant role in this disease [26]. Decreases in ALA-derived LC-PUFA such as EPA and DHA seen in endothelial cell PUFA deficiency, increases the production of proinflammatory cytokines and free radicals which results in the development of insulin resistance [26]. As an example, early studies in Greenland Eskimos, a population consuming a high-fat diet, but rich in n-3 PUFA, showed that ingestion of EPA and DHA led to decreases in the mortality rate from CVD [111]. Similarly, Japanese populations eat more fish than North Americans and present a lower rate of acute myocardial infarction and atherosclerosis [112, 113]. Other later studies have further demonstrated strong associations between n-3 PUFA intake and decreased risks of CVD [114–116].

The role of n-6 PUFA in CVD is much more complex than the role of n-3 PUFA. PGE2, PGF2α, TXA2, and LTs produced from AA metabolism are proinflammatory [110]. TXA2 acts as a potent vasoconstrictor and powerful activator of platelet aggregation [117]. Studies have shown that TXA2 promotes the initiation and progression of atherosclerosis by regulating platelet activation and leukocyte-endothelial cell interactions [118]. LTB4 acts as a potent chemotactic agent, inducing the generation of ROS, activating neutrophils, and inducing the aggregation and adhesion of leukocytes to the vascular endothelium [110]. The leukotrienes LTC4, LTD4, and LTE4 induce vasoconstriction and bronchospasm [110].

Since AA [arachidonic acid / omega-6] is derived from LA, a reduction of LA intakes will reduce tissue AA content, which in turn will reduce any inflammatory potential and therefore lower the risk for CVD [119]. There are many other lines of evidence that link LA with atherosclerosis. Endothelial dysfunction (ED) is a characteristic of early-state atherosclerosis common in patients

with insulin resistance and diabetes [120]. A recent review by Simopoulos reported that diets enriched in LA increase the LA content of LDL and its susceptibility to oxidation, whereby oxidative modification increases the atherogenicity of LDL cholesterol [121]. Studies have also shown that in patients with type 2 diabetes susceptible of developing ED, there are substantial increases in LA concentrations in all LDL subfractions [122]. Cellular oxidative stress associated with LA oxidation of LDL and LA mediated ED is a critical signal transduction pathway involved in NFκB activation, whereby NFκB is critical for the expression of inflammatory genes associated with ED [120]. The susceptibility of LDL to oxidation by LA and its associated metabolites is linked to the severity of coronary atherosclerosis development [121, 123]. Despite the evidence to suggest that n-6 PUFA consumption increases the risk of developing CVD, recent evidence has suggested that both LA and ALA have the ability to prevent CVD [34]. In this study, LA significantly reduced levels of CRP, an inflammatory marker, upregulated in CVD in Japanese men [34]. However, other evidence to suggest that n-6 PUFA have an anti-inflammatory effect when consumed in such high quantities, such as that seen in the Western diet, is limited.

Since it has been proposed that diets high in LA reduce ALA metabolism [124] and since ALA metabolites such as EPA/DHA have been shown to reduce mortality rates from CVD [111–113], the balance of n-6 to n-3 PUFA is important in the prevention of atherosclerosis and CVD."...

-Alimentary Pharmabiotic Centre, Biosciences Institute, County Cork, Ireland
-Teagasc Food Research Centre, Biosciences Department, Moorepark, Fermoy, County Cork, Ireland
-Department of Microbiology, University College Cork, County Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

"Eicosapentaenoic acid (EPA) is a key anti-inflammatory/anti-aggregatory long-chain polyunsaturated omega-3 fatty acid. Conversely, the omega-6 fatty acid, arachidonic acid (AA) is a precursor to a number of pro-inflammatory/pro-aggregatory mediators. EPA acts competitively with AA for the key cyclooxygenase and lipoxygenase enzymes to form less inflammatory products. As a result, the EPA:AA ratio may be a marker of chronic inflammation, with a lower ratio corresponding to higher levels of inflammation. It is now well established that inflammation plays an important role in cardiovascular disease. This review examines the role of the EPA:AA ratio as a marker of cardiovascular disease and the relationship between changes in the ratio (mediated by EPA intake) and changes in cardiovascular risk. Epidemiological studies have shown that a lower EPA:AA ratio is associated with an increased risk of coronary artery disease, acute coronary syndrome, myocardial infarction, stroke, chronic heart failure, peripheral artery disease, and vascular disease. Increasing the EPA:AA ratio through treatment with purified EPA has been shown in clinical studies to be effective in primary and secondary prevention of coronary artery disease and reduces the risk of cardiovascular events following percutaneous coronary

intervention. The EPA:AA ratio is a valuable predictor of cardiovascular risk. Results from ongoing clinical trials will help to define thresholds for EPA treatment associated with better clinical outcomes."

-California Cardiovascular Institute , Fresno , CA , USA.
-Lipid Clinic , Sutter East Bay Medical Foundation , Oakland , CA , USA.
https://pubmed.ncbi.nlm.nih.gov/31063407/

Fatty acid facts, Part III: Cardiovascular disease, or, a fish diet is not fishy

"Preclinical and clinical studies have demonstrated that omega-3 polyunsaturated fatty acids (n-3 PUFAs) play a significant role in the prevention of cardiovascular disease. These fatty acids are called essential fatty acids as they fulfil essential functions and the mammalian cell cannot synthesize them de novo. Dietary sources of n-3 PUFAs include fish oils rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The clinical relevance of these molecules is derived from the incorporation of EPA and DHA into cell membranes. The presence of EPA/DHA alters the physical characteristics of the membrane. Both these altered physicochemical membrane properties and the presence of n-3 PUFAs released by the action of phospholipid lipases (resulting in antiinflammatory eicosanoids) improve biological functions such as signal transduction, ion channelling and ligand binding to nuclear receptors. EPA/DHA also reduce or quench gene expression of cyclooxygenase-2 and other enzymes, thereby diminishing the formation of proinflammatory molecules. Increased EPA/DHA concentration also gives rise to antiinflammatory lipid mediators, called lipoxins, resolvins and protectins. Another important function of n-3 PUFAs is scavenging of free radicals, which diminishes inflammatory response and oxidation of lipoprotein particles, notably low density lipoproteins. The interplay of these molecular processes has distinct cardioprotective effects, which involve actions on lipid metabolism, lipoprotein particle size, blood pressure, vascular function, coagulation potential, inflammatory response, atheroma formation and antiarrhythmic. In view of these actions, fish oil preparations and/or intake of oily fish are recommended as primary and secondary prevention of cardiovascular disease and sudden cardiac death. Large, ongoing trials will further elucidate the presumed favorable effects of EPA/DHA in heart failure and diabetes. This review provides a summary of the physiological mechanisms of the action of EPA and DHA and highlights the epidemiological evidence for a reduction in cardiac events and mortality."

-Pisa University Medical School, Pisa, Italy.
https://pubmed.ncbi.nlm.nih.gov/19221636

Health benefits of n-3 polyunsaturated fatty acids: eicosapentaenoic acid and docosahexaenoic acid

“Marine-based fish and fish oil are the most popular and well-known sources of n-3 polyunsaturated fatty acids (PUFAs), namely, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These n-3 PUFAs are known to have variety of health benefits against cardiovascular diseases (CVDs) including well-established hypotriglyceridemic and anti-inflammatory effects. Also, various studies indicate promising antihypertensive, anticancer, antioxidant, antidepression, antiaging, and antiarthritis effects. Moreover, recent studies also indicate anti-inflammatory and insulin-sensitizing effects of these fatty acids in metabolic disorders. Classically, n-3 PUFAs mediate some of these effects by antagonizing n-6 PUFA (arachidonic acid)-induced proinflammatory prostaglandin E_2 (PGE_2) formation. Another well-known mechanism by which n-3 PUFAs impart their anti-inflammatory effects is via reduction of nuclear factor-κB activation. This transcription factor is a potent inducer of proinflammatory cytokine production, including interleukin 6 and tumor necrosis factor-α, both of which are decreased by EPA and DHA. Other evidence also demonstrates that n-3 PUFAs repress lipogenesis and increase resolvins and protectin generation, ultimately leading to reduced inflammation. Finally, beneficial effects of EPA and DHA in insulin resistance include their ability to increase secretion of adiponectin, an anti-inflammatory adipokine. In summary, n-3 PUFAs have multiple health benefits mediated at least in part by their anti-inflammatory actions; thus their consumption, especially from dietary sources, should be encouraged.”

-Department of Animal Science, University of Tennessee, Knoxville, TN, USA.
https://pubmed.ncbi.nlm.nih.gov/22361189/

Omega-3 polyunsaturated fatty acids: anti-inflammatory and anti-hypertriglyceridemia mechanisms in cardiovascular disease

“Cardiovascular disease (CVD) is the world's most recognized and notorious cause of death. It is known that increased triglyceride-rich lipoproteins (TRLs) and remnants of triglyceride-rich lipoproteins (RLP) are the major risk factor for CVD. Furthermore, hypertriglyceridemia commonly leads to a reduction in HDL and an increase in atherogenic small dense low-density lipoprotein (sdLDL or LDL-III) levels. Thus, the evidence shows that Ω-3 fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have a beneficial effect on CVD through reprogramming of TRL metabolism, reducing inflammatory mediators (cytokines and leukotrienes), and modulation of cell adhesion molecules. Therefore, the purpose of this review is to provide the molecular mechanism related to the beneficial effect of Ω-3 PUFA on the lowering of plasma TAG levels and other atherogenic lipoproteins. Taking this into account, this study also provides the TRL lowering and anti-inflammatory mechanism of Ω-3 PUFA metabolites

such as RvE1 and RvD2 as a cardioprotective function."

-Department of Biochemistry, School of Medicine, College of Medicine and Health Sciences, University of Gondar
https://pubmed.ncbi.nlm.nih.gov/33179122/

Cardiovascular disease prevention and treatment

"The incidence of fatal and non-fatal cardiovascular disease (sudden cardiac death (SCD), myocardial infarction, others) varies, depending on conventional risk factors. However, in Western countries, like the US or Germany, incidences of fatal and non-fatal cardiovascular disease are far higher than in countries like Japan. In the present article, these differences are discussed and related to eicosapentaenoic acid (C20:5omega-3 or C20:5n-3; EPA) and docosahexaenoic acid (C22:6omega-3; DHA). Dietary intake of EPA and DHA and a number of other factors determine levels of EPA and DHA in an individual--best assessed as the omega-3 index, defined as the percentage of EPA and DHA in red cells, and analyzed in a standardized fashion. A review of the literature, expanded by measurements of the omega-3 index, indicates that the risk of sudden cardiac death correlates inversely with the omega-3 index. For persons with an omega-3 index <4%, risk is tenfold, as compared to persons with an omega-3 index >8%. A similar, less-pronounced, correlation exists for non-fatal cardiovascular disease. EPA and DHA have anti-arrhythmic and anti-atherosclerotic mechanisms of action. In large-scale intervention studies, intake of EPA and DHA has been demonstrated to reduce SCD and non-fatal cardiovascular events. Assessing or recommending dietary intake of EPA and DHA does not predict the resulting omega-3 index. Taken together, the omega-3 index is a biomarker to assess a person's content of omega-3 fatty acids, and thus the risk for sudden cardiac death, as well as non-fatal cardiovascular events. EPA and DHA prevent fatal and non-fatal cardiovascular disease and complications of congestive heart failure."

-Preventive Cardiology, Medizinische Clinic and Policlinic Innenstadt, University of Munich, Ziemssensstr.
https://pubmed.ncbi.nlm.nih.gov/19520557/

Dietary Bioactive Fatty Acids as Modulators of Immune Function: Implications on Human Health

"Diet is major modifiable risk factor for cardiovascular disease that can influence the immune status of the individual and contribute to persistent low-grade inflammation. In recent years, there has been an increased appreciation of the role of polyunsaturated fatty acids (PUFA) in improving immune function and reduction of systemic inflammation via the modulation of pattern recognition receptors (PRR) on immune cells. Extensive research on the use of bioactive

lipids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and their metabolites have illustrated the importance of these pro-resolving lipid mediators in modulating signaling through PRRs. While their mechanism of action, bioavailability in the blood, and their efficacy for clinical use forms an active area of research, they are found widely administered as marine animal-based supplements like fish oil and krill oil to promote health. The focus of this review will be to discuss the effect of these bioactive fatty acids and their metabolites on immune cells and the resulting inflammatory response, with a brief discussion about modern methods for their analysis using mass spectrometry-based methods."…

-Department of Microbiology and Immunology, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA

-Department of Pharmacotherapy and Outcomes Sciences, School of Pharmacy, Virginia Commonwealth University, Richmond, VA, USA;

-Department of General Practice, School of Dentistry, Virginia Commonwealth University, Richmond, VA, USA; -Department of Kinesiology & Health Sciences, College of Humanities & Sciences, Virginia Commonwealth University, Richmond, VA, USA;

-VCU Pauley Heart Center, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA , USA

-da Vinci Center, Virginia Commonwealth University, Richmond, VA, USA

-Institute for Structural Biology, Drug Discovery and Development, Virginia Commonwealth University School of Pharmacy, Richmond, VA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6950193/

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…"Omega-3 fatty acids play an important role in reducing cardiovascular disease, a leading cause of death in the United States (Harris et al. 2009). They reduce events that lead to heart attack by stabilizing the heart muscles against arrhythmia (irregular heartbeat or abnormal heart rhythm) (Ballantyne 1999). For example, 200 milligrams DHA per day decreases the chance of death from cardiac arrest by 50% (Horrocks and Yeo 1999).

EPA and DHA metabolites stimulate the dilation of arterioles (small arteries) (Ye et al. 2002), which decreases blood pressure and inhibit the expression of inflammatory genes (Bouwens et al. 2009). A literature review covering 2002 to 2004 — including a pooled analysis of 48 randomized, controlled trials and 41 cohort trials — found no significant benefit of supplementation with omega-3 fatty acids for the reduction of total mortality, cardiovascular events or cancer (Hooper et al. 2004). However, as the authors point out, there was "significant statistical heterogeneity" among the results given that the dosages and formulations of omega-3 fatty acids and the outcomes evaluated varied substantially, with some studies showing benefits and others not. This suggests that further studies are needed to evaluate the specific effects of different dosages and formulations of omega-3 fatty acids in different population groups and at different supplementation levels."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See Supplements for related research quotes.

See also Atherosclerosis , DNA (Deoxyribonucleic Acid) , Inflammation in Health & Disease

Carotene

Diet, nutrition, and cancer

"Evidence pertaining to the role of dietary factors in carcinogenesis comes from both epidemiological studies and laboratory experiments. In 1982, the Committee on Diet, Nutrition, and Cancer of the National Research Council conducted a comprehensive evaluation of this evidence. That assessment as well as recent epidemiological and laboratory investigations suggest that a high fat diet is associated with increased susceptibility to cancer of different sites, particularly the breast and colon, and to a lesser extent, the prostate. Current data permit no definitive conclusions about other dietary macroconstituents including cholesterol, total caloric intake, protein, carbohydrates and total dietary fiber. Specific components of fiber, however, may have a protective effect against colon cancer. In epidemiological studies, frequent consumption of certain fruits and vegetables, especially citrus fruits and carotene-rich and cruciferous vegetables, is associated with a lower incidence of cancers at various sites. The specific components responsible for these effects are not clearly identified, although the epidemiological evidence appears to be most consistent for a protective effect of carotene on lung cancer and less so for vitamins A and C and various cancer sites. The laboratory evidence is most consistent for vitamin A deficiency and enhanced tumorigenesis, and for the ability of various nonnutritive components in cruciferous vegetables to block in-vivo carcinogenesis."….

- S Palmer, Progress in food & Nutrition Science
https://pubmed.ncbi.nlm.nih.gov/3010379

Cell Life Cycle

Effect of endocannabinoid signalling on cell fate: life, death, differentiation and proliferation of brain cells

“Cell fate events are regulated by different endogenous developmental factors such as the cell micro-environment, external or remote signals and epigenetic factors. Among the many regulatory factors, endocannabinoid-associated signalling pathways are known to conduct several of these events in the developing nervous system and in the adult brain. Interestingly, endocannabinoids exert modulatory actions in both physiological and pathological conditions. Endocannabinoid signalling can promote cell survival by acting on non-transformed brain cells (neurons, astrocytes or oligodendrocytes) and can have either a protumoural or antitumoural effect on transformed cells. Moreover, endocannabinoids are able to attenuate the detrimental effects on neurogenesis and neuroinflammation associated with ageing. Thus, the endocannabinoid system emerges as an important regulator of cell fate, controlling cell survival/cell death decisions depending on the cell type and its environment.”

-Health Department IES Teror, Ministry of Education and Universities of the Government of the Canary Islands, Las Palmas, Spain

-Neuroinflammation Laboratory, Research Unit, Hospital Nacional de Paraplegicos-SESCAM, Spain,

-Department of Life Sciences, University of Roehampton, Whitelands College, London, UK,

https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC6487559/

Cannabinoid receptor signaling in progenitor/stem cell proliferation and differentiation

“Cannabinoids, the active components of cannabis (Cannabis sativa) extracts, have attracted the attention of human civilizations for centuries, much earlier than the discovery and characterization of their substrate of action, the endocannabinoid system (ECS). The latter is an ensemble of endogenous lipids, their receptors [in particular type-1 (CB1) and type-2 (CB2) cannabinoid receptors] and metabolic enzymes. Cannabinoid signaling regulates cell proliferation, differentiation and survival, with different outcomes depending on the molecular targets and cellular context involved. Cannabinoid receptors are expressed and functional from the very early developmental stages, when they regulate embryonic and trophoblast stem cell survival and differentiation, and thus may affect the formation of manifold adult specialized tissues derived from the three different germ layers (ectoderm, mesoderm and endoderm). In the ectoderm-derived nervous system, both CB1 and CB2 receptors are present in neural progenitor/stem cells and control their self-renewal, proliferation and differentiation. CB1 and

CB2 show opposite patterns of expression, the former increasing and the latter decreasing along neuronal differentiation. Recently, endocannabinoid (eCB) signaling has also been shown to regulate proliferation and differentiation of mesoderm-derived hematopoietic and mesenchymal stem cells, with a key role in determining the formation of several cell types in peripheral tissues, including blood cells, adipocytes, osteoblasts/osteoclasts and epithelial cells. Here, we will review these new findings, which unveil the involvement of eCB signaling in the regulation of progenitor/stem cell fate in the nervous system and in the periphery. The developmental regulation of cannabinoid receptor expression and cellular/subcellular localization, together with their role in progenitor/stem cell biology, may have important implications in human health and disease."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, IUIN, CIBERNED and IRYCIS, Madrid, Spain
https://pubmed.ncbi.nlm.nih.gov/24076098/

The endocannabinoid system drives neural progenitor proliferation

"The discovery of multipotent neural progenitor (NP) cells has provided strong support for the existence of neurogenesis in the adult brain. However, the signals controlling NP proliferation remain elusive. Endocannabinoids, the endogenous counterparts of marijuana-derived cannabinoids, act as neuromodulators via presynaptic CB1 receptors and also control neural cell death and survival. Here we show that progenitor cells express a functional endocannabinoid system that actively regulates cell proliferation both in vitro and in vivo. Specifically, NPs produce endocannabinoids and express the CB1 receptor and the endocannabinoid-inactivating enzyme fatty acid amide hydrolase (FAAH). CB1 receptor activation promotes cell proliferation and neurosphere generation, an action that is abrogated in CB1-deficient NPs. Accordingly, proliferation of hippocampal NPs is increased in FAAH-deficient mice. Our results demonstrate that endocannabinoids constitute a new group of signaling cues that regulate NP proliferation and thus open novel therapeutic avenues for manipulation of NP cell fate in the adult brain."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/16037095

See also Cancer , Neuroprotection

Cellular Signaling

"The endocannabinoid system (ECS) is a key cellular signalling system that has been implicated in the regulation of diverse cellular functions. Importantly, growing evidence suggests that the biological actions of the ECS may, in part, be mediated through its ability to regulate the production and/or release of nitric oxide, a ubiquitous bioactive molecule, which functions as a versatile signalling intermediate."...

-Division of Cell Signalling and Immunology, Sir James Black Centre, School of Life Sciences, University of Dundee, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5439392/

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"In fact, AEA [anandamide] is a signal for the cells to make a choice between life and death and it might be a contributor responsible for the immune deficit observed in space."

-Nasa
https://www.nasa.gov/mission_pages/station/research/experiments/explorer/Investigation.html?#id=251
bit.do/nasa-quote

Communication is the key

..."Birth, life and death involve the integration of a complex array of biosignals that living cells sense and process to respond and adapt to modifications of their environment.

The signals that are sent and received by cells during their whole existence are essential for the harmonious development of tissues, organs and bodies. They also govern movement, thought and behavior.

It is now well established that cells do not behave as selfish entities but rather tend to form «microsocieties» whose proper functioning requires a precise coordination of emission and reception of signals. Dysfunctioning of the networks is associated with pathological situations that can range from abnormal proliferation to death."...

-Laboratoire d'Oncologie Virale et Moléculaire, Université Paris, Paris-France
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC280669

Central Nervous System (CNS)

Wiring and firing neuronal networks: endocannabinoids take center stage

"Endocannabinoids (eCBs) function as retrograde messengers at both excitatory and inhibitory synapses, and control various forms of synaptic plasticity in the adult brain. The molecular machinery required for specific eCB functions during synaptic plasticity is well established. However, eCB signaling plays surprisingly fundamental roles in controlling the acquisition of neuronal identity during CNS development."…

-Division of Molecular Neurobiology, Department of Medical Biochemistry and Biophysics, Karolinska Institute
https://pubmed.ncbi.nlm.nih.gov/18801434/

Therapeutic potential of cannabinoids in CNS disease

"The major psychoactive constituent of Cannabis sativa, delta(9)-tetrahydrocannabinol (delta(9)-THC), and endogenous cannabinoid ligands, such as anandamide, signal through G-protein-coupled cannabinoid receptors localised to regions of the brain associated with important neurological processes. Signalling is mostly inhibitory and suggests a role for cannabinoids as therapeutic agents in CNS disease where inhibition of neurotransmitter release would be beneficial. Anecdotal evidence suggests that patients with disorders such as multiple sclerosis smoke cannabis to relieve disease-related symptoms. Cannabinoids can alleviate tremor and spasticity in animal models of multiple sclerosis, and clinical trials of the use of these compounds for these symptoms are in progress. The cannabinoid nabilone is currently licensed for use as an antiemetic agent in chemotherapy-induced emesis. Evidence suggests that cannabinoids may prove useful in Parkinson's disease by inhibiting the excitotoxic neurotransmitter glutamate and counteracting oxidative damage to dopaminergic neurons. The inhibitory effect of cannabinoids on reactive oxygen species, glutamate and tumour necrosis factor suggests that they may be potent neuroprotective agents. Dexanabinol (HU-211), a synthetic cannabinoid, is currently being assessed in clinical trials for traumatic brain injury and stroke. Animal models of mechanical, thermal and noxious pain suggest that cannabinoids may be effective analgesics. Indeed, in clinical trials of postoperative and cancer pain and pain associated with spinal cord injury, cannabinoids have proven more effective than placebo but may be less effective than existing therapies. Dronabinol, a commercially available form of delta(9)-THC, has been used successfully for increasing appetite in patients with HIV wasting disease, and cannabinoid receptor antagonists may reduce obesity. Acute adverse effects following cannabis usage include sedation and anxiety. These effects are usually transient and may be less severe than those that

occur with existing therapeutic agents. The use of nonpsychoactive cannabinoids such as cannabidiol and dexanabinol may allow the dissociation of unwanted psychoactive effects from potential therapeutic benefits. The existence of other cannabinoid receptors may provide novel therapeutic targets that are independent of CB(1) receptors (at which most currently available cannabinoids act) and the development of compounds that are not associated with CB(1) receptor-mediated adverse effects. Further understanding of the most appropriate route of delivery and the pharmacokinetics of agents that act via the endocannabinoid system may also reduce adverse effects and increase the efficacy of cannabinoid treatment. This review highlights recent advances in understanding of the endocannabinoid system and indicates CNS disorders that may benefit from the therapeutic effects of cannabinoid treatment. Where applicable, reference is made to ongoing clinical trials of cannabinoids to alleviate symptoms of these disorders."

-Department of Microbiology-Immunology, Northwestern University Medical School, Chicago, Illinois, USA
https://pubmed.ncbi.nlm.nih.gov/12617697/

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…"Almost all CNS disorders, including multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD), are associated with some degree of neuroinflammation and related redox imbalances. In this context, microglial cells have been proposed as important contributors in chronic neurodegeneration and oxidative stress as they produce and release a variety of cytoactive factors, including ROS and NO•, glutamate, and cytokines [31]. In AD, for example, microglial cells surrounding the senile plaques express major histocompatibility complex (MHC) class II molecules, a feature of antigen-presenting cells. Aβ peptides or fragments of amyloid precursor protein increase O2•− production in rat peritoneal macrophages and cultured rat microglia [32]. NO• formation is also induced in mouse microglia by Aβ peptides [33]. As neurons are post-mitotic cells, their general incapability to divide explains some aging and degeneration-related dysfunction, considering that the capacity for neuronal replacement is very limited (although many parts of the CNS have considerable neuronal redundancy) [4]. Furthermore, considering the "neurohormesis" principle, neuronal cells are apparently functional under restricted redox conditions, in contrast to more versatile cells, such as hepatocytes and myocytes. In this respect, hypoxia and ischemia-reperfusion processes could be literally lethal for many neuronal cells in the affected brain region [34]."…

-Institute of Physical Activity and Sports Science (ICAFE), Cruzeiro do Sul University, Brazil
-Graduation Program in Health Sciences, Cruzeiro do Sul University, Brazil;
-Department of Veterinary Medicine, University Paulista (UNIP), Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3967194/

Ceramide

Ceramide: a new second messenger of cannabinoid action

"Cannabinoids, the active components of Cannabis sativa (marijuana), and their endogenous counterparts exert their effects by binding to specific G(i/o)-protein-coupled receptors that modulate adenylyl cyclase, ion channels and extracellular signal-regulated kinases. Recent research has shown that the CB(1) cannabinoid receptor is coupled to the generation of the lipid second messenger ceramide via two different pathways: sphingomyelin hydrolysis, and ceramide synthesis de novo. Ceramide in turn mediates cannabinoid-induced apoptosis, as shown by in vitro and in vivo studies. These findings provide a new perspective on how cannabinoids act, and raise exciting physiological and therapeutic questions."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, 28040, Madrid, Spain

https://pubmed.ncbi.nlm.nih.gov/11165667

Cannabinoids and ceramide: two lipids acting hand-by-hand

"Cannabinoids, the active components of Cannabis sativa (marijuana) and their endogenous counterparts, exert their effects by binding to specific G-protein-coupled receptors that modulate adenylyl cyclase and ion channels. Recent research has shown that the CB1 cannabinoid receptor is also coupled to the generation of the lipid second messenger ceramide via two different pathways: sphingomyelin hydrolysis and ceramide synthesis de novo. Sustained ceramide accumulation in tumor cells mediates cannabinoid-induced apoptosis, as evidenced by in vitro and in vivo studies. This effect seems to be due to the impact of ceramide on key cell signalling systems such as the extracellular signal-regulated kinase cascade and the Akt pathway. These findings provide a new conceptual view on how cannabinoids act, and raise interesting physiological and therapeutic questions."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, 28040 Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/15958274

Ceramides and skin function

"Ceramides are the major lipid constituent of lamellar sheets present in the intercellular spaces

of the stratum corneum. These lamellar sheets are thought to provide the barrier property of the epidermis. It is generally accepted that the intercellular lipid domain is composed of approximately equimolar concentrations of free fatty acids, cholesterol, and ceramides. Ceramides are a structurally heterogeneous and complex group of sphingolipids containing derivatives of sphingosine bases in amide linkage with a variety of fatty acids. Differences in chain length, type and extent of hydroxylation, saturation etc. are responsible for the heterogeneity of the epidermal sphingolipids. **It is well known that ceramides play an essential role in structuring and maintaining the water permeability barrier function of the skin**. In conjunction with the other stratum corneum lipids, they form ordered structures. An essential factor is the physical state of the lipid chains in the nonpolar regions of the bilayers. The stratum corneum intercellular lipid lamellae, the aliphatic chains in the ceramides and the fatty acids are mostly straight long-chain saturated compounds with a high melting point and a small polar head group. This means that at physiological temperatures, the lipid chains are mostly in a solid crystalline or gel state, which exhibits low lateral diffusional properties and is less permeable than the state of liquid crystalline membranes, which are present at higher temperatures. The link between skin disorders and changes in barrier lipid composition, especially in ceramides, is difficult to prove because of the many variables involved. However, **most skin disorders that have a diminished barrier function present a decrease in total ceramide content with some differences in the ceramide pattern. Formulations containing lipids identical to those in skin and, in particular, some ceramide supplementation could improve disturbed skin conditions.** Incomplete lipid mixtures yield abnormal lamellar body contents, and disorder intercellular lamellae, whereas complete lipid mixtures result in normal lamellar bodies and intercellular bilayers. The utilization of physiological lipids according to these parameters have potential as new forms of topical therapy for dermatoses. An alternative strategy to improving barrier function by topical application of the various mature lipid species is to enhance the natural lipid-synthetic capability of the epidermis through the topical delivery of lipid precursors."

-Instituto de Investigaciones Químicas y Ambientales de Barcelona, Barcelona, Spain.
https://pubmed.ncbi.nlm.nih.gov/12553851

High levels of modified ceramides are a defining feature of murine and human cancer cachexia

Background: Cancer cachexia (CCx) is a multifactorial energy-wasting syndrome reducing the efficiency of anti-cancer therapies, quality of life, and survival of cancer patients. In the past years, most studies focused on the identification of tumour and host-derived proteins contributing to CCx. However, there is still a lack of studies addressing the changes in bioactive

lipids. The aim of this study was to identify specific lipid species as a hallmark of CCx by performing a broad range lipid analysis of plasma from well-established CCx mouse models as well as cachectic and weight stable cancer patients."…

Results: A decrease in several lysophosphatidylcholine (LPC) species and an increase in numerous sphingolipids including sphingomyelins (SMs), ceramides (CERs), hexosyl-ceramides (HCERs) and lactosyl-ceramides (LCERs), were mutual features of CCx in both mice and cancer patients. Notably, sphingolipid levels gradually increased during cachexia development. Key enzymes involved in ceramide synthesis were elevated in liver but not in adipose, muscle, or tumour tissues, suggesting that ceramide turnover in the liver is a major contributor to elevated sphingolipid levels in CCx. LPC(16:1), LPC(20:3), SM(16:0), SM(24:1), CER(16:0), CER(24:1), HCER(16:0), and HCER(24:1) were the most consistently affected lipid species between mice and humans and correlated negatively (LPCs) or positively (SMs, CERs and HCERs) with the severity of body weight loss.

Conclusions: High levels of sphingolipids, specifically ceramides and modified ceramides, are a defining feature of murine and human CCx and may contribute to tissue wasting and skeletal muscle atrophy through the inhibition of anabolic signals. The progressive increase in sphingolipids during cachexia development supports their potential as early biomarkers for CCx."

-Institute for Diabetes and Cancer, Helmholtz Center Munich, Neuherberg, Germany.

-Joint Heidelberg-IDC Translational Diabetes Program, Inner Medicine 1, Heidelberg University Hospital, Heidelberg, Germany.

-German Center for Diabetes Research (DZD), Neuherberg, Germany.

-Research Unit Molecular Endocrinology and Metabolism, Helmholtz Center Munich, German Research Center for Environmental Health, Neuherberg, Germany.

-Cancer Metabolism Research Group, LIM 26 HC, Medical School, University of São Paulo, São Paulo, Brazil.

-Molecular Metabolic Control, Technical University of Munich, Munich, Germany.

-Experimentelle Genetik, Technical University of Munich, Freising-Weihenstephan, Neuherberg, Germany.

-Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7749558/

Ceramides as Novel Disease Biomarkers

"Ceramides are sphingolipids and integral components of the eukaryotic cell membrane. Apart from providing structural integrity, ceramides have also been shown to act as second messengers in cell signaling processes. In recent publications, ceramide modulation has been reported in pathological conditions such as cancer, diabetes, Alzheimer's disease (AD), coronary artery disease (CAD), multiple sclerosis (MS), as well as depression. Ceramides or ceramide panel combinations have been proposed as specific disease biomarkers that could be detected in

diseased tissue, synovial fluid, cerebrospinal fluid (CSF), and blood. This article reviews ceramide modulation in a selection of different diseases and the potential use of ceramides as biomarkers in diagnostics, determination of disease stage and personalized medicine."

-Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Branch for Translational Medicine and Pharmacology TMP, Theodor-Stern-Kai 7, 60596 Frankfurt am Main, Germany.

-pharmazentrum frankfurt/ZAFES, Institute of Clinical Pharmacology, Goethe University Hospital Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt/Main, Germany.

https://pubmed.ncbi.nlm.nih.gov/30477968

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"Ceramide is a sphingolipid that acts as a second messenger in ubiquitous, evolutionarily conserved, signaling systems. Emerging data suggest that radiation acts directly on the plasma membrane of several cell types, activating acid sphingomyelinase, which generates ceramide by enzymatic hydrolysis of sphingomyelin. Ceramide then acts as a second messenger in initiating an apoptotic response via the mitochondrial system. Radiation-induced DNA damage can also initiate ceramide generation by activation of mitochondrial ceramide synthase and de novo synthesis of ceramide. In some cells and tissues, BAX is activated downstream of ceramide, regulating commitment to the apoptotic process via release of mitochondrial cytochrome c. Genetic and pharmacologic studies in vivo showed that radiation targets the acid sphingomyelinase apoptotic system of microvascular endothelial cells in the lungs, intestines and brain, as well as in oocytes, to initiate the pathogenesis of tissue damage. Regulated ceramide metabolism may produce metabolites, such as sphingosine 1-phosphate, shown to signal antiapoptosis, thus controlling the intensity of the apoptotic response and constituting a mechanism for radiation sensitivity or resistance. An improved understanding of this signaling system may offer new opportunities for the modulation of radiation effects in the treatment of cancer."

-Laboratory of Signal Transduction, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

https://pubmed.ncbi.nlm.nih.gov/12947396/

See also Colon Cancer (Colorectal Cancer)

Cerebral Ischemia

"Cerebral ischemia is a condition in which a blockage in an artery restricts the delivery of oxygen-rich blood to the brain, resulting in damage to brain tissue."…

-Weill Cornell Brain and Spine Center
https://weillcornellbrainandspine.org/condition/ischemia-cerebral

Cannabinoid receptor subtypes 1 and 2 mediate long-lasting neuroprotection and improve motor behavior deficits after transient focal cerebral ischemia.

"The endocannabinoid system is crucially involved in the regulation of brain activity and inflammation. We have investigated the localization of cannabinoid CB1 and CB2 receptors in adult rat brains before and after focal cerebral ischemia due to endothelin-induced transient occlusion of the middle cerebral artery (eMCAO). Using immunohistochemistry, both receptor subtypes were identified in cortical neurons. After eMCAO, neuronal cell death was accompanied by reduced neuronal CB1 and CB2 receptor-linked immunofluorescence. In parallel, CB1 receptor was found in activated microglia/macrophages 3 days post eMCAO and in astroglia cells at days 3 and 7. CB2 receptor labeling was identified in activated microglia/macrophages or astroglia 3 and 7 days post ischemia, respectively. In addition, immune competent CD45-positive cells were characterized by pronounced CB2 receptor staining 3 and 7 days post eMCAO. KN38-72717, a potent and selective CB1 and CB2 receptor agonist, revealed a significant, dose-dependent and long-lasting reduction of cortical lesion sizes due to eMCAO, when applied consecutively before, during and after eMCAO. In addition, severe motor deficits of animals suffering from eMCAO were significantly improved by KN38-7271. KN38-7271 remained effective, even if its application was delayed up to 6h post eMCAO. Finally, we show that the endocannabinoid system assembles a comprehensive machinery to defend the brain against the devastating consequences of cerebral ischemia. In summary, this study underlines the therapeutic potential of CB1 and/or CB2 receptor agonists against neurodegenerative diseases or injuries involving acute or chronic imbalances of cerebral blood flow and energy consumption.."

- KeyNeurotek Pharmaceuticals AG, ZENIT Technology Park, Leipziger Straße 44, D-39120 Magdeburg, Germany.
https://www.ncbi.nlm.nih.gov/pubmed/23069763

KN38-72717 - synthetic cannabinoid which targets activates cannabinoid type 1 & 2 receptors

Cerebral Palsy

Prevention of cerebral palsy, autism spectrum disorder, and attention deficit-hyperactivity disorder

“This hypothesis states that cerebral palsy (CP), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) are all caused by an exaggerated central nervous system inflammatory response to a prenatal insult. This prenatal insult may be one or more episodes of ischemia-reperfusion, an infectious disease of the mother or the fetus, or other causes of maternal inflammation such as allergy or autoimmune disease. The resultant fetal inflammatory hyper-response injures susceptible neurons in the developing white matter of the brain in specific areas at specific gestational ages. The exaggerated neuroinflammatory response is theorized to occur between about 19 and 34 post-conception weeks for CP, about 32 and 40 weeks for ADHD, and about 36 and 48 weeks (i.e. 2 months after delivery) for ASD. The exaggerated inflammatory response is hypothesized to occur because present diets limit intake of effective antioxidants and omega-3 polyunsaturated fatty acids while increasing intake of omega-6 polyunsaturated fatty acids. Oxidation products of the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) limit neuroinflammation while oxidation products of the omega-6 fatty acid arachidonic acid exacerbate inflammation. Preventative treatment should begin in all pregnant women during the first trimester and should include both DHA and an effective antioxidant for prevention of neuroinflammation. The suggested antioxidant would be N-acetylcysteine, though melatonin could be chosen instead. Combined DHA and NAC therapy is theorized to decrease the incidence of the three disorders by more than 75%.”

-Dr. Alan D Strickland, Research Physician
https://pubmed.ncbi.nlm.nih.gov/24581674/

Cerebrovascular Events

“The word cerebrovascular is made up of two parts – "cerebro" which refers to the large part of the brain, and "vascular" which means arteries and veins. Together, the word cerebrovascular refers to blood flow in the brain. The term cerebrovascular disease includes all disorders in which an area of the brain is temporarily or permanently affected by ischemia or bleeding and one or more of the cerebral blood vessels are involved in the pathological process. Cerebrovascular disease includes stroke, carotid stenosis, vertebral stenosis and intracranial stenosis, aneurysms,

and vascular malformations.

Restrictions in blood flow may occur from vessel narrowing (stenosis), clot formation (thrombosis), blockage (embolism) or blood vessel rupture (hemorrhage). Lack of sufficient blood flow (ischemia) affects brain tissue and may cause a stroke."

- American Association of Neurological Surgeons

https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Cerebrovascular-Disease

Endocannabinoids in cerebrovascular regulation

"The cerebral blood flow is tightly regulated by myogenic, endothelial, metabolic, and neural mechanisms under physiological conditions, and a large body of recent evidence indicates that inflammatory pathways have a major influence on the cerebral blood perfusion in certain central nervous system disorders, like hemorrhagic and ischemic stroke, traumatic brain injury, and vascular dementia. All major cell types involved in cerebrovascular control pathways (i.e., smooth muscle, endothelium, neurons, astrocytes, pericytes, microglia, and leukocytes) are capable of synthesizing endocannabinoids and/or express some or several of their target proteins [i.e., the cannabinoid 1 and 2 (CB1 and CB2) receptors and the transient receptor potential vanilloid type 1 ion channel]. Therefore, the endocannabinoid system may importantly modulate the regulation of cerebral circulation under physiological and pathophysiological conditions in a very complex manner. Experimental data accumulated since the late 1990s indicate that the direct effect of cannabinoids on cerebral vessels is vasodilation mediated, at least in part, by CB1 receptors. Cannabinoid-induced cerebrovascular relaxation involves both a direct inhibition of smooth muscle contractility and a release of vasodilator mediator(s) from the endothelium. However, under stress conditions (e.g., in conscious restrained animals or during hypoxia and hypercapnia), cannabinoid receptor activation was shown to induce a reduction of the cerebral blood flow, probably via inhibition of the electrical and/or metabolic activity of neurons. Finally, in certain cerebrovascular pathologies (e.g., subarachnoid hemorrhage, as well as traumatic and ischemic brain injury), activation of CB2 (and probably yet unidentified non-CB1/non-CB2) receptors appear to improve the blood perfusion of the brain via attenuating vascular inflammation."

-Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary; and

-Laboratory of Cardiovascular Physiology and Tissue Injury, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4865067/

Cervical Cancer

"Cervical cancer is a type of cancer that occurs in the cells of the cervix — the lower part of the uterus that connects to the vagina. "…

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/cervical-cancer/symptoms-causes/syc-20352501

See also Gynecologic Cancer

Chia Seeds

Nutritional and therapeutic perspectives of Chia (Salvia hispanica L.): a review

"The ancient grain is becoming enormously popular in modern food regimen in many countries; the higher proportion of α-linolenic acid makes chia the superb source of omega-3 fatty (about 65 % of the oil content). Omega-3 fatty acid has been associated with a large number of physiological functions in human body. Chia seed is a potential source of antioxidants with the presence of chlorogenic acid, caffeic acid, myricetin, quercetin, and kaempferol which are believed to have cardiac, hepatic protective effects, anti-ageing and anti-carcinogenic characteristics. It is also a great source of dietary fibre which is beneficial for the digestive system and controlling diabetes mellitus with higher concentration of beneficial unsaturated fatty acids, gluten free protein, vitamin, minerals and phenolic compounds. Therapeutic effects of chia in the control of diabetes, dyslipidaemia, hypertension, as anti-inflammatory, antioxidant, anti-blood clotting, laxative, antidepressant, antianxiety, analgesic, vision and immune improver is scientifically established."…

-Department of Dairy Technology, University of Veterinary and Animal Sciences Lahore, Lahore, Pakistan
-Department of Animal Nutrition, University of Veterinary and Animal Sciences Lahore, Lahore, Pakistan
-Department of Food Science, Nutrition & Home Economics Institute of Home and Food Sciences Faculty of Science and Technology Govt, College University Faisalabad, Faisalabad, Pakistan
-Department of Poultry Production, University of Veterinary and Animal Sciences Lahore, Lahore, Pakistan
-Department of Wildlife and Ecology, University of Veterinary and Animal Sciences Lahore, Lahore, Pakistan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4926888

Chili Peppers

See Capsaicin

Childhood Inflammation

Dried blood spot omega-3 and omega-6 long chain polyunsaturated fatty acid levels in 7–9 year old Zimbabwean children: a cross sectional study

"Omega-3 long chain-polyunsaturated fatty acids (LC-PUFAs)–docosahexaenoic acid (DHA), docosapentaenoic acid (DPA) and eicosapentaenoic acid (EPA)– and omega-6 LC-PUFA arachidonic acid (ARA), are essential for optimum physical and mental development in children. Prior to this study, the blood omega-3 LC-PUFA levels were unknown in Zimbabwean children, particularly in those aged 7–9 years, despite the documented benefits of LC-PUFAs. Documentation of the LC-PUFA levels in this age group would help determine whether interventions, such as fortification, are necessary. This study aimed to determine dried whole blood spot omega-3 and omega-6 LC-PUFA levels and LC-PUFA reference intervals among a selected group of Zimbabwean children aged 7–9 years old."

…"In this cohort of children, lower EPA levels and higher ARA: EPA ratios were observed compared to those reported in apparently healthy children elsewhere. The high ARA: EPA ratios might increase the vulnerability of these children to inflammatory pathologies. Identification and incorporation into diet of locally produced foodstuffs rich in omega-3 LC-PUFAs is recommended as well as advocating for dietary supplementation with omega-3 fish oils and algae based oils."

-Department of Chemical Pathology, College of Health Sciences, University of Zimbabwe, PO BOX A178, Avondale, Harare, Zimbabwe.

-Department of Paediatrics and Child Health, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe.

-Department of Community Medicine, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe.

-Division of Women and Children, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

-Department of Obstetrics and Gynaecology, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe.

https://www.ncbi.nlm.nih.gov/pubmed/27499701

Chocolate

Researchers say chocolate triggers feel-good chemicals

…”Other researchers have also said chocolate contains substances that might mimic the effects of marijuana, boosting the pleasure you get from eating the stuff.

The ingredients might make the texture, smell and flavor of chocolate more enjoyable and combine with other ingredients like caffeine to make a person feel good, researcher Daniele Piomelli speculated.”…

“Piomelli found that chocolate contains anandamide, which is also produced naturally in the brain and which activates the same target that marijuana does.

He also found two chocolate ingredients that inhibit the natural breakdown of anandamide, which could lead to heightened levels of anandamide in the brain.”

“"It's Mother Nature's solution via food cravings to try to elevate those chemicals, help us feel better and to function more efficiently," said Deborah Waterhouse, author of "Why Women Need Chocolate." "We will crave chocolate or some other food that has sugar and fat to help bring those chemicals back into balance."…

-From Correspondent Linda Ciampa / ATLANTA (CNN) (Febuary 14, 1996)

~~https://edition.cnn.com/HEALTH/indepth.food/sweets/chocolate.cravings/index.html~~

https://web.archive.org/web/20190221024002/https://edition.cnn.com/HEALTH/indepth.food/sweets/chocolate.cravings/index.html

The neuroprotective effects of cocoa flavanol and its influence on cognitive performance

“Cocoa powder and chocolate contain numerous substances among which there is a quite large percentage of antioxidant molecules, mainly flavonoids, most abundantly found in the form of epicatechin. These substances display several beneficial actions on the brain. They enter the brain and induce widespread stimulation of brain perfusion. They also provoke angiogenesis, neurogenesis and changes in neuron morphology, mainly in regions involved in learning and memory. Epicatechin improves various aspects of cognition in animals and humans. Chocolate also induces positive effects on mood and is often consumed under emotional stress. In addition, flavonoids preserve cognitive abilities during ageing in rats, lower the risk for developing Alzheimer's disease and decrease the risk of stroke in humans. In addition to their beneficial effects on the vascular system and on cerebral blood flow, flavonoids interact with signalization

cascades involving protein and lipid kinases that lead to the inhibition of neuronal death by apoptosis induced by neurotoxicants such as oxygen radicals, and promote neuronal survival and synaptic plasticity. The present review intends to review the data available on the effects of cocoa and chocolate on brain health and cognitive abilities."….

"In addition, a few other compounds with biological activity can be found in cocoa beans and derived products. These are **anandamide**, an endogenous ligand for the cannabinoid receptor found in low amounts, 0.5 μg g−1, salsolinol and tetrahydro-β-carbolines (THBCs). The latter compounds are found in milk and dark chocolate, and cocoa (5, 20, 25 μg g−1 for salsolinol and 1.4, 5.5 and 3.3 μg g−1 for THBCs, respectively)."

-Faculty of Medicine, INSERM U, Strasbourg, France
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3575938/

See also Anandamide

Cholangiocarcinoma

The dual effects of delta(9)-tetrahydrocannabinol [THC] on cholangiocarcinoma cells: anti-invasion activity at low concentration and apoptosis induction at high concentration

"Currently, only gemcitabine plus platinum demonstrates the considerable activity for cholangiocarcinoma. The anticancer effect of Delta (9)-tetrahydrocannabinol (THC), the principal active component of cannabinoids has been demonstrated in various kinds of cancers. We therefore evaluate the antitumor effects of THC on cholangiocarcinoma cells. Both cholangiocarcinoma cell lines and surgical specimens from cholangiocarcinoma patients expressed cannabinoid receptors. THC inhibited cell proliferation, migration and invasion, and induced cell apoptosis. THC also decreased actin polymerization and reduced tumor cell survival in anoikis assay. pMEK1/2 and pAkt demonstrated the lower extent than untreated cells. Consequently, THC is potentially used to retard cholangiocarcinoma cell growth and metastasis."

-Faculty of Pharmacy, Rangsit University, Patumthani, Thailand
https://pubmed.ncbi.nlm.nih.gov/19916793/

Cholelithiasis (Gallstones)

See Gallstone Disease

Cholesterol

…"Cholesterol is one of the most important regulators of lipid organization as its structure allows it to fill interstitial spaces between hydrophobic fatty acid chains of phospholipids. The neutral lipids such as PC [phosphatidylcholine] and SM [sphingomyelin] predominantly reside on the outer or exofacial leaflet, whereas anionic phospholipids PS (exclusively inner leaflet), PE, and PI reside on the inner or cytofacial leaflet of the biological membrane. The transbilayer distribution of cholesterol between the leaflets determines membrane fluidity and can alter the membrane function."…

The endocannabinoid system is affected by cholesterol dyshomeostasis: Insights from a murine model of Niemann Pick type C disease

"The dyshomeostasis of intracellular cholesterol trafficking is typical of the Niemann-Pick type C (NPC) disease, a fatal inherited lysosomal storage disorder presenting with progressive neurodegeneration and visceral organ involvement. In light of the well-established relevance of cholesterol in regulating the endocannabinoid (eCB) system expression and activity, this study was aimed at elucidating whether NPC disease-related cholesterol dyshomeostasis affects the functional status of the brain eCB system. To this end, we exploited a murine model of NPC deficiency for determining changes in the expression and activity of the major molecular components of the eCB signaling, including cannabinoid type-1 and type-2 (CB1 and CB2) receptors, their ligands, N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), along with their main synthesizing/inactivating enzymes. We found a robust alteration of distinct components of the eCB system in various brain regions, including the cortex, hippocampus, striatum and cerebellum, of Npc1-deficient compared to wild-type pre-symptomatic mice. Changes of the eCB component expression and activity differ from one brain structure to another, although 2-AG and AEA are consistently found to decrease and increase in each structure, respectively. The thorough biochemical characterization of the eCB system was accompanied by a behavioral characterization of Npc1-deficient mice using a number of paradigms evaluating anxiety, locomotor activity, spatial learning/memory abilities, and coping response to stressful experience. Our findings provide the first description of an early and

region-specific alteration of the brain eCB system in NPC and suggest that defective eCB signaling could contribute at producing and/or worsening the neurological symptoms of this disorder."

-Faculty of Veterinary Medicine, University of Teramo, Teramo, Italy; Fondazione Santa Lucia, Italy.

-Fondazione Santa Lucia, IRCCS, Italy.

-Department of Psychology, Division of Neuroscience AND "Daniel Bovet" Neurobiology Research Center, Sapienza University of Rome, Rome, Italy.

-Department of Medicine, Campus Bio-Medico University of Rome, Italy.

https://pubmed.ncbi.nlm.nih.gov/31302243/

Role of activated endocannabinoid system in regulation of cellular cholesterol metabolism in macrophages

"Aims: Evidence from recent studies suggests that the endocannabinoid system participates in the regulation of lipid metabolism and body composition. We hypothesize that the system is activated by oxidized low-density lipoprotein (oxLDL) and regulates cellular cholesterol metabolism in macrophages.

Methods and results: Primary peritoneal macrophages isolated from Sprague-Dawley rats and RAW264.7 mice macrophages were cultured. A liquid chromatography/mass spectrometry (LC/MS) system was used to measure the endocannabinoid anandamide (AEA), 2-arachidonoylglycerol (2-AG), and cellular cholesterol levels in macrophages. The regulatory mechanisms of cellular cholesterol metabolism were also investigated by molecular biology methods. The results showed that the endocannabinoid system in macrophages was activated by oxLDL through elevation of the AEA and 2-AG levels and the up-regulation of the cannabinoid CB1 and CB2 receptor expression. Win55,212-2, a synthetic cannabinoid, promotes cellular cholesterol accumulation in macrophages, which was associated with an increase in the expression of CD36 and a decrease in the expression of ATP-binding cassette protein A1 (ABCA1) as mediated by an up-regulated peroxisome proliferator-activated receptor gamma (PPARgamma). AM251, a selective cannabinoid CB1 receptor antagonist, impaired the abilities of Win55,212-2-treated macrophages to accumulate cholesterol by down-regulating CD36 receptor expression and up-regulating ABCA1 expression.

Conclusion: We have demonstrated, for the first time, that the endocannabinoid system in macrophages is activated by oxLDL and that the activated endocannabinoid system promotes cellular cholesterol accumulation in macrophages. The results also indicate that selectively blocking the CB1 receptor can reduce oxLDL accumulation in macrophages, which might represent a promising therapeutic strategy for atherosclerosis."

-Department of Geriatrics, Ren Ji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, People's

Republic of China.
https://pubmed.ncbi.nlm.nih.gov/19074161/

Chorea Huntington

"Many people with Huntington disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin."…

-Medline Plus
-U.S National Library of Medicine
https://medlineplus.gov/genetics/condition/huntington-disease/

See Huntington's Disease

Chronic Diseases

Chronic diseases, inflammation, and spices: how are they linked?

"Extensive research within the last several decades has revealed that the major risk factors for most chronic diseases are infections, obesity, alcohol, tobacco, radiation, environmental pollutants, and diet. It is now well established that these factors induce chronic diseases through induction of inflammation. However, inflammation could be either acute or chronic. Acute inflammation persists for a short duration and is the host defense against infections and allergens, whereas the chronic inflammation persists for a long time and leads to many chronic diseases including cancer, cardiovascular disease, neurodegenerative diseases, respiratory diseases, etc. Numerous lines of evidence suggest that the aforementioned risk factors induced cancer through chronic inflammation. First, transcription factors NF-κB and STAT3 that regulate expression of inflammatory gene products, have been found to be constitutively active in most cancers; second, chronic inflammation such as pancreatitis, prostatitis, hepatitis etc. leads to cancers; third, activation of NF-κB and STAT3 leads to cancer cell proliferation, survival, invasion, angiogenesis and metastasis; fourth, activation of NF-κB and STAT3 leads to resistance to

chemotherapy and radiation, and hypoxia and acidic conditions activate these transcription factors. Therefore, targeting these pathways may provide opportunities for both prevention and treatment of cancer and other chronic diseases. We will discuss in this review the potential of various dietary agents such as spices and its components in the suppression of inflammatory pathways and their roles in the prevention and therapy of cancer and other chronic diseases. In fact, epidemiological studies do indicate that cancer incidence in countries such as India where spices are consumed daily is much lower (94/100,000) than those where spices are not consumed such as United States (318/100,000), suggesting the potential role of spices in cancer prevention."

-Cancer Biology Laboratory and DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB), Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Guwahati, Assam 781039 India
-University of Texas MD Anderson Cancer Center, Houston, TX USA
-Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, 221005 India
-Molecular Oncology Laboratory, Department of Zoology, University of Delhi (North Campus), Delhi, 110007 India
-Inflammation Research Center, San Diego, CA USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785894
bit.do/chronic-dis

Chronic Fatigue Syndrome (CFS)

In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation.

…"The results suggest that patients with CFS [Chronic Fatigue Syndrome] should respond favourably to treatment with--amongst other things--omega3 PUFAs, such as EPA and DHA."

-M-Care4U Outpatient Clinics, and the Clinical Research Center for Mental Health, Antwerp, Belgium.
https://www.ncbi.nlm.nih.gov/pubmed/16380690

See also Major Depression

Chronic Inflammation

"Inflammation is part of the body's defense mechanism. It is the process by which the immune system recognizes and removes harmful and foreign stimuli and begins the healing process. Inflammation can be either acute or chronic.[1][2][3]

Acute Inflammation

Tissue damage due to trauma, microbial invasion, or noxious compounds can induce acute inflammation. It starts rapidly, becomes severe in a short time and symptoms may last for a few days for example cellulitis or acute pneumonia. Subacute inflammation is the period between acute and chronic inflammation and may last 2 to 6 weeks.

Chronic Inflammation

Chronic inflammation is also referred to as slow, long-term inflammation lasting for prolonged periods of several months to years. Generally, the extent and effects of chronic inflammation vary with the cause of the injury and the ability of the body to repair and overcome the damage. This article reviews chronic inflammation.

Chronic inflammation can result from the following:

1. Failure of eliminating the agent causing an acute inflammation such as infectious organisms including Mycobacterium tuberculosis, protozoa, fungi, and other parasites that can resist host defenses and remain in the tissue for an extended period.

2. Exposure to a low level of a particular irritant or foreign material that cannot be eliminated by enzymatic breakdown or phagocytosis in the body including substances or industrial chemicals that can be inhaled over a long period, for example, silica dust.

3. An autoimmune disorder in which the immune system recognizes the normal component of the body as a foreign antigen, and attacks healthy tissue giving rise to diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE).

4. A defect in the cells responsible for mediating inflammation leading to persistent or recurrent inflammation, such as auto-inflammatory disorders (Familial Mediterranean Fever).

5. Recurrent episodes of acute inflammation. However, in some cases, chronic inflammation is an independent response and not a sequel to acute inflammation for example diseases such as tuberculosis and rheumatoid arthritis.

6. Inflammatory and biochemical inducers are causing oxidative stress and mitochondrial dysfunction such as increased production of free radical molecules, advanced glycation end products (AGEs), uric acid (urate) crystals, oxidized lipoproteins, homocysteine, and others.

Epidemiology

Chronic inflammatory diseases are the most significant cause of death in the world. The World Health Organization (WHO) ranks chronic diseases as the greatest threat to human health. The prevalence of diseases associated with chronic inflammation is anticipated to increase persistently for the next 30 years in the United States. in 2000, nearly 125 million Americans

were living with chronic conditions and 61 million (21%) had more than one. In recent estimates by Rand Corporation, in 2014 nearly 60% of Americans had at least one chronic condition, 42% had more than one and 12% of adults had 5 or more chronic conditions. Worldwide, 3 of 5 people die due to chronic inflammatory diseases like stroke, chronic respiratory diseases, heart disorders, cancer, obesity, and diabetes. [4][5][6]The prevalence of some specific chronic inflammation-mediated diseases are as follows:

Diabetes*:* According to the American Diabetes Association, 30.3 million people or 9.4% of the American population, had diabetes in 2015 and it was the 7th leading cause of death in the United States.

Cardiovascular diseases: In line with 2017 updated report from the American Heart Association, cardiovascular diseases (CVDs) accounts for 1 out of every three deaths or approximately 800,000 deaths in the United States. Globally, CVD accounts for 31% of all deaths, and coronary heart disease (CHD) accounts for most deaths due to CVD, followed by stroke (1 of 20 deaths in the United States) and heart failure.

Arthritis and Joint Diseases: These affect approximately 350 million people worldwide and nearly 43 million people in the United States or almost 20% of the population. This number is expected to exceed 60 million by 2020. Nearly, 2.1 million Americans suffer from rheumatoid arthritis.

Allergies: These rank among the sixth leading cause of chronic human diseases in the United States and affect more than 50 million Americans each year. Asthma affects more than 24 million people in the United States including more than 6 million children. In 2015, 8.2% of adults and 8.4% of children were diagnosed with hay fever.

Chronic Obstructive Pulmonary Disease (COPD): The third most common cause of death in the United States in 2014, and nearly 15.7 million Americans (6.4%) were reported to have been diagnosed with COPD."

- National Institute of Health
- Marietta Memorial Hospital
- Mayo Clinic Health System
- VA MEDICAL CENTER, MATHER , CA
https://www.ncbi.nlm.nih.gov/books/NBK493173/

Chronic inflammation in the etiology of disease across the life span

"Although intermittent increases in inflammation are critical for survival during physical injury and infection, recent research has revealed that certain social, environmental and lifestyle factors can promote systemic chronic inflammation (SCI) that can, in turn, lead to several

diseases that collectively represent the leading causes of disability and mortality worldwide, such as cardiovascular disease, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease and autoimmune and neurodegenerative disorders. In the present Perspective we describe the multi-level mechanisms underlying SCI and several risk factors that promote this health-damaging phenotype, including infections, physical inactivity, poor diet, environmental and industrial toxicants and psychological stress. Furthermore, we suggest potential strategies for advancing the early diagnosis, prevention and treatment of SCI."

Inflammation

"One of the most important medical discoveries of the past two decades has been that the immune system and inflammatory processes are involved in not just a few select disorders, but a wide variety of mental and physical health problems that dominate present-day morbidity and mortality worldwide[1–4]. Indeed, chronic inflammatory diseases have been recognized as the most significant cause of death in the world today, with more than 50% of all deaths being attributable to inflammation-related diseases such as ischemic heart disease, stroke, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD) and autoimmune and neurodegenerative conditions[5]. Evidence is emerging that the risk of developing chronic inflammation can be traced back to early development, and its effects are now known to persist throughout the life span to affect adulthood health and risk of mortality6–8. In this Perspective, we describe these effects and out-line some promising avenues for future research and intervention.A normal inflammatory response is characterized by the temporally restricted upregulation of inflammatory activity that occurs when a threat is present and that resolves once the threat has passed[9,13,15]. However, the presence of certain social, psychological, environmental and biological factors has been linked to the prevention of resolution of acute inflammation and, in turn, the promotion of a state of low-grade, non-infective (that is, 'sterile') systemic chronic inflammation (SCI) that is characterized by the activation of immune components that are often distinct from those engaged during an acute immune response[13,16].

Shifts in the inflammatory response from short- to long-lived can cause a breakdown of immune tolerance[9,15] and lead to major alterations in all tissues and organs, as well as normal cellular physiology, which can increase the risk for various non-communicable diseases in both young and older individuals[1,9–11,15,17–21]. SCI can also impair normal immune function, leading to increased susceptibility to infections and tumors and a poor response to vaccines[22–25]. Furthermore, SCI during pregnancy and childhood can have serious developmental consequences that include elevating the risk of non-communicable diseases over the life span[7,8,26,27]. "…

-Buck Institute for Research on Aging, Novato, CA, USA.

-Stanford 1000 Immunomes Project, Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, CA, USA.

-Institute for Research in Translational Medicine, Universidad Austral, CONICET, Pilar, Buenos Aires, Argentina.

-Iuve Inc., San Mateo, CA, USA.

-Lawrence Berkeley National Laboratory, Berkeley, CA, USA.

-Center for Primary Health Care Research, Lund University/Region Skåne, Skåne University Hospital, Malmö, Sweden.

-Medical Scientist Training Program, University of California, San Francisco, San Francisco, CA, USA.

-IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy.

-Department of Applied Mathematics and Laboratory of Systems Biology of Aging, Lobachevsky University, Nizhny Novgorod, Russia.

-Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA.

-Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, University College London, London, UK.

-MassGeneral Hospital for Children, Harvard Medical School, Boston, MA, USA.

-Department of Environmental Health Sciences, School of Public Health, Columbia University Medical Center, New York, NY, USA.

-Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA.

-Humanitas Clinical and Research Center, Rozzano, Milan, Italy.

-Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy.

-William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University, London, UK.

-Division of Immunology and Rheumatology, Department of Medicine, Stanford University, Stanford, CA, USA.

-Departments of Medicine and Genetics, Albert Einstein College of Medicine, New York, NY, USA.

-Paul F. Glenn Center for the Biology of Aging, Stanford University School of Medicine, Stanford, CA, USA.

-Center for Tissue Regeneration, Repair and Restoration, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA.

-Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA.

-Department of Pathology, University of California, Los Angeles, Los Angeles, CA, USA.

-Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain.

-Research Institute of the Hospital 12 de Octubre (i+12), Madrid, Spain.

-Biostatistics and Computational Biology Branch, Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA.

-NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA.

-Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147972/

■■■

…"Classically, inflammation is classically known as the crucial response to microbe invasion or tissue injury to keep maintenance of tissue homeostasis. In recent years, our knowledge of the

inflammation role is greatly enlarged. Inflammatory pathway has been recognized as a pivotal molecular basis in the pathogenesis of many chronic diseases. By far, increasing literatures have shown that excessive inflammation play critical roles in the progression, and/or onset of stress-related diseases. There has been a growing number of evidence supporting that inflammatory response constitutes the "common soil" of the multifactorial diseases, including cardiovascular and metabolic diseases, psychotic neurodegenerative disorders and cancer (Scrivo et al., 2011)."…

-Laboratory of Stress Medicine, Faculty of Psychology and Mental Health, Second Military Medical University, Shanghai, China

-Edited by: Dieter J. Meyerhoff, University of California, San Francisco, United States

-Reviewed by: Masaaki Murakami, Hokkaido University, Japan; Leonardo Roever, Federal University of Uberlandia, Brazil; Hector A. Cabrera-Fuentes, Justus Liebig Universität

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5476783/

Chronic Inflammation in the Context of Everyday Life: Dietary Changes as Mitigating Factors

"The lifestyle adopted by most people in Western societies has an important impact on the propensity to metabolic disorders (e.g., diabetes, cancer, cardiovascular disease, neurodegenerative diseases). This is often accompanied by chronic low-grade inflammation, driven by the activation of various molecular pathways such as STAT3 (signal transducer and activator of transcription 3), IKK (IκB kinase), MMP9 (matrix metallopeptidase 9), MAPK (mitogen-activated protein kinases), COX2 (cyclooxigenase 2), and NF-Kβ (nuclear factor kappa-light-chain-enhancer of activated B cells). Multiple intervention studies have demonstrated that lifestyle changes can lead to reduced inflammation and improved health. This can be linked to the concept of real-life risk simulation, since humans are continuously exposed to dietary factors in small doses and complex combinations (e.g., polyphenols, fibers, polyunsaturated fatty acids, etc.). Inflammation biomarkers improve in patients who consume a certain amount of fiber per day; some even losing weight. Fasting in combination with calorie restriction modulates molecular mechanisms such as m-TOR, FOXO, NRF2, AMPK, and sirtuins, ultimately leads to significantly reduced inflammatory marker levels, as well as improved metabolic markers. Moving toward healthier dietary habits at the individual level and in publicly-funded institutions, such as schools or hospitals, could help improving public health, reducing healthcare costs and improving community resilience to epidemics (such as COVID-19), which predominantly affects individuals with metabolic diseases."…

Introduction

“Chronic inflammation is a central process involved in a high number of metabolic disorders (e.g., obesity, metabolic syndrome, diabetes, dyslipidemia, etc.), including neurodegenerative (Alzheimer), malignant diseases, and autoimmune diseases. In most if not all chronic inflammatory conditions, there is an extensively failed resolution of inflammation with high influx of leukocytes, which in their effort to resolve inflammation stimulate the synthesis of pro-inflammatory molecules and establish a highly inflammatory micro-environment, leading to extensive fibrosis and tissue damage [1]. Chronic low-grade inflammation has been shown to either induce or aggravate metabolic disturbances, including insulin resistance and dyslipidemia, which contributes to the development of other complications [2]. There is accumulating evidence that, in the case of autoimmune diseases, when the immune system loses self-tolerance and attacks the body’s cells and tissues, metabolic disturbances are key contributors to disease progression. Results from the type 1 diabetes mellitus (T1DM) prediction and prevention studies on T1DM showed that metabolic disturbances preceded the seroconversion to positive autoantibodies by several months or years in type 1 diabetes mellitus [3,4].

Many chronic inflammatory diseases originate or have their development promoted by an unbalanced diet. Although the exact mechanism remains unclear, De Rosa et al. suggest that metabolic pressure, as a result of increased caloric intake, leads to an altered adipose tissue homeostasis. This results in the synthesis of adipokines and facilitates the overactivation of nutrient-sensing mechanisms, altering the balance between pro-inflammatory and regulatory T-cells, ultimately resulting in the loss of immunotolerance [5,6,7]. In addition, dietary components have the ability to influence the immune response through the modulation of gut bacteria metabolism, impacting the risk of developing chronic diseases either directly in the gastrointestinal tract, or in other more distant organs that impact general metabolism [8,9,10,11]. Recent studies have investigated long term exposure to low doses of chemical mixtures that can be a part of modern lifestyles, such as pesticides, food additives, or additives contained in food coating materials, proving that different disturbances appeared from minor biochemical disturbances. These early alterations are generally followed by oxidative stress induction and organ damage depending on the period of exposure [12,13,14,15,16,17]. Recently, it has been shown that long term exposure to stressors might also have a positive association with increased vulnerability of the population to the microbial and viral infections [18].

Metabolomics are an emerging biological field that allow for the identification and simultaneous measurement of a large number of small molecules called metabolites in biological matrixes. It has become the most accurate method to detect metabolic imbalances and is useful for prevention and early detection of diseases. Moreover, metabolomics have vast applications in clinical practice [19]. Targeted metabolomic analysis provides insights regarding the normal

function of endogenous metabolism, dietary intake, microbiota, drug metabolism, and nutrient adequacy [20]. The challenge of chronic inflammatory diseases with respect to early diagnosis can be tackled with metabolomics through the identification of biomarkers that can discriminate high-risk populations. In a group of autoimmune patients, it was found that their fatty acid-based metabolic profile and lifestyle factors including physical activity and alcohol consumption were valuable predictive markers of autoimmune diseases [21].

Humans are exposed to a large number of substances from food, water, cosmetics, air, and so forth, each at low levels of exposure, and are able to induce cumulative/synergistic effects. Many studies have focused on the effects induced by administering a single substance at medium-high doses to laboratory animals. Recently, the concept of real-life risk simulation has emerged, since there is growing evidence that the effects of chemical mixtures at concentrations for which individual components failed to elicit have adverse effects when tested individually [14]. The concept of real-life risk simulation can also incorporate dietary interventions because, in our diets, we expose the human body to myriad substances in diverse doses [14,22,23].

The discovery of inflammation regulators opened a new window in therapeutics to clear low-grade chronic inflammation. A large number of physiological processes promote the physiological process of regulating inflammation. The development of such an approach targets the stimulation of endogenous processes that naturally occur during inflammation, which are hampered mainly by the lack of suitable human models and the heterogeneity of inflammatory disorders. Another limitation includes the lack of sensitive measurements able to capture the different stages of inflammation and metabolites [24,25,26,27,28].

The present paper aims to evaluate the impact diet might have on immune response, with special attention as to how lifestyle changes can help mitigate low-grade inflammation. real-life risk simulation (RLRS) concept. This analysis can be highly relevant in the context of the present viral spread of SARS-COV-2, since the inflammation is once again in the front line of an acute pathological response. Identifying strategies to modulate the immune response might prove useful for reducing the virus's impact on the respiratory tract and thus diminishing its impact on each patient, as well as on the general medical system."...

"Decreasing inflammatory burden is more important than ever during the COVID-19 pandemic. This can be accomplished through everyday actions (e.g., lifestyle, diet, smoking cessation, weight decrease, sport, etc.). There is a lot of information available in the scientific community regarding the risk of COVID-19 complications; even the likelihood of death is highly increased by some chronic diseases, mostly associated with an impaired inflammatory profile (e.g., obesity, type II diabetes, hypertension, chronic pulmonary disease, etc.) [81,82]. The literature data shows that people without comorbidities have a much lower risk of severe symptoms as a result of the

SARS-COV-2 infection [83]. On the other hand, increased levels of inflammatory markers cytokines with pro-inflammatory outcomes constitute predictors of adverse outcome in COVID-19 patients [84]. Evidence proves that some dietary elements such as zinc or vitamin D might provide protective effects against viral load [84]. As such, this reduces the inflammatory burden through a healthy diet, associating (based on RLRS principles) several protective components (e.g., fiber, polyphenols, PUFAs, vitamins, etc.) that constantly increase our chance of being better protected against different immune challenges."

-Department of Biochemistry, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Traian Vuia 6, 020956 Bucharest, Romania;

-Department of Toxicology, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Traian Vuia 6, 020956 Bucharest, Romania;

-European Institute of Nutritional Medicine EINuM, 00198 Rome, Italy;

-Metabolomic Medicine Clinic, Health Clinics for Autoimmune and Chronic Diseases, 10674 Athens, Greece;

-Laboratory of Toxicology and Forensic Sciences, Medical School, University of Crete, 71003 Heraklion, Greece

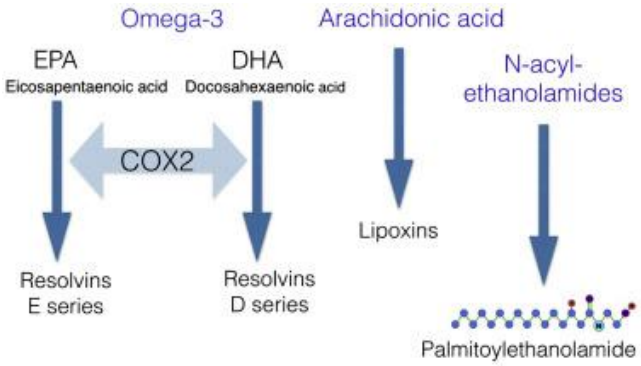
-Department of Biochemistry-Biotechnology, School of Health Sciences, 41500 Larisa, Greece; -Gene Expression and Therapy Group, King's College London, Faculty of Life Sciences and Medicine, Department of Medical and Molecular Genetics, 8th Floor, Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK;

https://pubmed.ncbi.nlm.nih.gov/32531935

■■■

…"Autacoids are locally produced modulating factors, influencing locally the function of cells and/or tissues, which are produced on demand and which subsequently are metabolized in the same cells and/or tissues."[27] There are many classes of lipid autacoids, among which the groups of the NAEs [N-acylethanolamines], Lxs, Pts, Rvs, and Mss seem currently most important. The key function of autacoids belonging to these lipid classes is to inhibit overactive and activated immune cascades and thus act like a "stop" signal in inflammation processes otherwise becoming pathological—like a break. Such autacoids are already referred to in literature as nature's way to resolve inflammation, clearly supporting the vision of to follow where nature leads of Ermine Costa in 1988.[28]

NAEs are derived from membrane phospholipids, N-acylphosphatidylethanolamine (NAPE).[29] PEA is one such NAE. Rvs are metabolites of the polyunsaturated omega-3 fatty acids: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA). The metabolites of EPA are termed E resolvins (RvEs), those of DHA are termed D resolvins (RvDs), and those of DPA are termed resolvins D (RvDsn-3DPA) and resolvins T (RvTs). Pts and Mss are also derived from omega-3 fatty acid DHA. Lxs are synthesized from arachidonic acid (see Fig. 4.2) [30]."



Synthesis of a number of lipid autacoids

"The inflammation-resolving Lxs were first isolated by Sherhan et al. in 1984.[31] As reported in 2012, the putative value of many of these classes as therapy for a great number of different and complex inflammatory disorders has been recognized: "Recent studies demonstrate that human and animal cells convert ω-3 [omega-3] polyunsaturated fatty acids into resolvins (Rvs), which are novel, highly potent, short-lived, anti-inflammatory agents that control the duration and magnitude of inflammation in models of complex diseases."[32] Various forms of these compounds have been tested in a number of different animal models for acute and chronic inflammation, such as asthma, mucoviscidosis, dry eyes, ischemia and reperfusion injury, hyperangiogenesis, conjunctivitis, retinitis, periodontitis, peritonitis, and skin inflammation.[33–35] Moreover, as of 2016, some companies have been developing new formulations of omega-3 fatty acids in order to locally boost the synthesis of, for instance, the Rvs. Such a specific eye formulation has been developed based on a microemulsion of polyunsaturated fatty acids and moisturizing polymers (registered as a medical device). Perhaps certain liposomal omega-3 formulations, creating a retard and reservoir effect, could be developed too, in order to further stimulate endogenous lipid autacoid synthesis. Another possibility is to adapt diet in such a way that its lipid profile enhances lipid autacoid synthesis and, for instance, the efficacy of PEA."

-J.M.Keppel Hesselink
-University of Witten/Herdecke, Witten, Germany
https://www.sciencedirect.com/science/article/pii/B9780128052983000049?via%3Dihub
https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/n-acylphosphatidylethanolamine

■■■

…"**Dysregulated inflammation is a common feature in most human diseases**, including several neurodegenerative and cerebrovascular diseases. Lipid mediators play a central role in the regulation of inflammation [52]. Therefore, the identification of anti-inflammatory lipid mediators with unique signaling properties is critical for the development of new therapeutics targeting inflammatory disease.

In particular, lipid mediators from the epoxyeicosanoid and endocannabinoid pathways are attractive targets for therapeutic intervention. Epoxyeicosanoid EETs are generated from AA by CYP epoxygenases [41] and have recently been demonstrated to exert potent anti-inflammatory effects in vitro and in vivo [53]. Notably, stable EET analogs have been developed for the

treatment of cardiovascular disease and inflammation via interaction with the putative EET receptor [54]. Endocannabinoids also have been shown to contain anti-inflammatory and anticancer properties. Drugs targeting the endocannabinoid-degrading enzymes such as FAAH are in clinical development to prolong endocannabinoid half-life for the treatment of a wide range of diseases [55]. In this study, we report the discovery of anti-inflammatory and vasoactive ω-3 endocannabinoid epoxides that are produced by CYP epoxygenases. These molecules share structural similarity with both their endocannabinoid and epoxide parent compounds and have the ability to exert physiological effects through cross-talk between the endocannabinoid and epoxide signaling pathways."…

-Department of Comparative Biosciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Medical Scholars Program, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Biochemistry, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Materials Science and Engineering, University of Illinois at Urbana–Champaign, Champaign, IL,
-Department of Pharmacology, University of Michigan, Ann Arbor, MI;
-Division of Nutritional Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-College of Veterinary Medicine, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Animal Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Bioengineering, University of Illinois at Urbana–Champaign, Champaign IL;
-Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI;
-Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana–Champaign, Champaign, IL,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5544256

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…"Dietary changes over the past few decades in the intake of n-6 [omega-6] and n-3 [omega-3] PUFA show striking increases in the (n-6) to (n-3) ratio (~15:1), which are associated with greater metabolism of the n-6 PUFA compared with n-3 PUFA. Coinciding with this increase in the ratio of (n-6):(n-3) PUFA are increases in chronic inflammatory diseases such as nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, obesity, inflammatory bowel disease (IBD), rheumatoid arthritis, and Alzheimer's disease (AD). By increasing the ratio of (n-3):(n-6) PUFA in the Western diet, reductions may be achieved in the incidence of these chronic inflammatory diseases."…

-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland
-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

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"Upon invasion of foreign pathogens or tissue damage, the innate immune system is immediately activated in response to molecules bearing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), recruits granulocytes to the injured tissue to clear pathogens, produces inflammatory mediators, including pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 and lipid mediators such as PGs [Prostaglandins] and leukotrienes (LTs), and evokes an acute inflammatory process (hours to days) to clear the pathogens and damaged tissues. Acute inflammation is resolved and the tissue is repaired when PAMPs, DAMPs, pathogens and damaged tissues are cleared, granulocyte recruitment ceases with a down-regulation and scavenging of chemokines, and recruited granulocytes are subsequently cleared by efferocytosis. However, inflammation often becomes chronic (weeks to months to years), and this underlies various chronic disorders such as autoimmune, neurodegenerative, vascular and metabolic diseases and cancer. Recent studies in various experimental systems have begun to unravel the possible mechanisms through which inflammation is sustained and becomes chronic. They include the generation of positive feedback mechanisms that self-amplify inflammatory responses and the suppression of negative feedback mechanisms that prevent resolution, which leads to the recruitment, activation, phenotypic transformation and synergistic interaction of various types of cells and sustains pro-inflammatory cytokine signalling at inflammatory sites."

-Centre for Inflammation Research, Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, UK,
-Alliance Laboratory for Advanced Medical Research and Department of Drug Discovery Medicine, Medical Innovation Center, Kyoto University Graduate School of Medicine, Kyoto, Japan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6329627/
bit.do/chronic-inflammation

Resolution of Inflammation

…"To prevent progression from acute inflammation to persistent, chronic inflammation, the inflammatory response must be suppressed to prevent additional tissue damage. Inflammation resolution is a well-managed process involving the spatially- and temporally-controlled production of mediators, during which chemokine gradients are diluted over time. Circulating white blood cells eventually no longer sense these gradients and are not recruited to sites of injury. Dysregulation of this process can lead to uncontrolled chronic inflammation [78]. Inflammation resolution processes that rectify tissue homeostasis include reduction or cessation of tissue infiltration by neutrophils and apoptosis of spent neutrophils, counter-regulation of chemokines and cytokines, macrophage transformation from classically to alternatively activated cells, and initiation of healing [79, 80].

Chronic inflammation occurs when acute inflammatory mechanisms fail to eliminate tissue injury [81], and may lead to a host of diseases, such as cardiovascular disease, atherosclerosis, type 2 diabetes, rheumatoid arthritis, and cancers[82]. Understanding the common mechanisms that orchestrate dysfunction in the various organ systems will allow for development and production of improved targeted therapies."…

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, Chengdu, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

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"The study of marijuana cannabinoid biology has led to many important discoveries in neuroscience and immunology. These studies have uncovered a new physiological system, the endocannabinoid system, which operates in the regulation of not only brain function but also the regulation of the immune system. Studies examining the effect of cannabinoid-based drugs on immunity have shown that many cellular and cytokine mechanisms are suppressed by these agents leading to the hypothesis that these drugs may be of value in the management of chronic inflammatory diseases. In this report, we review current information on cannabinoid ligand and receptor biology, mechanisms involved in immune suppression by cannabinoids with emphasis on antigen-presenting cells, and preclinical and clinical models analyzing the therapeutic potential of cannabinoid-based drugs."

-Department of Medical Microbiology and Immunology, University of South Florida College of Medicine, USA.

https://pubmed.ncbi.nlm.nih.gov/18040791

n-6 PUFA Contribution to Chronic Inflammatory Conditions in Humans'

"Clinical studies indicate that inflammation is at the base of many diseases including NAFLD, cardiovascular disease, atherosclerosis, IBD, and neurodegenerative diseases such as AD (Figure 2). The contribution of n-6 PUFA to these inflammatory conditions will be reviewed below with a particular focus on NAFLD."…

"Effects of unbalanced n-6:n-3 dietary fatty acid intake on development of various diseases of inflammation. Dietary imbalance in the consumption of n-6 and n-3 PUFA, representative of the Western diet. Greater consumption of n-6 PUFA leads to an increase in their metabolism to their LC-PUFA derivatives (AA). Decreases in n-3 PUFA consumption leads to a decrease in their metabolism to their LC-PUFA derivatives (EPA/DHA). The increase in AA in cell membrane phospholipids leads to an increase in COX and LOX enzyme production of AA-derived eicosanoids

and a decrease in EPA/DHA-derived eicosanoids, leading to an increase in inflammation and proinflammatory cytokine production. This in turn leads to a decrease in PPARα gene expression, while there is an increase in both SREBP-1c and NFκB gene expression. This change in gene expression can also cause an increase in lipogenesis, as well as increasing inflammation. The result is an increase in various diseases of inflammation, some of which are highlighted in the figure."…

-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland
-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

See also Cancer & Inflammation , Inflammaging

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

"Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy that responds to various immunosuppressive treatments. Oral daily prednisone therapy is effective and inexpensive, but the long-term treatment that is usually necessary leads to serious adverse effects. Consequently, intravenous immunoglobulin and plasma exchange have been widely used to treat CIDP, making treatment expensive and inconvenient. A steroid regimen that reduces adverse effects but preserves efficacy would simplify treatment. Pulsed steroids have nongenomic actions not seen with low-dose steroids, **including rapid inhibition of arachidonic acid** [omega-6] **release** and of calcium and sodium cycling across plasma membranes of immune cells."…

"**Conclusions**: Pulsed oral **methylprednisolone** may be efficacious in the long-term treatment of CIDP and is relatively well tolerated. Remission can be induced in most patients, especially those with a shorter duration of disease."

-Department of Neurology, University of Minnesota, Minneapolis, MN, USA.
https://pubmed.ncbi.nlm.nih.gov/19001164/

…"Methylprednisolone is a corticosteroid (cortisone-like medicine or steroid). It works on the immune system to help relieve swelling, redness, itching, and allergic reactions."

-Mayo Clinic
https://www.mayoclinic.org/drugs-supplements/methylprednisolone-oral-route/description/drg-20075237

Inhibition of arachidonic acid release from cells as the biochemical action of anti-inflammatory corticosteroids.

"This inhibition of arachidonic acid [omega-6] release from phospholipids may be the mechanism for the anti-inflammatory action of corticosteroids."

-Proceedings of the National Academy of Sciences of the USA
-S L Hong and L Levine

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC430374/

Chronic Migraine (CM)

…"Chronic daily headache (CDH), defined here as the presence of headaches lasting 4 hours or more for 15 or more days per month over at least 3 months, is a heterogeneous group of debilitating chronic pain syndromes affecting an estimated 10 million adults in the United States [10,45]. Loss of work and medical expenses add up to billions of dollars per year [14,38]. The term CDH encompasses several primary headache types including chronic migraine and chronic tension-type headache [10,45], which together account for up to 40% of patients presenting to headache specialty clinics. Conventional treatment relies heavily on medications that often provide only partial or transient relief and can be associated with significant side effects and costs [6–8,31,57,59]. Many chronic headache patients continue to have frequent headaches and impaired quality of life despite taking numerous pain-related medications [47,50]. Given the incomplete effectiveness and potential side effects of many headache medications, it is essential to investigate novel mechanisms and alternative approaches to manage pain."…

-Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA
-Department of Physical Medicine and Rehabilitation, Program on Integrative Medicine, University of North Carolina-Chapel Hill, NC, USA
-Department of Biostatistics, School of Public Health, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

-Nutrition Research and Metabolism Core, North Carolina Translational Clinical Sciences Institute, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

-Department of Pediatric Gastroenterology, Hepatology and Nutrition, University of California, San Diego, San Diego, CA, USA

-School of Medicine and Pharmacology, Royal Perth Hospital, The University of Western Australia, Perth, Australia

-Division of Gastroenterology and Hepatology, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

-School of Dentistry, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

-Department of Neurology, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3850757/

Degradation of endocannabinoids in chronic migraine and medication overuse headache.

"Chronic migraine (CM) is frequently associated with medication overuse headache (MOH). The endocannabinoid system plays a role in modulating pain including headache and is involved in the common neurobiological mechanism underlying drug addiction and reward system. Anandamide (AEA) and 2-arachidonoylglycerol are the most biologically active endocannabinoids, which bind to both central and peripheral cannabinoid receptors. The level of AEA in the extracellular space is controlled by cellular uptake via a specific AEA membrane transporter (AMT), followed by intracellular degradation by the enzyme AEA hydrolase (fatty acid amide hydrolase, FAAH). AMT and FAAH have also been characterized in human platelets. We assayed the activity of AMT and of FAAH in platelets isolated from four groups of subjects: MOH, CM without MOH, episodic migraine and controls. AMT and FAAH were significantly reduced in CM and MOH, compared to either controls or episodic migraine group. This latter finding was observed in both males and females with CM and MOH. Changes observed in the biochemical mechanisms degrading endogenous cannabinoids may reflect an adaptative behaviour induced by chronic headache and/or drug overuse."

-U.O.C. Neurologia, Dipartimento Cranio Spinale, Ospedale S. Eugenio, Roma, Italy.

https://www.ncbi.nlm.nih.gov/pubmed/18358734

Endocannabinoids in chronic migraine: CSF findings suggest a system failure

"Based on experimental evidence of the antinociceptive action of endocannabinoids and their role in the modulation of trigeminovascular system activation, we hypothesized that the endocannabinoid system may be dysfunctional in chronic migraine (CM). We examined whether the concentrations of N-arachidonoylethanolamide (anandamide, AEA), palmitoylethanolamide (PEA), and 2-arachidonoylglycerol (2-AG) in the CSF of patients with CM and with probable CM

and probable analgesic-overuse headache (PCM+PAOH) are altered compared with control subjects. The above endocannabinoids were measured by high-performance liquid chromatography (HPLC), and quantified by isotope dilution gas-chromatography/mass-spectrometry. Calcitonin gene-related peptide (CGRP) levels were also determined by RIA method and the end products of nitric oxide (NO), the nitrites, by HPLC. CSF concentrations of AEA were significantly lower and those of PEA slightly but significantly higher both in patients with CM and PCM+PAOH than in nonmigraineur controls ($p<0.01$ and $p<0.02$, respectively). A negative correlation was found between AEA and CGRP levels in CM and PCM+PAOH patients ($r=0.59$, $p<0.01$ and $r=-0.65$, $p<0.007$; respectively). A similar trend was observed between this endocannabinoid and nitrite levels. Reduced levels of AEA in the CSF of CM and PCM+PAOH patients may reflect an impairment of the endocannabinoid system in these patients, which may contribute to chronic head pain and seem to be related to increased CGRP and NO production. These findings support the potential role of the cannabinoid (CB)1 receptor as a possible therapeutic target in CM."

-Neurologic Clinic, Department of Medical and Surgical Specialties and Public Health, University of Perugia, Perugia, Italy

https://pubmed.ncbi.nlm.nih.gov/17119542

Chronic Obstructive Pulmonary Disease (COPD)

Feasibility of omega-3 fatty acid supplementation as an adjunct therapy for people with chronic obstructive pulmonary disease: study protocol for a randomized controlled trial

…"Chronic obstructive pulmonary disease (COPD) is a progressive, terminal disease characterized by persistent airflow limitation, lung and systemic inflammation. To date, one randomized controlled trial has been published that assessed the efficacy of LCn-3PUFA [omega-3] in people with this condition. The aim of this article is to discuss the feasibility of conducting a trial to evaluate fish oil supplementation as adjunct therapy in people with COPD."…

"People with COPD have an accumulation of inflammatory cells in the respiratory tissue that causes damage to the lungs [64]. This is further compounded by the effects of systemic inflammation such as reduced muscle function and skeletal integrity, which are often associated with comorbidities such as cardiovascular disease and osteoporosis [5-7]. The anti-inflammatory properties of LCn-3PUFA have been beneficial in other inflammatory diseases with recent systematic reviews in rheumatoid arthritis and cardiovascular disease concluding that the

benefits of LCn-3PUFA are modest but clinically relevant [65,66]. In people with rheumatoid arthritis all included studies showed some clinical benefit with LCn-3PUFA supplementation [66], while in cardiovascular disease those supplemented with LCn-3PUFA had a 10% reduction in the number of cardiovascular events [65]. Given the impact of lung and systemic inflammation, dietary supplementation with LCn-3PUFA may be beneficial for people with COPD."…

-Nutritional Physiology Research Centre, Sansom Institute for Health Research, School of Health Sciences, University of South Australia, City East Campus, Frome Road, Adelaide, South Australia, Australia

-Clinical Nutrition Research Centre, School of Biomedical Sciences & Pharmacy, University of Newcastle, University Drive, Callaghan, New South Wales, Australia

-Respiratory Medicine, Flinders University, Faculty of Health Sciences, Repatriation General Hospital, Daws Road, Daw Park, South Australia, Australia

-School of Population Health, University of South Australia, City East Campus, Frome Road, Adelaide, South Australia , Australia

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3748832/

…"There is strong rationale for a protective effect of omega-3 fatty acids in the lungs, critical in inflammatory lung diseases such as COPD and supporting plausibility of results. Downstream products of EPA and DHA include specialized pro-resolving mediators, found within the lung and circulation [6] which have the ability to promote resolution of inflammation [32, 33]. These include resolvins, protectins, and maresins, which work by regulating neutrophil infiltration, cytokine production, and macrophage clearance of apoptosed inflammatory leukocytes, culminating in dampening and resolution of inflammatory response [6, 34]."…

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6533751

Chronic Traumatic Encephalopathy (CTE)

…"Chronic Traumatic Encephalopathy is a progressive neurodegenerative disease caused by repeated brain trauma. Mild concussions and sub-concussive blows as well as concussions with loss of consciousness cause TAU protein expression (Tauopathy). Professional athletes such as football players, hockey players and soccer players are at risk for CTE. Additionally, collegiate and high school players may be at risk.

The Endocannabinoid System in the human brain normally protects the neuronal cells and regulates immune responses. CTE causes an endocannabinoid deficiency, which causes a significant decrease in circulating cannabinoids and damages CB1 receptors and CB2 receptors that bind to the endocannabinoids. Cannabidiol has been shown to provide anti-inflammatory,

neuroprotective, and anti-convulsive effects.”…

-CNNMoney (October 02, 2014)

~~https://money.cnn.com/news/newsfeeds/articles/marketwire/1148929.htm~~

http://bit.do/ctececd

Cinnamon

“Cinnamon is one of the most important herbal drugs and has been widely used in Asia for more than 4000 years. As a folk medicine, cinnamon has been traditionally applied to the treatment of inflammatory disorders and gastric diseases. After chemical profiling of cinnamon's components, their biological activities including antimicrobial, antiviral, antioxidant, antitumor, antihypertension, antilipemic, antidiabetes, gastroprotective and immunomodulatory were reported by many investigators.”…

“Cinnamon bark (**肉桂** ròu guì) is an important source for these purposes, since it contains a great amount of the function-bearing essential oil. The bark-derived cinnamon (termed cinnamon hereafter) contains 45% ~65% cinnamaldehyde, 12% ~18% eugenol (Cheng, 1983) and small amounts of cinnzeylanine, cinnzeylanol, arabinoxylan, 2’-hydroxycinnamalde-hyde, and 2’-benzoloxycinnamaldehyde (Lee, 1999). As a major ingredient, cinnamaldehyde has been well investigated; and its diverse biological activities against central nervous system depression (Harada, 1976) and high blood pressure (Harada, 1975), as well as its analgesic effect (Harada, 1972), have been reported. A water extract of cinnamon was reported to have anti-allergic, anti-inflammatory (Nagai, 1982a; 1982b; 1982c), antipyretic, analgesic (Ozaki,1972) and antithrombotic effects (Terasawa, 1983). Recently, the interest of investigators seems to have shifted to become narrowly centered on the verification of cinnamon's potential for preventing the metabolic syndrome (Kannappan, 2006; Blevins, 2007) and diabetes (Anderson, 2004; Chase, 2007; Pham, 2007; Shen, 2010).”

-Laboratory of Nutrition and Physiology, Department of Chemistry and Life Science, Nihon University College of Bioresource Sciences, Nihon University Graduate School of Bioresource Sciences, Kanagawa, Japan
-School of Pharmacy, Nihon University; 7-7-1 Narashinodai, Funabashi, Chiba, Japan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3943007/

See Beta-caryophyllene (β-caryophyllene)

Cirrhosis

The endocannabinoid system in advanced liver cirrhosis: pathophysiological implication and future perspectives.

"Endogenous cannabinoids (EC) are ubiquitous lipid signalling molecules providing different central and peripheral effects that are mediated mostly by the specific receptors CB1 and CB2. The EC system is highly upregulated during chronic liver disease and consistent experimental and clinical findings indicate that it plays a role in the pathogenesis of liver fibrosis and fatty liver disease associated with obesity, alcohol abuse and hepatitis C. Furthermore, a considerable number of studies have shown that EC and their receptors contribute to the pathogenesis of the cardio-circulatory disturbances occurring in advanced cirrhosis, such as portal hypertension, hyperdynamic circulatory syndrome and cirrhotic cardiomyopathy. More recently, the EC system has been implicated in the development of ascites, hepatic encephalopathy and the inflammatory response related to bacterial infection. Rimonabant, a selective CB1 antagonist, was the first drug acting on the EC system approved for the treatment of obesity. Unfortunately, it has been withdrawn from the market because of its neuropsychiatric side effects. Compounds able to target selectively the peripheral CB1 receptors are under evaluation. In addition, molecules stimulating CB2 receptor or modulating the activity of enzymes implicated in EC metabolism are promising areas of pharmacological research. Liver cirrhosis and the related complications represent an important target for the clinical application of these compounds."

-Department of Medical and Surgical Sciences, Center for Applied Biomedical Research (C.R.B.A.), Alma Mater Studiorum University of Bologna, Bologna, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/23890208

Endocannabinoid Overactivity has been linked to inflammation. Blocking CB1 receptors has been shown to cause many issues as this paper mentions happened with the recalled medication known as rimonabant. Resolving the inflammation with proper diet, avoiding inflammatory foods, and correcting Omega Ratio should be considered. It has also been reported that there is a DHA / Omega-3 deficiency in cirrhotic livers as seen in the research below.

The cirrhotic liver is depleted of docosahexaenoic acid (DHA), a key modulator of NF-κB and TGFβ pathways in hepatic stellate cells

"Liver cirrhosis results from chronic hepatic damage and is characterized by derangement of the organ architecture with increased liver fibrogenesis and defective hepatocellular function. It frequently evolves into progressive hepatic insufficiency associated with high mortality unless

liver transplantation is performed. We have hypothesized that the deficiency of critical nutrients such as essential omega-3 fatty acids might play a role in the progression of liver cirrhosis. Here we evaluated by LC-MS/MS the liver content of omega-3 docosahexaenoic fatty acid (DHA) in cirrhotic patients and investigated the effect of DHA in a murine model of liver injury and in the response of hepatic stellate cells (HSCs) (the main producers of collagen in the liver) to pro-fibrogenic stimuli. We found that cirrhotic livers exhibit a marked depletion of DHA and that this alteration correlates with the progression of the disease. Administration of DHA exerts potent anti-fibrogenic effects in an acute model of liver damage. Studies with HSCs show that DHA inhibits fibrogenesis more intensely than other omega-3 fatty acids. Data from expression arrays revealed that DHA blocks TGFβ and NF-κB pathways. Mechanistically, DHA decreases late, but not early, SMAD3 nuclear accumulation and inhibits p65/RelA-S536 phosphorylation, which is required for HSC survival. Notably, DHA increases ADRP expression, leading to the formation of typical quiescence-associated perinuclear lipid droplets. In conclusion, a marked depletion of DHA is present in the liver of patients with advanced cirrhosis. DHA displays anti-fibrogenic activities on HSCs targeting NF-κB and TGFβ pathways and inducing ADPR expression and quiescence in these cells."

"DHA has been reported to be decreased in the plasma of cirrhotic patients[6,7], but there is no information concerning its values in the cirrhotic liver, a site where DHA biological effects could be crucial in maintaining tissue homeostasis."…

"We found that DHA, but not AA or DPA, values were markedly reduced in the cirrhotic liver tissue (Fig. 1a and Supplementary Fig. 1). Accordingly, the ratio DHA/AA in hepatic tissue was significantly diminished in cirrhotic patients compared to controls (Fig. 1a). Interestingly, the stratification of the patients according to Child-Pugh score indicated that DHA abundance decreased in association with the progression of the disease (Fig. 1b). DHA and the ratio DHA/AA were also significantly decreased in fibrotic mouse livers compared to control livers (Fig. 1c). "…

-Department of Gene Therapy and Hepatology, Center for Applied Medical Research (CIMA), University of Navarra (UNAV), Pamplona, Spain

-Navarra Institute for Health Research (IdiSNA), Pamplona, Spain

-Department of Experimental Medicine, University of Lleida (IRB), Lleida, Spain

-Liver Unit, Clínica Universidad de Navarra, Pamplona, Spain

-Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Pamplona, Spain

-CIMA/UNAV, Pamplona, Spain

https://www.nature.com/articles/s41419-018-1243-0

The Role of Cannabinoids in the Setting of Cirrhosis

"The endocannabinoid system has been shown to play a role in liver disease, and cirrhosis specifically, with intriguing possible therapeutic benefits. The endocannabinoid system comprises cannabinoid receptors 1 (CB1) and cannabinoid receptor 2 (CB2) and their ligands, endocannabinoids and exocannabinoids. CB1 activation enhances fibrogenesis, whereas CB2 activation counteracts progression to fibrosis. Conversely, deletion of CB1 is associated with an improvement of hepatic fibrosis and steatosis, and deletion of CB2 results in increased collagen deposition, steatosis, and enhanced inflammation. CB1 antagonism has also demonstrated vascular effects in patients with cirrhosis, causing an increase in arterial pressure and vascular resistance as well as a decrease in mesenteric blood flow and portal pressure, thereby preventing ascites. In mice with hepatic encephalopathy, CB1 blockade and activation of CB2 demonstrated improved neurologic score and cognitive function. Endocannabinoids, themselves also have mechanistic roles in cirrhosis."

-Division of Gastroenterology, Women and Infants Hospital/Warren Alpert School of Medicine, Brown University, USA
-Department of Medicine, Stanford University School of Medicine, Stanford, USA
-Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, USA
-Department of Medicine, Mary Imogene Bassett Hospital , USA
-Division of Gastroenterology and Hepatology, University of Tennessee Health Science Center, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023500/

Circulating and hepatic endocannabinoids and endocannabinoid-related molecules in patients with cirrhosis

"**Background/aims**: Endocannabinoids include anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Endocannabinoid-related molecules like oleoyl-ethanolamine (OEA) and palmitoyl-ethanolamine (PEA) have also been identified. AEA contributes to the pathogenesis of cardiovascular alterations in experimental cirrhosis, but data on the endocannabinoid system in human cirrhosis are lacking. Thus, we aimed to assess whether circulating and hepatic endocannabinoids are upregulated in cirrhotic patients and whether their levels correlate with systemic haemodynamics and liver function.

Methods: The endocannabinoid levels were measured in peripheral and hepatic veins and liver tissue by isotope-dilution liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry. Systemic haemodynamics were assessed by the transthoracic electrical bioimpedance technique. Portal pressure was evaluated by hepatic venous pressure gradient.

Results: Circulating AEA and, to a greater extent, PEA and OEA were significantly higher in cirrhotic patients than in controls. PEA and OEA were also increased in the cirrhotic liver tissue.

AEA, OEA and PEA levels were significantly higher in peripheral than in the hepatic veins of cirrhotic patients, while the opposite occurred for 2-AG. Finally, circulating AEA, OEA and PEA correlated with parameters of liver function, such as serum bilirubin and international normalized ratio. No correlations were found with systemic haemodynamics.

Conclusions: The endocannabinoid system is upregulated in human cirrhosis. Peripheral AEA is increased in patients with a high model of end-stage liver disease score and may reflect the extent of liver dysfunction. In contrast, the 2-AG levels, the other major endocannabinoid, are not affected by cirrhosis. The upregulation of the endocannabinoid-related molecules, OEA and PEA, is even greater than that of AEA, prompting pharmacological studies on these compounds."

-Dipartimento di Medicina Clinica, Alma Mater Studiorum University of Bologna, Bologna, Italy.
https://pubmed.ncbi.nlm.nih.gov/19840245

Creutzfeldt-Jakob Disease (CJD)

See Prion Disease

Clinical Endocannabinoid Deficiency (CECD)

Also known as Clinical Endocannabinoid Deficiency Syndrome (CEDS) & Endocannabinoid / Cannabinoid Deficiency

Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system.

"The "classic" endocannabinoid (eCB) system includes the cannabinoid receptors CB1 and CB2, the eCB ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and their metabolic enzymes. An emerging literature documents the "eCB deficiency syndrome" as an etiology in migraine, fibromyalgia, irritable bowel syndrome, psychological disorders, and other conditions. ... Evidence indicates that several classes of pharmaceuticals upregulate the eCB system, including analgesics (acetaminophen, non-steroidal anti-inflammatory drugs, opioids, glucocorticoids), antidepressants, antipsychotics, anxiolytics, and anticonvulsants. Clinical interventions characterized as "complementary and alternative medicine" also upregulate the eCB system: massage and manipulation, acupuncture, dietary supplements, and herbal medicines. Lifestyle modification (diet, weight control, exercise, and the use of psychoactive

substances--alcohol, tobacco, coffee, cannabis) also modulate the eCB system."

..."The eCB system's salient homeostatic roles have been summarized as, "relax, eat, sleep, forget, and protect" [5]. It modulates embryological development, neural plasticity, neuroprotection, immunity and inflammation, apoptosis and carcinogenesis, pain and emotional memory, and most importantly from the viewpoint of recent drug development: hunger, feeding, and metabolism. Obese individuals seem to display an increased eCB tone, driving CB1 activation in a chronic, feed-forward dysfunction (reviewed by [6]). An antagonist or inverse agonist of CB1 called rimonabant (aka, SR141716 in preclinical studies) was approved for the treatment of obesity. It was subsequently withdrawn from the market due to adverse effects [7].

Other diseases are associated with suboptimal functioning of the eCB system. Russo [8] proposed that migraine, fibromyalgia, irritable bowel syndrome, and related conditions represent CEDS, "clinical endocannabinoid deficiency syndromes." Fride [9] speculated that a dysfunctional eCB system in infants contributes to "failure to thrive" syndrome. Hill and Gorzalka [10] hypothesized that deficient eCB signaling could be involved in the pathogenesis of depressive illnesses. In human studies, eCB system deficiencies have been implicated in uncompensated schizophrenia [11], migraine [12], multiple sclerosis [13], Huntington's [14], [15], uncompensated Parkinson's [16], irritable bowel syndrome [17], uncompensated anorexia [18], and chronic motion sickness [19]."

-GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom; Department of Family Medicine, University of Vermont, Burlington, Vermont, USA.

-GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom.

-Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei, Pozzuoli, Napoli, Italy.

http://www.ncbi.nlm.nih.gov/pubmed/24622769

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..."Altogether, these observations suggest that alterations of the endocannabinoid tone might be associated with the development of stress-related diseases, including anxiety, depression and obesity."

Department of Psychiatry, Obesity Research Center, Genome Research Institute, University of Cincinnati, Cincinnati, OH, USA.

https://www.ncbi.nlm.nih.gov/pubmed/18426497

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"Expression of cannabinoid receptor 1 is increased in human Achilles tendinosis suggesting that the cannabinoid system may be dysregulated in this disorder."

Pharmacology Unit, Department of Pharmacology and Clinical Neuroscience, Umeå University, Umeå, Sweden.

http://www.ncbi.nlm.nih.gov/pubmed/21931835

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…"AEA [anandamide] (and all the endocannabinoid system) is recognized to influence the progress of AD, by regulating neurogenesis, cognitive and neuroinflammatory processes during senescence (Koppel and Davies, 2008; Marchalant et al., 2012; Bedse et al., 2014). Decreased levels of AEA have been found in the brain of AD transgenic mice and patients with AD, and were correlated with the cognitive deficits of the subjects (Jung et al., 2012; Maroof et al., 2014). Interestingly, the increase in AEA levels in vitro was reported to reduce tau phosphorylation through the inhibition of the activity of protein kinases (Lin et al., 2016)."

-Center for Mathematics, Computing and Cognition, Universidade Federal do ABC, São Bernardo do Campo, Brazil
-Center for Natural and Human Sciences, Universidade Federal do ABC, São Bernardo do Campo, Brazil
-Faculty of Medicine, University of Coimbra, Coimbra, Portugal
-Center for Neuroscience and Cell Biology (CNC), University of Coimbra, Coimbra, Portugal
-Edited by: Fabricio A. Pamplona, Entourage Phytolab, Brazil
-Reviewed by: Salim Yalcin Inan, Meram Faculty of Medicine, Turkey; Mychael V. Lourenco, Universidade Federal do Rio de Janeiro, Brazil; Vincenzo Micale, Università di Catania, Italy; Grasielle Clotildes Kincheski, Universidade Federal do Rio de Janeiro, Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6176656

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"Hi everyone, its Dr. Michelle Ross. I'm introducing my new book Vitamin Weed - Get Healthy Not High. It's a four step plan to reversing Endocannabinoid deficiency which is a disease you probably have and you've never even heard of. Now the endocannabinoid system is your brain's natural marijuana. Yes, your brain makes drugs haha. Actually, to be fair, the endocannabinoid system is the largest neurotransmitter system in your body. It's bigger than dopamine system, serotonin system GABA, glutamate all these other neurotransmitters you might have heard of, well, the endocannabinoid system is pretty much present in almost every single cell in your body. Every major organ it regulates the immune system, your nervous system, everything I mean there's not one single function that I can think of the endocannabinoid system not playing a role in. So what is Endocannabinoid deficiency? Well, it's when your body doesn't make enough endocannabinoids or the signaling is impaired somehow that when you have no cannabinoids released into your body, they're just not making the same effects, physiologically or behavior wise."….

-Dr. Michelle Ross PhD. Neuroscientist
http://bit.do/drross2

The endocannabinoid system and the treatment of mood and anxiety disorders.

“The central endocannabinoid system is a neuroactive lipid signalling system in the brain which acts to control neurotransmitter release. The expression patterns of this system throughout limbic regions of the brain ideally situate it to exert regulatory control over emotional behaviour, mood and stress responsivity. A growing body of evidence unequivocally demonstrates that deficits in endocannabinoid signalling may result in depressive and anxiogenic behavioral responses, while pharmacological augmentation of endocannabinoid signalling can produce both antidepressive and anxiolytic behavioral responses. The aim of this review is to summarize current knowledge of the role of the endocannabinoid system in the etiology and treatment of mood and anxiety disorders, such as depression, anxiety and post-traumatic stress disorder. Collectively, both clinical and preclinical data argue that cannabinoid receptor signalling may be a realistic target in the development of a novel class of agent for the pharmacotherapy of mood and anxiety disorders.”

Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY, USA.
https://www.ncbi.nlm.nih.gov/pubmed/19839936

Neurobiology of cannabinoid receptor signaling

“The endocannabinoid system (ECS) is a highly versatile signaling system within the nervous system. Despite its widespread localization, its functions within the context of distinct neural processes are very well discernable and specific. This is remarkable, and the question remains as to how such specificity is achieved. One key player in the ECS is the cannabinoid type 1 receptor (CB1), a G protein-coupled receptor characterized by the complexity of its cell-specific expression, cellular and subcellular localization, and its adaptable regulation of intracellular signaling cascades. CB1 receptors are involved in different synaptic and cellular plasticity processes and in the brain's bioenergetics in a context-specific manner. CB2 receptors are also important in several processes in neurons, glial cells, and immune cells of the brain. As polymorphisms in ECS components, as well as external impacts such as stress and metabolic challenges, can both lead to dysregulated ECS activity and subsequently to possible neuropsychiatric disorders, pharmacological intervention targeting the ECS is a promising therapeutic approach. Understanding the neurobiology of cannabinoid receptor signaling in depth will aid optimal design of therapeutic interventions, minimizing unwanted side effects.”

-Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University, Mainz,

Germany
https://pubmed.ncbi.nlm.nih.gov/33162764/

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….“A ‘clinical endocannabinoid deficiency syndrome’ resulting from defects in the endocannabinoid system (i.e. receptor mutations, alterations in endocannabinoid production), has already been proposed to underlie certain diseases including treatment resistant conditions (Russo, 2008). To date a mutation is yet to be identified in the human cannabinoid receptor that results in conclusive alteration of ligand-receptor interactions; however, molecular biologists have discovered amino acids residues important for selective ligand recognition and maintaining receptor-ligand interactions in vitro (Kapur et al., 2008; Song and Bonner, 1996). “…

-Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA
-Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378782/

Cloves

See Beta-caryophyllene (β-caryophyllene)

Coats' Disease

“Coats' disease is characterized by abnormal retinal vascular development (so-called 'retinal telangiectasis') which results in massive intraretinal and subretinal lipid accumulation (exudative retinal detachment). “…

University Department of Medical Genetics and Regional Genetics Service, St Mary's Hospital, Manchester, UK.
https://www.ncbi.nlm.nih.gov/pubmed/10484772

Coconuts

“Lauric acid makes up about 50% of the fatty acids in coconut oil (7).

When your body digests lauric acid, it forms a substance called monolaurin. Both lauric acid and monolaurin can kill harmful pathogens, such as bacteria, viruses, and fungi (8).

For example, test-tube studies show that these substances help kill the bacteria Staphylococcus aureus, which causes staph infections, and the yeast Candida albicans, a common source of yeast infections in humans [9, 10]."

- *Healthline*
https://www.healthline.com/nutrition/top-10-evidence-based-health-benefits-of-coconut-oil#TOC_TITLE_HDR_5

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"Coconut oil is extracted from the kernel of matured coconuts harvested from the coconut palm and is high in saturated fats. Coconut oil is a common edible oil in certain countries, and there is a controversy regarding its effects on lipid profiles and cardiovascular disease risk. The high content of SFA [saturated fatty acids] raised concerns that it could lead to more artherogenic lipid profiles, and thus, health professionals in the 1980s recommended that coconut oil should not be used. This has changed however, as it was noted that countries with high intake of tropical oils had some of the lowest rates of cardiovascular heart disease, and recently, the use of coconut oil has become more popular because of the potential cardiovascular benefits.

SFAs in coconut oil increase serum HDL cholesterol more than LDL cholesterol to give a more favorable lipid profile relative to dietary carbohydrates. Recently, it has been shown that replacing high-PUFA vegetable oils by 75% with coconut oil in the diet of broilers is associated with a reduced fat deposition and increases lipoprotein lipase, hepatic lipase, and total lipase activities, thus affecting favorably lipid profile. In pigs, replacement of standard diet with coconut oil modulates the adipose tissue gene expression and fatty acid composition, with minimal effect on serum lipid profile. Interestingly, in mice with stress-induced injury, coconut oil was recently shown to improve lipid profile and restore oxidative stress.

Other potential outcomes have also been described with use of coconut oil. In breast cancer patients, virgin coconut oil consumption during chemotherapy helped improve the quality of life and reduced symptoms related to side effects of chemotherapy."

-S.C. Savva, A. Kafatos, in Encyclopedia of Food and Health, 2016
https://www.sciencedirect.com/topics/medicine-and-dentistry/coconut-oil

The lauric acid-activated signaling prompts apoptosis in cancer cells

"The saturated medium-chain fatty-acid lauric acid (LA) has been associated to certain health-promoting benefits of coconut oil intake, including the improvement of the quality of life in breast cancer patients during chemotherapy. As it concerns the potential to hamper tumor growth, LA was shown to elicit inhibitory effects only in colon cancer cells. Here, we provide

novel insights regarding the molecular mechanisms through which LA triggers antiproliferative and pro-apoptotic effects in both breast and endometrial cancer cells. In particular, our results demonstrate that LA increases reactive oxygen species levels, stimulates the phosphorylation of EGFR, ERK and c-Jun and induces the expression of c-fos. In addition, our data evidence that LA via the Rho-associated kinase-mediated pathway promotes stress fiber formation, which exerts a main role in the morphological changes associated with apoptotic cell death. Next, we found that the increase of p21Cip1/WAF1 expression, which occurs upon LA exposure in a p53-independent manner, is involved in the apoptotic effects prompted by LA in both breast and endometrial cancer cells. Collectively, our findings may pave the way to better understand the anticancer action of LA, although additional studies are warranted to further corroborate its usefulness in more comprehensive therapeutic approaches."

-Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy
-Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5601385/

Coconut Oil Food Data by U.S Department of Agriculture

https://fdc.nal.usda.gov/fdc-app.html#/food-details/171412/nutrients

Cognition

Cognition is the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.

- Oxford / Google

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"Cannabinoid and endocannabinoid systems have been implicated in several physiological functions including modulation of cognition."…

-Department of Biology, School of Basic Sciences, Bu-Ali Sina University, Hamedan, Iran.
https://www.ncbi.nlm.nih.gov/pubmed/25689415

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"The endocannabinoid system regulates a wide range of physiological processes including pain, inflammation, and cognitive/emotional states."

-Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA 92037, USA.

https://www.ncbi.nlm.nih.gov/pubmed/20493882

Omega-6/omega-3 fatty acid intake of children and older adults in the U.S.: dietary intake in comparison to current dietary recommendations and the Healthy Eating Index

"Omega-6 and omega-3 fatty acids (FAs) and their ratio have been shown to affect cognitive function in children and older adults. With these analyses, we aimed to describe omega-6 and omega-3 FA intake among children and older adults in light of FA intake recommendations and with consideration of overall diet."…

"American children and older adults are able to consume more balanced omega-6 to omega-3 ratios than has been indicated by commodity data. However, very few American children met even the lowest recommendations for EPA and DHA intake. Research is needed to clarify recommendations for the optimal ratio across development, which may aid in increasing EPA and DHA intake and improving health outcomes in the United States."

-Lipids in Health and Disease volume 17, Article number: 43 (2018)
https://lipidworld.biomedcentral.com/articles/10.1186/s12944-018-0693-9

Omega-3 fatty acid ethyl-eicosapentaenoate, but not soybean oil, attenuates memory impairment induced by central IL-1beta administration

"Proinflammatory cytokine interleukin (IL)-1beta can cause cognitive impairment, activate the hypothalamic-pituitary-adrenal axis and impair monoaminergic neurotransmission in the rat. IL-1beta has also been shown to increase the concentration of the inflammatory mediator prostaglandin E2 (PGE2) in the blood. Omega (n)-3 fatty acids, such as eicosapentaenoic acid (EPA), which are components of fish oil, have been shown to reduce both the proinflammatory cytokines and the synthesis of PGE2. The purpose of this study was to determine whether dietary supplements of EPA would attenuate the inflammation-induced impairment of spatial memory by centrally administered IL-1beta. Rats were fed with a diet of coconut oil (contained a negligible quantity of fatty acids), soybean oil (contained mainly n-6 fatty acids), or a diet of coconut oil enriched with ethyl-EPA (E-EPA). The rats were then injected intracerebroventricularly with IL-1beta or saline. The results of this study demonstrated that the IL-1-induced deficit in spatial memory was correlated with an impairment of central noradrenergic and serotonergic (but not dopaminergic) function and an increase in the serum corticosterone concentration. IL-1beta also caused an increase in the hippocampal PGE2

concentration. These effects of IL-1 were attenuated by the chronic administration of E-EPA. By contrast, rats fed with the soybean oil diet showed no effect on the changes induced by the IL-1 administration."

-Neuroscience Division, Department of Psychiatry, University of British Columbia, 2255 Westbrook Mall, Vancouver, BC Canada V6T 2A1.

https://pubmed.ncbi.nlm.nih.gov/15060086/

Colitis

"Colitis is a chronic digestive disease characterized by inflammation of the inner lining of the colon. Infection, loss of blood supply in the colon, Inflammatory Bowel Disease (IBD) and invasion of the colon wall with collagen or lymphocytic white blood cells are all possible causes of an inflamed colon."

-The George Washington University Hospital

https://www.gwhospital.com/conditions-services/digestive-disorder-center/colitis

Omega Fatty Acids and Inflammatory Bowel Diseases: An Overview

"Inflammatory bowel diseases (IBD) are chronic, inflammatory processes that affect the gastrointestinal tract and are mainly represented by ulcerative colitis (UC) and Crohn's disease (CD). Omega 3 (ω3) fatty acids (eicosapentanoic acid and docosahexaenoic acid) show an indispensable role in the inflammatory processes and, for these reasons, we aimed to review the effects of these acids on UC and CD. Databases such as PUMED and EMBASE were searched, and the final selection included fifteen studies that fulfilled the inclusion criteria. The results showed that ω3 fatty acids reduce intestinal inflammation, induce and maintain clinical remission in UC patients, and are related with the reduction of proinflammatory cytokines, decrease disease activity and increase the quality of life of CD patients. Furthermore, the consumption of these fatty acids may be related to a reduced risk of developing IBD. Many studies have shown the beneficial effects of ω3 as adjunctive in the treatment or prevention of UC or CD. Nevertheless, most were performed with a small number of patients and there are many variations in the mode of consumption, the type of food or the type of formulation used. All these factors substantially interfere with the results and do not allow reliable comparisons."….

"IBD is a condition associated with the quality of life of the patient and can be considered as a public health problem. Many studies have shown that ω3 FA are substrate to the production of protectins, resolvins, and maresins, which may regulate and attenuate the inflammatory processes and lead to remission of IBD and, thus, could be considered as a new complementary

approach to the treatment of these inflammatory conditions.

However, there is still much controversy about the effects of these acids both on CD or UC, possibly due to the variability in the doses and way of delivery, in the size of the samples, and the biases found in different clinical trials. We suggest that further studies should be performed to clarify the doses that would be necessary and the proper way of delivery that could offer an efficient bioavailability and long-term tolerability of these FA."

-Department of Biochemistry and Pharmacology-Medicine, School of Medicine, University of Marília, Av. ,São Paulo, Brazil;

-Gastroenterology Department, University Hospital- Associação Beneficente Hospital Universitário -UNIMAR-Marília, São Paulo, Brazil

-Postgraduate Program in Structural and Functional Interactions in Rehabilitation-UNIMAR-Marília, São Paulo, Brazil;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6801729/

Colitis Associated Cancer (CAC)

"Colitis associated cancer (CAC) is the most serious complication of inflammatory bowel disease. Pro-inflammatory cytokines were suggested to regulate pre-neoplastic growth during CAC tumorigenesis. Interleukin 6 (IL-6) is a multifunctional NF-κB–regulated cytokine which acts on epithelial and immune cells. Using genetic tools we now demonstrate that IL-6 is a critical tumor promoter during early CAC tumorigenesis. In addition to enhancing proliferation of tumor initiating cells, IL-6 produced by lamina propria myeloid cells protects normal and pre-malignant intestinal epithelial cells (IEC) from apoptosis. The proliferative and survival effects of IL-6 are largely mediated by transcription factor STAT3, whose IEC-specific ablation has profound impact on CAC tumorigenesis. Thus, the NF-κB-IL-6-STAT3 cascade is an important regulator of the proliferation and survival of tumor initiating IEC."

- Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology, School of Medicine, University of California, San Diego, USA

- Department of Medicine, School of Medicine, University of California, San Diego, USA

- La Jolla Institute for Allergy and Immunology, USA

- Department of Biochemistry, Christian-Albrechts-Universität zu Kiel, Medical Faculty, Germany

- School of Medicine, University of Split, Croatia

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2667107/

Colon Cancer (Colorectal Cancer)

Induction of apoptosis by cannabinoids in prostate and colon cancer cells is phosphatase dependent.

…"Cannabinoid receptor agonists induce phosphatases and phosphatase-dependent apoptosis in cancer cell lines; however, the role of the CB receptor in mediating this response is ligand-dependent."

-Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine, Texas A&M University, College Station, TX, USA.

https://www.ncbi.nlm.nih.gov/pubmed/22110202

Apoptosis - the death of cells which occurs as a normal and controlled part of an organism's growth or development. (Oxford/Google)

Omega-3 fatty acid is a potential preventive agent for recurrent colon cancer

…"Increasing evidence supports the contention that many malignancies, including sporadic colorectal cancer (CRC), are driven by the self-renewing, chemotherapy-resistant cancer stem/stem-like cells (CSCs/CSLCs) underscoring the need for improved preventive and therapeutic strategies targeting CSCs/CSLCs. Omega-3 polyunsaturated fatty acids (ω-3 PUFA), have been reported to inhibit the growth of primary tumors, but their potential as a preventive agent for recurring cancers is un-explored. The primary objectives of this investigation are to examine whether eicosapentaenoic acid (EPA; one of the ω-3 PUFA) synergizes with FuOx (5-FU+Oxaliplatin), the backbone of colon cancer chemotherapy, and (b) whether EPA by itself or in combination with conventional chemotherapy prevents the recurrence of colon cancer via eliminating/suppressing CSCs/CSLCs. FuOx-resistant (chemo-resistant; CR) colon cancer cells, highly enriched in CSCs, were utilized for this study. While EPA alone was effective, combination of EPA and FuOx was more potent in (a) inhibiting cell growth, colonosphere formation and sphere-forming frequency, (b) increasing sphere disintegration, (c) suppressing the growth of SCID mice xenografts of CR colon cancer cells, and (d) decreasing pro-inflammatory metabolites in mice. Additionally, EPA + FuOx caused a reduction in CSC/CSLC population. The growth reduction by this regimen is the result of increased apoptosis as evidenced by PARP cleavage. Furthermore, increased pPTEN, decreased pAkt, normalization of β-catenin expression, localization and transcriptional activity by EPA suggests a role for PTEN/Akt axis and Wnt signaling in regulating this process. Our data suggest that EPA by itself or in combination with FuOx could be an effective preventive strategy for recurring CRC."….

-Veterans Affairs Medical Center, Wayne State University, Detroit, Michigan
-Karmanos Cancer Institute, Wayne State University, Detroit, Michigan
-Department of Internal Medicine, Wayne State University, Detroit, Michigan
-Department of Pathology, Wayne State University, Detroit, Michigan
-Lipidomics Core Facility, Wayne State University, Detroit, Michigan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4221533

Interaction of endocannabinoid system and steroid hormones in the control of colon cancer cell growth

"Increasing evidence suggest the role of the cannabinoid receptors (CBs) in the control of cell survival or death and signaling pathways involved in tumor progression. Cancer cell lines are characterized by a subtle modulation of CB levels which produces a modified responsiveness to specific ligands, but the molecular mechanisms underlying these events are poorly and partially understood. We previously provided evidence that the endocannabinoid (EC) anandamide (AEA) exerts anti-proliferative effect likely by modulation of the expression of genes involved in the cellular fate. In this study we focused on the role of the CB1 receptor, ECs, and steroids in the mechanisms involved in colorectal cancer (CRC) cell growth inhibition in vitro. We demonstrated that, in DLD1 and SW620 cells, 17β-estradiol induced a specific and strong up-regulation of the CB1 receptor by triggering activation of the CB1 promoting region, localized at the exon 1 of the CNR1 gene. Moreover, treatment of DLD1 and SW620 cells with Met-F-AEA, a stable AEA-analogous, or URB597, a selective inhibitor of FAAH, induced up-regulation of CB1 expression by co-localization of PPARγ and RXRα at the promoting region. Finally, increased availability of AEA, of both exogenous and endogenous sources, induced the expression of estrogen receptor-beta in both cell lines. Our results partially elucidated the role of EC system in the molecular mechanisms enrolled by steroids in the inhibition of colon cancer cell growth and strongly suggested that targeting the EC system could represent a promising tool to improve the efficacy of CRC treatments."

-Department of Pharmaceutical Sciences, University of Salerno, Fisciano, SA, Italy.
https://pubmed.ncbi.nlm.nih.gov/21412772

Intake of fat, meat, and fiber in relation to risk of colon cancer in men

..."These data support the hypothesis that intake of red meat is related to an elevated risk of colon cancer."

-Channing Laboratory, Department of Medicine, Harvard Medical School, Boston, Massachusetts.
https://pubmed.ncbi.nlm.nih.gov/8162586

Cannabinoid receptor activation induces apoptosis through tumor necrosis factor alpha-mediated ceramide de novo synthesis in colon cancer cells

…"The present study shows that either CB1 or CB2 receptor activation induces apoptosis through ceramide de novo synthesis in colon cancer cells. Our data unveiled, for the first time, that TNF-alpha acts as a link between cannabinoid receptor activation and ceramide production."

-Department of Medical and Surgical Critical Care, University of Florence, Florence, Italy.
https://pubmed.ncbi.nlm.nih.gov/19047095/

Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women

"The rates of colon cancer in various countries are strongly correlated with the per capita consumption of red meat and animal fat and, to a lesser degree, inversely associated with the consumption of fiber."..

"Conclusions: These prospective data provide evidence for the hypothesis that a high intake of animal fat increases the risk of colon cancer, and they support existing recommendations to substitute fish and chicken for meats high in fat."

-Channing Laboratory, Department of Medicine, Harvard Medical School, Boston.

https://pubmed.ncbi.nlm.nih.gov/2172820

Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients

…"Postoperative supplementation of omega-3 fatty acids may have a favorable effect on the outcomes in colorectal cancer patients undergoing radical resection by lowering the magnitude of inflammatory responses and modulating the immune response."…

-Division of Surgical Oncology, Peking University People's Hospital, Beijing, China.
https://pubmed.ncbi.nlm.nih.gov/18416476

n-3 [omega-3] polyunsaturated fatty acids and colon cancer prevention

"The incidence of colon cancer in industrialised countries has increased since the early 1970s. It

is estimated that more than one-third of cases are associated with factors related to a Western diet. Both the type and amount of dietary fats consumed have been implicated in colon cancer aetiology. Recent studies have demonstrated that n-3 polyunsaturated fatty acids (PUFAs), commonly found in fish oil (FO), could prevent colon cancer development. Evidences show that n-3 PUFAs act at different stages of cancer development and through several mechanisms including the modulation of arachidonic acid-derived prostaglandin synthesis, and Ras protein and protein kinase C expression and activity. As a result, n-3 PUFAs limit tumour cell proliferation, increase apoptotic potential along the crypt axis, promote cell differentiation and possibly limit angiogenesis. The modulatory actions of n-3 PUFAs on the immune system and their anti-inflammatory effects might also play a role in reducing colon carcinogenesis. There remains, nevertheless, some ambiguity over the safety of n-3 PUFAs with respect to secondary tumour formation. However, it appears that n-3 PUFAs may be of use in colon cancer prevention."

-Clinical Nutrition Unit, University Hospital of Geneva, 24 rue Micheli-du-Crest, 1211 Geneva 14, Switzerland.
https://pubmed.ncbi.nlm.nih.gov/15030953/

Fish, n-3 polyunsaturated fatty acid and colorectal cancer prevention: a review of experimental and epidemiological studies

"Colorectal cancer demonstrates high incidences in the developed countries and is the second largest cause of deaths from neoplasia. In Japan, about 12% of all cancer deaths are due to colorectal cancer and the rate continues to increase remarkably. Dietary factors are clearly linked to the development of tumors in the colorectum, and the increase in mortality from colorectal cancer over the last few decades in Japan has been attributed to Westernization of the diet. On the other hand, the intake of fish/n-3 polyunsaturated fatty acids has long been considered as a factor decreasing the risk of colorectal cancer. In the present study, we investigated the effect of fish/n-3 polyunsaturated fatty acids on colorectal cancer by reviewing papers on both experimental and epidemiological studies overall to obtain a perspective for research and practice for prevention. This review covers the following areas. 1. Relationships between n-3 polyunsaturated fatty acids and colon carcinogenesis in experimental studies. 1) Aberrant crypt foci (ACF). 2) Tumors. 2. Relationships between fish intake and colorectal cancer in epidemiological studies. 1) Ecological studies. 2) Case-control studies. 3) Cohort studies. 4) Randomized controlled trials. There are substantial data from experimental studies in support of anticarcinogenic effects of fish/ n-3 polyunsaturated fatty acids in the colon. Several epidemiological studies have also provided evidence that fish/n-3 polyunsaturated fatty acids have anticarcinogenic effects in the colon, but not all data are consistent. However, increasing intake of fish/n-3 polyunsaturated fatty acids for preventing colon cancer is suggested from

review of experimental and epidemiological research overall. In the future, it is necessary to improve precision regarding exposure to carcinogens and fish/n-3 polyunsaturated fatty acids intake using a detoiled dietary survey and biomarkers in epidemiological studies."

-Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University.
https://pubmed.ncbi.nlm.nih.gov/17144568/

Endocannabinoid and ceramide levels are altered in patients with colorectal cancer

"Endocannabinoids and ceramides have demonstrated growth inhibition, cell death induction and pro-apoptotic activity in cancer research. In the present study, we describe the profiles of two major endocannabinoids, ceramides, free fatty acids and relevant metabolic enzymes in 47 pairs of human colorectal cancer tissues and adjacent non-tumor tissues. Among them, anandamide (AEA) and its metabolite, arachidonic acid (AA), were markedly upregulated in cancer tissues particularly in those with lymphatic metastasis. The levels of C16 and C24 ceramides were significantly elevated in the colorectal tumor tissues, while levels of C18 and C20 ceramides showed opposite trends. Levels of two enzymes participating in the biosynthesis and degradation of AEA, N-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D (NPLD) and fatty acid amide hydrolase (FAAH), together with the most abundant ceramide synthases (CerS1, CerS2, CerS5 and CerS6) in the colon were also determined. Quantitative-PCR analysis indicated that the mRNA levels of these enzymes were overexpressed in the tumor tissues. The activities of NPLD and FAAH were also upregulated. In addition, both gene and protein expression levels of cannabinoid receptor 1 (CB1) were elevated but not of CB2. Elevation of AEA and alteration of ceramides (C16, C24, C18, C20) may qualify as potential endogenous biomarkers and novel drug targets for colorectal cancer."

-Department of Medical Sciences, Medical College, Xiamen University, Xiamen 361102, P.R. China.
https://pubmed.ncbi.nlm.nih.gov/25975960/

See also Quercetin

Colorectal Cancer

"Colorectal cancer starts in the colon or the rectum. These cancers can also be called colon cancer or rectal cancer, depending on where they start. Colon cancer and rectal cancer are often

grouped together because they have many features in common. Cancer starts when cells in the body start to grow out of control."…

- *American Cancer Society*
https://www.cancer.org/cancer/colon-rectal-cancer/about/what-is-colorectal-cancer.html#

Omega-3 polyunsaturated fatty acids as adjuvant therapy of colorectal cancer

"Omega-3 polyunsaturated fatty acids (O3FAs) including C20:5ω3 eicosapentaenoic acid (EPA) and C22:6ω3 docosahexaenoic acid (DHA) occur naturally in highest quantities in fish (hence the frequently used term marine) [1]. Humans are inefficient at synthesising longer-chain O3FAs from C18:3ω3 α-linolenic acid (LNA) found in vegetable and seed oils. Therefore, the predominant source of EPA and DHA is dietary [2]. O3FAs have well-established anti-inflammatory properties [3] and have found clinical utility for cardiovascular disease prophylaxis and severe hypertriglyceridaemia [4], with emerging evidence that they may be beneficial for treatment of inflammatory bowel diseases [5].

Evidence is also accumulating that O3FAs may have anti-colorectal cancer (CRC) properties. Dietary O3FA intake was originally linked to primary CRC prevention through large epidemiological studies [6]. However, observational human data are now emerging that dietary O3FA status predicts post-diagnosis CRC outcomes and complements a larger body of preclinical evidence that O3FAs may find clinical utility for treatment of CRC, as opposed to primary CRC prevention. Given the excellent safety and tolerability profile of O3FAs, compared with existing treatment strategies for CRC, aligned with the unmet clinical need for improved adjuvant therapy of CRC, O3FAs have huge potential for use in the advanced post-diagnosis setting. Therefore, this article is restricted to review and interpretation of data supporting treatment of CRC by O3FAs and potential benefit of O3FAs on advanced CRC outcomes."

Scope of the review

"We last reviewed the potential role of O3FAs for prevention and treatment of CRC in 2012 [7]. By then, a large body of preclinical evidence had accumulated to support the case for O3FAs as potential anti-CRC agents, particularly in the prevention setting [7]. A randomised controlled trial in familial adenomatous polyposis patients had demonstrated chemopreventive efficacy of EPA at the early (adenoma) stages of intestinal tumorigenesis [8]. A subsequent review by Komiya et al. in 2013 highlighted the potential of natural compounds such as O3FAs for cancer prevention [9]. Since then, new preclinical and clinical evidence has further strengthened the case for O3FAs as adjuvant therapy for CRC, rather than prevention. This review will focus on data regarding O3FA

use for adjuvant CRC therapy in colorectal cancer since our 2012 review, highlighting ongoing studies and gaps to be filled in the evidence base, which may support translation of O3FA therapy into clinical practice. We make a clear distinction between observational data on dietary marine O3FA intake and therapeutic 'nutraceutical' supplement use of O3FAs."

Preclinical data supporting the anti-CRC activity of O3FAs

"Multiple mechanisms of actions and molecular targets have been described to explain the anti-inflammatory and anti-cancer activity of O3FAs. These have been reviewed extensively elsewhere [7, 10, 11]. Many of these have been shown to occur in CRC models. They are briefly summarised here before focusing on data that have emerged since 2012 (Table (Table11)."…

Mechanisms shown to contribute to the anti-CRC activity of O3FAs by direct effects on CRC cells

Mechanisms of action	O3FA shown to modulate the pathway	Reports involving CRC models published over the last 5 years
Modulation of cyclooxygenase metabolism	EPA and DHA[a]	[12, 13]
Alteration of lipid raft behaviour	EPA and DHA	
Increase in lipid peroxidation	EPA and DHA	[14]
Induction of pro-apoptotic pathways	EPA and DHA	[15, 16]
Regulation of kinase pathways	EPA and DHA	
G protein-coupled receptor signalling	EPA and DHA	[17]
WNT/ß-catenin pathway modulation	EPA and DHA	
Downregulation of Granzyme B expression	DHA	[18]
Downregulation of P-	EPA and DHA	[19]

Mechanisms of action	O3FA shown to modulate the pathway	Reports involving CRC models published over the last 5 years
glycoprotein expression		
mTor signalling inhibition	EPA and DHA	[20]

A comprehensive overview of O3FA molecular targets established in preclinical models in a range of cancer types can be found elsewhere [10]

[a]In all cases, EPA and DHA were tested independently

"O3FAs can modulate cyclooxygenase (COX) metabolism and reduce production of several prostanoids including prostaglandin (PG) E2 in tumours [21, 22], whilst possibly increasing the production of lipid mediators involved in the resolution of inflammation such as lipoxins and resolvins [21, 22], which may have anti-cancer properties [23–25]. Elevated COX-2 expression is found in greater than 90% of CRCs [26–28], associated with high levels of PGE2, which drives pro-tumorigenic proliferation, migration, and invasion, but also promotes an immune-suppressive tumour microenvironment beneficial for tumour growth [29, 30].

Proliferation and survival of cancer cells is linked to the activation of signalling pathways from surface molecules, such as cytokine or growth factor receptors [e.g. epidermal growth factor receptor (EGFR)], which transduce signals upon activation via protein linked the cytoplasmic membrane and kinase signalling cascades [31]. O3FAs have been shown to incorporate into the plasma membrane of cancer cells, where they alter lipid raft composition and fluidity. This can result in an inhibition of signal transduction, limiting cancer cell survival and promoting apoptosis [32]. O3FAs will also incorporate into non-cancer cell membranes within the tumour microenvironment and potentially alter their phenotype.

O3FAs have also been shown to downregulate other CRC promoting signalling pathways such as the Wnt/ß-catenin pathway [33], the MAPK/ERK pathway [34], and PI3K-PTEN pathway [35, 36].

O3FA accumulation in CRC cells is known to increase lipid peroxidation and cellular oxidative stress [37].

O3FAs can exert anti-CRC activity following their interaction with surface free fatty acid (FFA) G protein-coupled receptors (GPCRs), thereby activating pro-apoptotic signalling [17]. These GPCRs have been shown to be expressed on non-epithelial cells such as adipocytes [38, 39] and macrophages [40], on which activation can alter macrophage polarisation and reduce

inflammation that is potentially important for anti-cancer activity of O3FAs.

The respective contribution of these putative diverse mechanisms of action described in in vitro and in vivo models to potential anti-CRC activity in man is not known and will likely be context-dependent, e.g. tumour type and composition of the microenvironment. Due to the diversity of likely molecular targets of O3FAs, preclinical studies on the potential activity of O3FAs against established CRC, rather than prevention, have focussed on pharmacodynamic endpoints relevant to the hallmarks of cancer such as cell proliferation, apoptosis, and migration."…

-Leeds Institute of Biomedical and Clinical Sciences, St James's University Hospital, University of Leeds, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6133177/

Complex Regional Pain Syndrome

Enhanced anandamide plasma levels in patients with complex regional pain syndrome following traumatic injury: a preliminary report.

"The complex regional pain syndrome (CRPS) is a disabling neuropathic pain condition that may develop following injuries of the extremities. The pathogenesis of this syndrome is not clear; however, it includes complex interactions between the nervous and the immune system resulting in chronic inflammation, pain and trophic changes. This interaction may be mediated by chronic stress which is thought to activate the endogenous cannabinoid (endocannabinoid) system (ECS). We conducted an open, prospective, comparative clinical study to determine plasma level of the endocannabinoid anandamide by high-performance liquid chromatography and a tandem mass spectrometry system in 10 patients with CRPS type I versus 10 age- and sex-matched healthy controls. As compared to healthy controls, CRPS patients showed significantly higher plasma concentrations of anandamide. These results indicate that the peripheral ECS is activated in CRPS. Further studies are warranted to evaluate the role of the ECS in the limitation of inflammation and pain."

Department of Anesthesiology, Ludwig Maximilians University, Munich, Germany
https://www.ncbi.nlm.nih.gov/pubmed/19729930

Do omega-6 and trans fatty acids play a role in complex regional pain syndrome? A pilot study.

"The study aims to compare the omega-6 (n-6) and omega-3 (n-3) highly unsaturated fatty acids (HUFA), and trans fatty acid (trans FA) status of Complex Regional Pain Syndrome (CRPS) patients to pain-free controls."

…"Compared with controls, CRPS patients demonstrated elevated concentrations of n-6 HUFA and trans FA. No differences in n-3 HUFA concentrations were observed. Plasma concentrations of the n-6 HUFA docosatetraenoic acid were inversely correlated with the "vitality" section of the SF-36. Trans FA concentrations positively correlated with pain-related disability and anxiety."

…"These pilot data suggest that elevated n-6 HUFA and trans FA may play a role in CRPS pathogenesis. These findings should be replicated, and more research is needed to explore the clinical significance of low n-6 and trans FA diets with or without concurrent n-3 HUFA supplementation, for the management of CRPS."

-Rehabilitation Institute of Chicago, Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
https://www.ncbi.nlm.nih.gov/pubmed/20545870

Omega-6 fatty acids

"Omega-6 fatty acids are essential fatty acids. They are necessary for human health, but the body cannot make them. You have to get them through food. Along with omega-3 fatty acids, omega-6 fatty acids play a crucial role in brain function, and normal growth and development. As a type of polyunsaturated fatty acid (PUFA), omega-6s help stimulate skin and hair growth, maintain bone health, regulate metabolism, and maintain the reproductive system.

A healthy diet contains a balance of omega-3 and omega-6 fatty acids. Omega-3 fatty acids help reduce inflammation, and some omega-6 fatty acids tend to promote inflammation. In fact, some studies suggest that elevated intakes of omega-6 fatty acids may play a role in complex regional pain syndrome. The typical American diet tends to contain 14 to 25 times more omega-6 fatty acids than omega-3 fatty acids.

The Mediterranean diet, on the other hand, has a healthier balance between omega-3 and omega-6 fatty acids. Studies show that people who follow a Mediterranean-style diet are less likely to develop heart disease. The Mediterranean diet does not include much meat (which is high in omega-6 fatty acids, though grass fed beef has a more favorable omega-3 to omega-6 fatty acid ratio), and emphasizes foods rich in omega-3 fatty acids, including whole grains, fresh fruits and vegetables, fish, olive oil, garlic, as well as moderate wine consumption.

There are several different types of omega-6 fatty acids, and not all promote inflammation. Most omega-6 fatty acids in the diet come from vegetable oils, such as linoleic acid (LA), not to be confused with alpha-linolenic acid (ALA), which is an omega-3 fatty acid. Linoleic acid is converted to gamma-linolenic acid (GLA) in the body. It can then break down further to arachidonic acid (AA). GLA is found in several plant-based oils, including evening primrose oil

(EPO), borage oil, and black currant seed oil.

GLA may actually reduce inflammation. Much of the GLA taken as a supplement is converted to a substance called DGLA that fights inflammation. Having enough of certain nutrients in the body (including magnesium, zinc, and vitamins C, B3, and B6) helps promote the conversion of GLA to DGLA."

-PennState Hershey Milton S. Hershey Medical Center
http://pennstatehershey.adam.com/content.aspx?productid=107&pid=33&gid=000317

See also Cooking Oils

■■■

…"Heightened pain perception can be rooted in a malfunctioning neurological system or a structural problem, but it can also arise from chronic inflammation, of which pain is a primary symptom. In fact, multiple studies have shown persistent inflammation associated with CRPS [Complex Regional Pain Syndrome], evidenced by significantly elevated levels of inflammatory factors in the blood, blister fluid of affected limbs, and in the cerebrospinal fluid of CRPS sufferers.[6] Chronic pain is often associated with inflammation and points to a confused immune system, which regulates inflammation in the body. Functional medicine focuses on restoring balance to the immune system to reduce inflammation using natural methods such as an anti-inflammatory diet, proteolytic enzymes, omega-3 fatty acids, bioflavonoids, and botanicals that target the inflammatory pathways of the immune system to reduce inflammatory factors."…
-Dr. David Brady
https://rsds.org/complex-regional-pain-syndrome-brady/

■■■

"Serum metabolite profiling can be used to identify pathways involved in the pathogenesis of and potential biomarkers for a given disease. Both restless legs syndrome (RLS) and Parkinson`s disease (PD) represent movement disorders for which currently no blood-based biomarkers are available and whose pathogenesis has not been uncovered conclusively. We performed unbiased serum metabolite profiling in search of signature metabolic changes for both diseases."

…"A first discovery approach using serum metabolite profiling in two dopamine-related movement disorders compared to a large general population sample identified significant alterations in the polyunsaturated fatty acid metabolism in PD and implicated the inositol metabolism in RLS. These results provide a starting point for further studies investigating new perspectives on factors involved in the pathogenesis of the two diseases as well as possible points of therapeutic intervention."

-Neurologische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany
-Institut für Humangenetik, Helmholtz Zentrum München, Neuherberg, Germany
-Institute of Genetic Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany
-Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany
-Institute of Computational Biology, Helmholtz Zentrum München, Neuherberg, Germany
-Institute of Bioinformatics and Systems Biology, Helmholtz Zentrum München, Neuherberg, Germany
-Institute of Epidemiology II, Helmholtz Zentrum München, Neuherberg, Germany
-Institute of Experimental Genetics, Genome Analysis Center, Helmholtz Zentrum München, Neuherberg, Germany
-Lehrstuhl für Experimentelle Genetik, Technische Universität München, Freising-Weihenstephan, Germany
-Department of Physiology and Biophysics, Weill Cornell Medical College in Qatar, Qatar Foundation–Education City, Doha, Qatar
-Schön Klinik München Schwabing, Munich, Germany
-Institut für Humangenetik, Technische Universität München, Munich, Germany
-Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
-Department of Neurology and Neurosciences, Stanford University, Palo Alto, CA, USA
-University of Ulm, GERMANY
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4726488/

Cooking Oils

Omega Ratio of Common Cooking oils

	Fatty acid, g/100 g of oil*				
Vegetable oil	Saturated	Monounsaturated	Linoleic (omega-6)	α-Linolenic (omega-3)	Linoleic:α-linolenic ratio
Canola	7.4	61.7	19.0	9.1	2.1
Canola high in oleic acid	7.4	78.7	7.8	2.6	3.0
Soybean	15.7	22.7	50.9	6.8	7.5
Corn	12.9	27.6	27.3	1.1	24.8
Safflower	6.2	14.4	74.6	< 0.1	> 100
Sunflower	10.3	19.5	65.7	< 0.1	> 100
Olive	13.8	72.9	9.7	0.8	12.1

-Department of Nutritional Sciences, Faculty of Medicine (Bazinet), University of Toronto, Toronto, Ont.
-Division of Cardiac Surgery, Department of Surgery (Chu), Western University, London, Ont.
-Lawson Health Research Institute (Chu), London, Ont.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3971029/

Vegetable Oils

…"Today's topic is very important. It's about vegetable oils and how they can cause cancer,

various diseases increase in body fat and also inflammation, which can lead to arthritis and other problems and other health ailments. And I'm gonna get right to the point today and basically stop eating these vegetable and seed oils, such as soybean and canola oil, corn oil, cottonseed, sunflower, peanut oil, sesame oil, and even rice bran oil. Now, these polyunsaturated oils cause multiple health problems, diseases and increase in body fat, diabetes, cancer and also inflammation. Even though they aren't really vegetable oils or vegetables. These oils are commonly referred to as vegetable oils. And these oils contain very large amounts of a biologically active fats called omega-6 polyunsaturated fatty acids, which are harmful in excess. However, this does not apply to healthy plant oil such as olive oil, or coconut oil, which are extremely good for you. I'll name a few other oils. At the end of today's video. Simply stated, these industrial seed oils such as you know, again, corn, cottonseed, sunflower, soybean oil and sunflower oil are not foods that we should look to increase in our diets. These are what I call fake manmade fats. Now, these oils were never a significant part or contributor to the human diet up until maybe the past 50 years. And this is because they're just cheap to make. Remember, these plants are not potent fat sources, especially corn. So to concentrate the oil and make it usable, it has to be exposed to high heat, which is not what you want D-gummed refined, bleached, deodorized, and just other nasty stuff to produce a cheap, clear oil with a long shelf life. Unfortunately, these oils are now devoid of the healthy polyphenols that would provide antioxidant protection for these easily oxidized polyunsaturated fats. Now there are two types of fatty acids that are termed essential basically, because the body can't produce them on their own. These are omega-3 and omega-6 fatty acids. Now it is absolutely essential for the human body to get these fatty acids from the diet, but it must get them in certain balances and ratios. While humans were evolving. You know, for 1000s and millions of years, our omega-6, omega-3 ratios were around 3 to 1, or even two or one to two, almost in similar ratios to each other unfortunate today, their ratio is as high as 20 to 1 on average with you know, omega-6 to omega-3 ratios with even higher ratios towards the Omega sixes with those who eat you know, processed and packaged foods, as well as those who eat out most of their meals. And these higher omega-6 fat ratio is known to cause type two diabetes, heart disease, inflammation, you know, can lead to arthritis, depression, weight gain, and even cancer. Now, in addition to the Omega-6 ratio problem, right, vegetable oils are also high in trans fats. And these fats are highly toxic and are also associated with an increased risk of again various diseases like heart disease, cancer, diabetes, and obesity. And these transplants are found in the vegetable oils that you see on the shelves, which have a very long and unnatural shelf life. Now they're also found in most baked goods because they're cheap and extend the shelf life of these packaged products. Also, these fats are bad for you know, heart disease or cholesterol levels. You see polyunsaturated fats are promoted to help lower that bad LDL cholesterol the lipoprotein However, they also

decrease the more important and beneficial good HDL cholesterol as well and to a greater extent. So what's the point right, this imbalance is another reason these vegetable oils cause your you know, an increased risk for heart disease, heart attacks and strokes. Now, you need to have fat in your diet, right? It's essential to your survival and to your health. Just stay away from these unnatural fake fats and read all the labels for these hidden fats."…

-Dr. Sam Robbins
https://www.youtube.com/watch?v=GywtvPwFG7k

Olive Oil Is Not Healthy

"Eat food as grown as Dr. Hans Diehl deal says, which brings us around to restaurant food. It's delicious. And as a bachelor, I used to live in restaurants. And my blood pressure was up and I was carrying 10 pounds too much. The reality is that restaurant food is ethnic flavored salts, sugar and fat, when my friends asked me to go out for dinner, I'd say hmm , let's see well"…."do I want to Italian flavored, salt, sugar and fat, oh maybe Chinese salt, sugar and fat, 'whoo' haven't had East Indian salt, sugar and fat in a while. 'Whoo' Thai flavored salt, sugar and fats really nice. Restaurant food is full of salt and sugar and fat. That's what makes it taste so good. That's what the chefs are putting in the ingredients, back in the kitchen there and then they serve it to a seared flesh or overcooked vegetables. It's the reality, does that mean you should never ever step foot in a restaurant you're going to have to their social pressures etc. to do that, all I can tell you is that don't kid yourself that anything healthy is happening in those kitchens they are not and you don't want to hold a lot of it. I've gotten my restaurant eating down to very seldom as possible less is more when it comes to restaurant meals. And you know what I do before I go out to eat I eat and I have a salad and or a bowl of soup at home so I'm not famished when I walk into the restaurant. I don't polish off the half the basket of bread before the waiter gets there. So eat before you go and order as healthily as possible order the vegetable soup the steamed greens and eat it and get the heck out of there as soon as you can.

Okay, so let's get to it and back of everybody's mind what what about olive oil? Oh, no, not olive oil, it's heart healthy. There is a lot of literature back and forth about olive oil. And I'm not going to wade around in this study in that study, but I'm going to tell you some facts that are absolutely indisputable about olive oil. Both animal fats and vegetable oils are fats and they all have nine calories and every gram a tablespoon of olive oil has 13 and a half grams of fat and every tablespoon there's 120 calories in every tablespoon. As a result, you're a big olive oil fan liquid oils will help do that. And very importantly, it'll keep you there. If you are overweight or your friends overweight and they're trying to lose weight and they are eating olive oil, they are

kidding themselves is going to keep you stuck. It is liquid fat that I can tell you, so yes, olive oil has some adverse health effects and mostly it contributes to obesity. And studies have been done they've looked at overweight women in Greece. The Greeks, by the way, are [one of] the fattest country in Europe. They have the highest rate of obesity of all the European nations. And when they looked at the women who were obese, they did fat biopsies analyze the actual fat in their fat stores. 55% of the fat came from olive oil it sticks to you. So the reality is olive oil is really dense with calories it is the most calorie dense food we have 4000 calories in every pound. We're trying to get a four to one ratio of omega-6 to omega-3 olive oil ratio is 14 to 1 omega-6 versus omega-3. And we're trying to lower saturated fat they want no more than 7% saturated fat in our diet. olive oils 14% saturated fat. How does pouring 14% saturated fat help you get to your intake of 7%, its irrational. Pouring Well, the take on trying to get there was at pouring olive oil and foods does not suddenly make them heart healthy. This salad is not being made heart healthier. Because this person is pouring olive oil on it. These greens are perfectly healthy on their own even more so. The meal this person is about to eat would not be classified as hard healthy. If she pours some olive oil on her salad before eating this sandwich is still not a hard healthy meal. It is still not a Mediterranean dinner she's having here even though she bought olive oil on her salad. This is what Mediterranean diet has become I've used olive oil and my salad. Unhealthy eating as unhealthy eating. This is how your blood looks after you eat rice and beans."..."You eat a meal filled with fats and oils and this lovely Blood turns into a substance that looks like this. Not everybody shows that this grossly but this is fat in the bloodstream. This is like lipemia and every time you eat a fatty meal, a wave of fat goes through your bloodstream, as I said, and everybody shows it this densely, but everyone has a wave of fat going through their bloodstream when they eat fatty foods. Remember, your body is never not looking.

You can't tell your body look over here and have a cheeseburger down there. Your arteries know, your liver knows, your heart knows. If you are going to be eating a gooey, greasy pizza like that. It's going to turn your blog Fatty, even if you pour olive oil on your salad, before you eat this greasy piece of pizza. It's still going to turn your blog fatty your body is not full. It's never not looking. Don't kid yourself about olive oil, making things hard healthy. Mmm Spaghetti Alfredo with a little bit of bacon and egg yolks there to make it really challenging. This is dripping with oil if you then pour some olive oil on your salad before you eat the Alfredo do not think this is now a hard healthy meal. It's become a cover for the rationalization of atrociously dangerous eating. Again, your body's never not lucky. It's not good to make your blood fatty with any oil after you eat. And as Dr. Ellison is trying to tell us, the olive oil and all these are fine oils, they're not friendly to your arteries, they make your arteries stiff, and they keep your arteries from dilating and relaxing in response to nitric oxide, which helps keep our tissues healthy by allowing blood to be delivered to them. And this has been documented. Dr. Vogel has given people food

with olive oil in it and to study the effects of their arteries and he looked at the Mediterranean diet and endothelial function and the blue blood pressure cuff. He gave him some olive oil blue blood pressure cuff for a few minutes deflated it and instead of the usual increase in blood flow, there was no increase in blood. So olive oil paralyzes the blood vessels from the normal dilation. It's not friendly to artery stuff, and and as they said in the study in terms of their postprandial that means after eating effect on endothelial function, the beneficial components of the Mediterranean diet and Lyon Heart study diet appear to be the antioxidant rich foods including vegetables, fruits and their derivatives. Most likely the heart benefits of Mediterranean diet are due to it being a basically a vegetarian diet. They're probably getting healthier in spite of the olive oil not because of it. So don't see olive oil as a health food. It turns pouring oil on your food is pouring oil on your food. You don't really want to do it, there's no reason to do it medically, nutritionally, and it leaves you places you don't want to go. So no, no, he's taken away olive oil too. What do we do about olive oil? Well, what do you really use olive oil for, two things, you stir fry your veggies in it and mix it well you really use it for well, you can certainly stir fry your vegetables in season vegetable broth and work just as well. With a nonstick pan no reason that you have to use olive oil. In fact, you think you don't want to use olive oil it breaks down into skillet never heat olive oil if you are going to be using it. What about salad dressings, well you can certainly make salad dressing without oil. We do it at our clinic three times a day you just take a blender, put some fresh vegetables in it, maybe half an apple maybe you have an orange slice and and hit the buttons "Zoooo" and turns into into salad dressing. You want a little fat in there then throw in a piece of avocado or a couple of walnuts. It's easy to make salad dressings without olive oil, you don't need the stuff. And then again the whole world of flavored vinegars lots of ways to make the salad dressings tastes good. So what's the take home of all of this? Where do we go with all this? Salt, sugar and oils outside of a little bit in Whole Foods that nature naturally put there. These are not health foods, they are tasty treats have that firmly in your understanding and they are too easy to use too much of and that's the problem. There salt in the in the restaurant and packaged foods. We eat sugar as a food or pouring oil over our foods and the results is the hospitals are filled with people with strokes, heart attacks, colon cancers, etc. So for that reason, more and more nutritionally oriented physicians, dieticians, etc. are saying you know, Americans when people in Western diet have clearly shown that moderation does not work they cannot do it a little bit turns into a lot. And so for that reason the policy that a lot of us are coming to you know when it comes to added salt added sugar added oils, none is probably the best just just don't use the stuff and throw the oils out. And that's gives you, it leaves you at the interesting position of having an SOS free diet Salt, Oil and sugar free diet, eating style."

-Dr. Michael Klaper M.D

https://www.youtube.com/watch?v=OGGQxJLuVjg

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"The presence in vegetable oil of heavy metals such as arsenic, lead, cadmium or mercury is mostly due to environmental contamination"..

-ITERG, French Institute for Fats and Oils, Pessac, France
https://www.ocl-journal.org/articles/ocl/full_html/2014/01/ocl130041/ocl130041.html#

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…"Omega-6 fatty acids are abundant in the Western diet and are found in high proportions in most cooking oils, grains and grain-fed animal products. On the other hand, omega-3 fatty acids are generally deficient in the foods typically consumed by Americans. Certain foods — including leafy greens, walnuts, canola oil**, flax-fed chicken eggs and fatty fish (e.g., wild salmon, anchovies, mackerel and tuna) — have relatively large concentrations of omega-3. Historically, humans consumed diets with much higher relative proportions of omega-3, with ratios of omega-6 to omega-3 of 1-to-1 or 2-to-1, in contrast to modern diets with ratios as high as 15-to-1 to 25-to-1 (Simopoulos 2008)."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

**NOTE: Canola oil has a much higher omega-6 ratio than omega-3s as per University of Toronto, Toronto, Western University, London, Lawson Health Research Institute (Chu), London & Dr. Sam Robbins. It is not considered safe to consume as per a number of sources.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3971029/
https://www.youtube.com/watch?v=GywtvPwFG7k (bit.do/drsam)

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…"Arachidonic acid (AA) derived (omega-6 or n-6) eicosanoids (primarily from refined vegetable oils such as corn, sunflower, and safflower) increase the production of proinflammatory cytokines IL-1, TNF-α, and IL-6, operating as precursors of the proinflammatory eicosanoids of the prostaglandin (PG)2-series (26-27). In contrast, the omega-3 (n-3) PUFAs, found in fish, fish oil, walnuts, wheat germ, and some dietary supplements such as flax seed products can curb the production of AA-derived eicosanoids (26-27). The n-6 and n-3 PUFAs compete for the same

metabolic pathways, and thus their balance is important [28]. Accordingly, it is not surprising that both higher levels of n-3 PUFAs as well as lower n-6:n-3 ratios are associated with lower proinflammatory cytokine production [29].”…

-Janice K. Kiecolt-Glaser, Ph.D.

-Department of Psychiatry and The Ohio State Institute for Behavioral Medicine Research, The Ohio State University College of Medicine, Columbus, Ohio;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2868080

See also Omega Ratio

Copper Sulfate

“Oxidative stress and inflammation are commonly present in many chronic diseases. These responses are closely related to pathophysiological processes. The inflammatory process can induce oxidative stress and vice versa through the activation of multiple pathways. Therefore, agents with antioxidant and/or anti-inflammatory activities are very useful in the treatment of many pathologies. Clerodendrum cyrthophyllum Turcz, a plant belonging to the Verbenaceae family, is used in Vietnamese traditional medicine for treating migraine, hypertension, inflammation of the throat, and rheumatic arthritis. Despite its usefulness, studies on its biological properties are still scarce. In this study, ethanol extract (EE) of leaves of C. cyrtophyllum showed protective activity against CuSO4 [Copper Sulfate] toxicity. The protective activity was proven to relate to antioxidant and anti-inflammatory properties. EE exhibited relatively high antioxidant activity (IC50 of 16.45 µg/mL) as measured by DPPH assay. In an in vivo anti-antioxidant test, three days post fertilization (dpf) zebrafish larvae were treated with different concentrations of EE for 1 h and then exposed to 10 µM CuSO4 for 20 min to induce oxidative stress. Fluorescent probes were used to detect and quantify oxidative stress by measuring the fluorescent intensity (FI) in larvae. FI significantly decreased in the presence of EE at 5 and 20 µg/mL, demonstrating EE’s profound antioxidant effects, reducing or preventing oxidative stress from CuSO4. Moreover, the co-administration of EE also protected zebrafish larvae against oxidative damage from CuSO4 through down-regulation of hsp70 and gadd45bb expression and upregulation of sod. **Due to copper accumulation in zebrafish tissues, the damage and oxidative stress were exacerbated overtime, resulting in the upregulation of genes related to inflammatory processes such as cox-2, pla2, c3a, mpo, and pro- and anti-inflammatory cytokines (il-1ß, il-8, tnf-α, and il-10, respectively). However, the association of CuSO4 with EE significantly decreased the expression of cox-2, pla2, c3a, mpo, il-8, and il-1ß. Taken together,**

the results suggest that EE has potent antioxidant and anti-inflammatory activities and may be useful in the treatment of various inflammatory diseases."

-Research Unit in Environmental and Evolutionary Biology (URBE), Institute of Life, Earth and Environment (ILEE), University of Namur, Belgium.
-Pharmacology Department, Hanoi University of Pharmacy, Vietnam.
-VNU University of Science, Vietnam National University, Vietnam.
-Faculty of Fisheries, Vietnam National University of Agriculture, Vietnam.
https://pubmed.ncbi.nlm.nih.gov/32106612

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"As copper sulfate can induce auditory cell injury and lead to an inflammatory reaction, neutrophils accumulate at the site of inflammation, thereby establishing an inflammatory cell model."….

-The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China
-Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, China
https://www.hindawi.com/journals/ecam/2020/5604654

Liposomal Curcumin Attenuates the Incidence of Oxidative Stress, Inflammation, and DNA Damage Induced by Copper Sulfate in Rat Liver

"Copper is an essential element that is used widely in agriculture as fungicides and insecticides; for example, it is used to control schistosomiasis and as an antiseptic and germicide. Copper sulfate ($CuSO_4$) induces multiorgan dysfunction through the stimulation of reactive oxygen species and oxidative stress."…

-Pharmacology Department, Faculty of Pharmacy, King Saud University, Riyadh, Saudi Arabia
https://journals.sagepub.com/doi/full/10.1177/1559325818790869

Coronary Artery Disease

"The identification of risks associated with sudden cardiac death requires further investigations. The question was addressed whether parameters can be established which not only describe an increased risk for an enhanced electrical instability of the heart but also of inflammatory events underlying plaque rupture. Emphasis is placed on dose-dependent effects of the long-chain omega-(omega-)3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Since free acids of EPA and DHA are required for most of their biological effects, it appears

essential not only to build up stores in the body for release of these fatty acids, but also to provide a sustained uptake of EPA and DHA in the form of ethyl esters. In contrast to rapidly absorbed triacylglycerols from fish, ethyl esters are taken up more slowly within 24 h. For the administration of 1 g/day highly purified EPA+DHA ethyl esters (Omacor) to healthy volunteers, it is shown that EPA is increased from 0.6% to 1.4% within 10 days, while DHA is increased from 2.9% to 4.3%. After withdrawal, EPA and DHA approach baseline values within 10 days. A gas chromatographic procedure was established which requires only 10 microl of whole blood for the identification of more than 35 fatty acids. Evidence is summarized strengthening the concept that a low "EPA+DHA level" presents a risk for sudden cardiac death and that the administration of 840 mg/day of EPA+DHA ethyl esters raises the "EPA+DHA level" to approximately 6% that is associated with a marked protection from sudden cardiac death. For reducing pro-inflammatory eicosanoids and cytokines, a higher "EPA+DHA level" is required which can be achieved with an intake of 2-4 g/day of 84% EPA+DHA ethyl esters. For assessing influences from pro-inflammatory eicosanoids and cytokines, the EPA/arachidonic acid ratio ("EPA/AA ratio") was identified as diagnostic parameter. To assess the dietary EPA+DHA intake, fatty acids were determined in fish dishes of the cafeteria of the Philipps University Hospital Marburg, Germany. The EPA+DHA content of the popular Alaska Pollock was 125 +/- 70 mg/100 g. A once daily fish dish can thus not provide the 840 mg/day EPA+DHA administered in the GISSI Prevention Study in the form of ethyl ester which markedly reduced the risk of sudden cardiac death in postmyocardial infarction patients. Nonetheless, at least two preferably oily fish meals per week should be consumed as preventive measure by persons without coronary artery disease. With documented coronary heart disease, it was advised to consume approximately 1 g/day of EPA+DHA."

-Molecular Cardiology Laboratory, Department of Internal Medicine and Cardiology, Philipps University of Marburg, Marburg, Germany.

https://pubmed.ncbi.nlm.nih.gov/15580322/

Costochondritis

"Inflammation is the body's natural response to infection, irritation or injury. It's not known exactly why the costochondral joint becomes inflamed, but in some cases it's been linked to: severe coughing, which strains your chest area. an injury to your chest."

-National Health Services UK

https://www.nhs.uk/conditions/costochondritis

"Because costochondritis is an inflammatory condition, it may or may not have other contributing causes. If you have an inflammatory condition going on elsewhere in your body, it may be possible that costochondritis is caused by a ripple effect from the other condition. Consuming inflammatory foods may also be contributory. "

In the clinic we always run a 96-food IgG Food Sensitivity panel to determine whether the foods a person is eating are contributing to the inflammation.

Getting the inflammation under control is important and we use several natural, versus dangerous NSAID type anti-inflammatories including:

1. Curcumin – known as one of the most powerful natural anti-inflammatories, it has very specific anti-inflammatory effects. But be careful, not all curcumin is effective! Curcumin Relief is one of the most potent and well-researched forms of curcumin available.

2. We also double up with Anti-Inflammatory Formula, which is a powerful combination that contains several of the strongest natural anti-inflammatories known.

3. Omega-3 fatty acids are super important for controlling inflammation in the body. I recommend that basically everyone take an omega-3 (only - not an omega-6 as well!) to help control inflammation.

Identifying and removing inflammatory foods along with a couple natural anti-inflammatories and fish oil can help resolve costochondritis and keep it from recurring (as it can) without trashing your gut with NSAIDs or other more powerful prescription anti-inflammatory drugs."

- Dr Jason Barker, National Athlete's Clinic
https://www.naturalathleteclinic.com/collections/costochondritis

COVID-19

The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Inflammatory Cytokine Storms

"Inflammation is important in treating infections and wounds as it promotes tissue healing and the killing of pathogens. The omega-6 fat linoleic acid, and arachidonic acid (AA) formed from it, are important in responses such as redness, swelling, heat, and pain.[1] However, acute inflammatory responses are meant to be quickly suppressed by resolvins formed from the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Thus, a balance in the dietary omega-6/3 ratio may be important for ensuring that an excessive and prolonged inflammatory response does not occur, which could lead to tissue damage and

potentially to autoimmune disease.

Up until about 100 years ago, the omega-6/3 ratio had been around 4:1 or less.[2] However, the typical Western diet now provides an omega-6/3 ratio approximately 20-fold higher in favor of omega-6.2 While foods such as nuts, seeds, and eggs are high in omega-6, the increase in the omega-6/3 ratio is primarily due to an increase in the intake of industrial seed oils (soybean, corn, safflower, cottonseed, and canola). Additionally, there has been a reduction in the intake of long-chain omega-3s, which can primarily be found in fatty fish and shellfish. A high omega-6/3 ratio predisposes to supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation.[3] The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of EPA and DHA, has been proposed to put the population in a pro-inflammatory and pro-thrombotic state.[3, 4]"…

"One of the functions of our immune system is to fight against pathogenic viruses, fungi, bacteria, and parasites.[5] The immune system does this by releasing inflammatory cytokines during infections to defend against these pathogens. If our immune system, and especially our gastrointestinal system is healthy, then there is a lower risk of autoimmunity.[5]

There are two main types of immunity: Innate (natural immunity) and acquired (adaptive immunity).[5] Immune cells concentrate in lymphoid organs (lymph nodes, thymus, spleen and gastrointestinal lymphoid tissue) and in the circulation as well as other parts of the body. The innate immune system is a first line of defense against infection. It functions to prevent and eliminate infectious pathogens. Examples of the innate immune system include complement, skin, phagocytic cells (neutrophils, eosinophils, basophils), monocytes, and macrophages."…

"There is a need for an effective immune system to prevent and eliminate infectious agents. However, the immune system can become over activated leading to self-attack. This can start by the immune system mounting a response to dietary or environmental allergens. Arachidonic acid is the main fatty acid in immune cell membrane phospholipids and mainly forms the inflammatory 2,4-series eicosanoids, whereas incorporation of EPA/DHA will decrease AA-derived eicosanoids and increase the anti-inflammatory 3/5-series eicosanoids, docosanoids and resolvins/protectins, leading to an overall anti-inflammatory state.[5] Consuming a typical Western diet leads to immune cells (neutrophils, lymphocytes and monocytes) that contain ~20% of fatty acids as arachidonic acid with just 1% EPA and 2.0–2.5% DHA.[5] However, supplementing the diet with 3.2 grams of EPA/DHA for 12 weeks has been shown to increase phospholipid long-chain omega-3 fatty acids to around 3.5% EPA and 3.5% DHA.[5] Thus, a dietary increase in omega-3 PUFAs will lower the omega-6/3 ratio in immune cells.

Animal models have demonstrated that omega-3 polyunsaturated fatty acids (PUFAs) have immunomodulatory effects and are useful in inflammatory disorders.[6] Infections can also

increase arachidonic acid and decrease the anti-inflammatory omega-3 PUFA DHA.7 Dietary, or supplemental omega-3 PUFAs, can incorporate into the cellular membranes of all immune cells investigated to date.[8] Numerous clinical studies in humans have found that supplementing with EPA/DHA (reducing the omega-6/3 ratio) lowers inflammation in humans, whereas oxidized linoleic acid metabolites (OXLAMs) activate nuclear factor kappa-beta (NF-kB), which increases proinflammatory cytokines.[3] Importantly, cytokine storms and lung injury in persons infected with coronaviruses, such as severe acute respiratory syndrome (SARS-CoV) or middle east respiratory syndrome (MERS), are usually the result of NF-kB activation.[9, 10] Studies show that inhibiting NF-kB-mediated inflammation increases survival in animal models of SARS-CoV.[11] Considering that SARS-CoV and SARS-CoV2 are both coronaviruses, and that the latter can lead to COVID-19, inhibiting NF-kB activation by increasing omega-3 intake and reducing processed omega-6 seed oil intake,[3] may be an important strategy in combating inflammatory cytokine storms in the lungs and acute respiratory distress in patients infected with RNA viruses such as influenza and coronaviruses. Moreover, considering that the dietary intake of omega-6/3 is now ~ 20:1 or higher, compared to an ancestral intake of ~ 4:1 or less, this may predispose to inflammatory cytokine storms and chronic inflammatory conditions.[2, 3] Omega-3 PUFAs are important for resolving inflammation and may improve survival in sepsis and acute respiratory distress syndrome (ARDS).[12–14]

EPA/DHA not only reduces AA-metabolites by competition in the cellular membrane phospholipids, but they also inhibit AA metabolism via inhibition of cyclooxygenase and lipoxygenase. Inhibiting the metabolism of arachidonic acid to proinflammatory metabolites is likely more consequential in preventing a supraphysiological inflammatory response than reducing the phospholipid content of arachidonic acid. Many studies have shown that fish oil (between 2.4 and 14.4 grams of EPA/DHA/day) suppresses the arachidonic acid-derived eicosanoids and leukotrienes produced from immune cells as well as inflammatory interleukins and cytokines.[15–21] Moreover, the metabolites from EPA/DHA are considered less inflammatory compared to those from arachidonic acid.[5, 22, 23]

A higher omega-6/3 ratio is also associated with lower immune cell function, which may result in lower immunity.[24] DHA-rich fish oil (3 grams per day, 26% EPA, 54% DHA) has been shown to increase neutrophil and monocyte phagocytic activity by 62% and 145%, respectively,[25] whereas changes in neutrophil and monocyte phagocytic activity was not found with EPA-rich fish oil.[26] In other words, DHA may strengthen the immune system while at the same time suppressing its overactivation.

Long-chain omega-3s can also inhibit inflammatory cytokine production from monocytes, macrophages, and endothelial cells. Many of the benefits of long-chain omega-3s are due to

their ability to reduce gene expression for producing inflammatory cytokines partly by reducing the activation of NF-kB.1 Thus, supplementing with long-chain omega-3s not only reduces inflammatory eicosanoids derived from arachidonic acid but also increases the anti-inflammatory eicosanoids and resolvins/protectins/maresins/lipoxins derived from EPA/DHA, thereby reducing inflammatory cytokine production from NF-kB. Table 1 summarizes the potential mechanisms of omega-3s for reducing cytokine storm in the lungs."

-MSMA member since 2003, Saint Luke's Mid America Heart Institute, Kansas City, Missouri.
-Dr James J. DiNicolantonio
-Dr. James O'Keefe, MD
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7721408

The inflammation theory of disease

"The entire field of inflammation and disease has reached a point where large controlled studies are needed to identify specific targets for therapeutic intervention. There is also hope of establishing a common framework for understanding a variety of conditions previously considered to be unrelated, through the underlying inflammatory mechanisms. One study at Carnegie Mellon University in the USA attempted to link stress, inflammation and the risk of infectious disease by looking at glucocorticoid receptor resistance, which is known to have a role in other inflammation-related diseases such as asthma. The study, led by Sheldon Cohen, Director of the university's Laboratory for the Study of Stress, Immunity and Disease, focused on the common cold to assess the link between chronic psychological stress and the risk of contracting upper respiratory infections in general. The researchers found that reduced glucocorticoid receptor sensitivity leads to increased levels of circulating leukocytes and neutrophils, triggered by the increased release of pro-inflammatory cytokines. The authors concluded that this same inflammatory process upregulates immunity to the cold virus and is responsible for well-known cold symptoms such as increased mucus production in the nose. The implication is that stress does not necessarily increase the probability of infection, but it does amplify the symptoms. **This suggests that anti-inflammatory rather than anti-viral mechanisms might constitute the most effective remedy for many upper respiratory infections. Cohen pointed out that these findings were consistent with the viral-challenge theory, which suggests a positive association between pro-inflammatory cytokine levels and the expression of symptoms.**

More fundamentally, Cohen argued that this model might help to understand the development of many other conditions associated with prolonged stress, including cardiovascular disease, diabetes, autoimmune conditions and even clinical depression. It might also lead to a new and better understanding of the interplay between the immune system, inflammation and infectious

disease, and how they trigger chronic inflammation leading to other conditions."

- Philip Hunter is a freelance journalist in London, UK.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3492709

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..."Mortality in COVID-19 cases is strongly associated with progressive lung inflammation and eventual sepsis."...

-Department of Oral and Craniofacial Biology, Louisiana State University Health—School of Dentistry, New Orleans, Louisiana, USA
-Department of Microbiology and Immunology, Tulane University School of Medicine, New Orleans, Louisiana, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7304316

See also Sepsis

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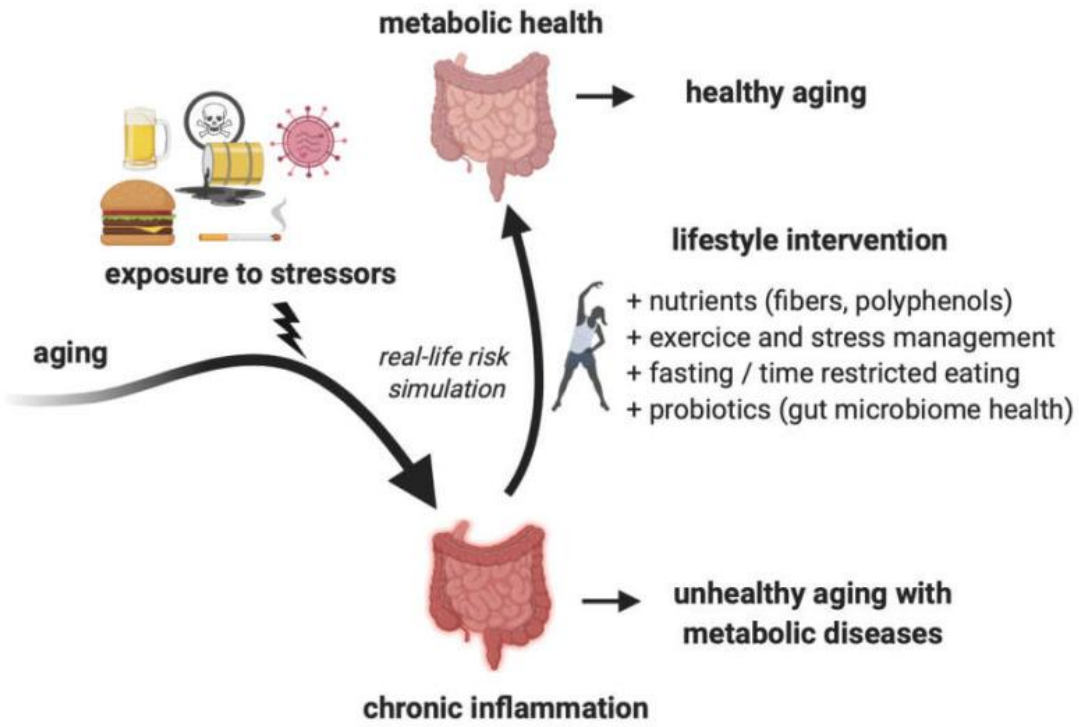
"Given that a large part of the global population suffers from various metabolic disorders, it is important to look for non-pharmacological ways to deal with these conditions. Targeted changes in lifestyle and especially diet can be economical tools to mitigate the development of metabolic disorders when they are at an early stage. These changes include increased fiber and polyphenol intake compared to the current western diets, but also well-structured, personalized fasting protocols, which can reduce the risk of metabolic disorders (Figure 3)."



"This could be implemented in various institutions by improving the nutritional quality of foods served in schools, hospitals, prisons, government buildings, or senior centers. Moving toward healthier food options in hospitals might ultimately help improve patient health and reduce healthcare costs.

Improving diet can have a positive effect on the immune response as a hallmark of RLRS. Since inflammation is associated with the acute pathological response to COVID-19 and other infectious diseases, improvement of the immune response and inflammatory markers may lead to an improved physiological resilience to disturbances by infectious agents such as viruses and bacteria, and possibly milder symptoms."

-Department of Biochemistry, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Traian Vuia 6, 020956 Bucharest, Romania;

-Department of Toxicology, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Traian Vuia 6, 020956 Bucharest, Romania;

-European Institute of Nutritional Medicine EINuM, 00198 Rome, Italy;

-Metabolomic Medicine Clinic, Health Clinics for Autoimmune and Chronic Diseases, 10674 Athens, Greece;

-Laboratory of Toxicology and Forensic Sciences, Medical School, University of Crete, 71003 Heraklion, Greece

-Department of Biochemistry-Biotechnology, School of Health Sciences, 41500 Larisa, Greece; -Gene Expression and Therapy Group, King's College London, Faculty of Life Sciences and Medicine, Department of Medical and Molecular Genetics, 8th Floor, Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK;

https://pubmed.ncbi.nlm.nih.gov/32531935

…"Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). SARS-CoV-2 triggers an immune response with local inflammation in the lung, which may extend to a systemic hyperinflammatory reaction. Excessive inflammation has been reported in severe cases with respiratory failure and cardiovascular complications. In addition to the release of cytokines, referred to as cytokine release syndrome or "cytokine storm," increased pro-inflammatory lipid mediators derived from the omega-6 polyunsaturated fatty acid (PUFA) arachidonic acid may cause an "eicosanoid storm," which contributes to the uncontrolled systemic inflammation. Specialized pro-resolving mediators, which are derived from omega-3 PUFA, limit inflammatory reactions by an active process called resolution of inflammation. Here, the rationale for omega-3 PUFA supplementation in COVID-19 patients is presented along with a brief overview of the study protocol for the trial "Resolving Inflammatory Storm in COVID-19 Patients by Omega-3 Polyunsaturated Fatty Acids - A single-blind, randomized, placebo-controlled feasibility study""…

"Polyunsaturated fatty acids (PUFA) serve as the substrate for pro-inflammatory, anti-inflammatory, and specialized pro-resolving lipid mediators (SPM) (Chiang and Serhan, 2020). Specifically, the omega-6 PUFA arachidonic acid (AA) is substrate for the lipoxygenase and cyclooxygenase pathways, which generate leukotrienes and prostaglandins, respectively, collectively referred to as eicosanoids (Figure 1). In contrast, the omega-3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) serve as the substrate for pro-resolving SPM (Figure 1). PUFA can also be metabolized by cytochrome (CYP) P450 epoxygenases into their respective epoxides (Figure 1), which also regulate the inflammatory reaction.

Increasing omega-3 PUFA and decreasing omega-6 PUFA hence represent a possible mean to skew the immune response toward resolution of inflammation (Figure 1). It should however, be considered that AA also gives rise to pro-resolving lipoxins, which is favored by the CYP450-derived AA epoxides (Hammock et al., 2020; Figure 1). In addition, another omega-6 PUFA, adrenic acid, has recently been ascribed anti-inflammatory actions (Brouwers et al., 2020). Nevertheless, a low omega-3 to omega-6 ratio is in general indicating a nutritional state favoring inflammation (Artiach et al., 2020b; Xue et al., 2020), which can also be reflected in the ratios of the respective lipid mediators, e.g., the resolvin to leukotriene ratio (Thul et al., 2017)."

-Translational Cardiology, Karolinska Institutet, Stockholm, Sweden
-Department of Cardiology, Theme Heart, Vessels, and Neuro, Karolinska University Hospital, Stockholm, Sweden
-Theme Ageing, Karolinska University Hospital, Stockholm, Sweden
-Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden
-Department of Cardiology, Södersjukhuset, Stockholm, Sweden
-Karolinska Trial Alliance, Sabbatsberg's Hospital, Stockholm, Sweden

-Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

-Edited by: Adriana Castello Costa Girardi, University of São Paulo, Brazil

-Reviewed by: Philip Calder, University of Southampton, United Kingdom; Martin Giera, Leiden University Medical Center, Netherlands

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7830247

Targeting arachidonic acid–related metabolites in COVID-19 patients: potential use of drug-loaded nanoparticles

"In March 2020, The World Health Organization (WHO) has declared that the coronavirus disease 2019 (COVID-19) is characterized as a global pandemic. As of September 2020, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread to 213 countries and territories around the world, affected more than 31.5 million people, and caused more than 970,000 deaths worldwide. Although COVID-19 is a respiratory illness that mainly targets the lungs, it is currently well established that it is a multifactorial disease that affects other extra-pulmonary systems and strongly associated with a detrimental inflammatory response. Evidence has shown that SARS-CoV-2 causes perturbation in the arachidonic acid (AA) [omega-6] metabolic pathways; this disruption could lead to an imbalance between the pro-inflammatory metabolites of AA including mid-chain HETEs and terminal HETE (20-HETE) and the anti-inflammatory metabolites such as EETs and subterminal HETEs. Therefore, we propose novel therapeutic strategies to modulate the level of endogenous anti-inflammatory metabolites of AA and induce the patient's endogenous resolution mechanisms that will ameliorate the virus-associated systemic inflammation and enhance the primary outcomes in COVID-19 patients. Also, we propose that using nanoencapsulation of AA and its associated metabolites will contribute to the development of safer and more efficacious treatments for the management of COVID-19."…

-Faculty of Pharmacy & Pharmaceutical Sciences, Katz Group-Rexall Centre for Pharmacy and Health Research, University of Alberta, Edmonton, Alberta, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7670111

Eicosanoids: The Overlooked Storm in Coronavirus Disease 2019 (COVID-19)?

"Severe coronavirus disease 2019 (COVID-19) symptoms, including systemic inflammatory response and multisystem organ failure, are now affecting thousands of infected patients and causing widespread mortality. Coronavirus infection causes tissue damage, which triggers the endoplasmic reticulum stress response and subsequent eicosanoid and cytokine storms. Although proinflammatory eicosanoids, including prostaglandins, thromboxanes, and leukotrienes, are critical mediators of physiological processes, such as inflammation, fever,

allergy, and pain, their roles in COVID-19 are poorly characterized. Arachidonic acid–derived epoxyeicosatrienoic acids could alleviate the systemic hyperinflammatory response in COVID-19 infection by modulating endoplasmic reticulum stress and stimulating the resolution of inflammation. Soluble epoxide hydrolase (sEH) inhibitors, which increase endogenous epoxyeicosatrienoic acid levels, exhibit potent anti-inflammatory activity and inhibit various pathologic processes in preclinical disease models, including pulmonary fibrosis, thrombosis, and acute respiratory distress syndrome. Therefore, targeting eicosanoids and sEH could be a novel therapeutic approach in combating COVID-19. In this review, we discuss the predominant role of eicosanoids in regulating the inflammatory cascade and propose the potential application of sEH inhibitors in alleviating COVID-19 symptoms. The host-protective action of omega-3 fatty acid–derived epoxyeicosanoids and specialized proresolving mediators in regulating anti-inflammation and antiviral response is also discussed. Future studies determining the eicosanoid profile in COVID-19 patients or preclinical models are pivotal in providing novel insights into coronavirus-host interaction and inflammation modulation."…

"Although elevated cytokine levels in COVID-19 have been identified as a major factor contributing to morbidity and mortality, the role of eicosanoids in COVID-19 as key mediators of both inflammation and its active resolution remains poorly characterized.[3,28, 29, 30] More important, not all eicosanoids are proinflammatory as arachidonic acid and related fatty acids are also metabolized into anti-inflammatory and proresolution docosanoids in certain temporal situations.[22,31, 32, 33] Infectious processes often activate inflammasome formation and the subsequent formation of an eicosanoid storm consisting of both proinflammatory and anti-inflammatory mediators, thereby disrupting the temporal progression of inflammation and its resolution.[34] Namely, phospholipase A2 regulates eicosanoid class switching during inflammasome and caspase activation, triggering arachidonic acid to generate proresolution mediators, such as lipoxins.[34,35] As increased proinflammatory cytokines may be a driving force in severe COVID-19, the balance of proinflammatory/anti-inflammatory eicosanoids and proresolution lipid mediators during the initiation and resolution of infection can regulate the cytokine storm.34 Thus, we hypothesize that SARS-CoV-2 may trigger a temporal production of an eicosanoid storm, including an imbalance of both proinflammatory and proresolution mediators.[3,22]"

-Department of Entomology and Nematology, University of California, Davis, California

-UCD Comprehensive Cancer Center, University of California, Davis, California

-Center for Vascular Biology Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

-Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7340586/

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…"However, it is known that patients with up-regulated COX-2 levels and inflammatory conditions have high incidences of Epstein Barr Virus associated malignancies indicating a possible role of COX-2 in virus-mediated tumorigenesis [44]. Finally, recently published preliminary results from a randomized controlled trial, carried out on 120 inpatients with influenza A (H3N2), showed that the reduction in mortality and cytokine levels was higher for the combination of celecoxib-oseltamivir compared to oseltamivir alone, without increasing adverse effects [45].

In conclusion, inflammation represents a physiologic response to tissue damage due to several factors, such as pathogen infection, chemical irritation, and injury. Gradually the inflammation process advances various types of cells are activated and attracted to the inflammation site through a signalling network involving a large number of mediators such as growth factors, cytokines, and chemokines. All recruited cells at the inflammatory site participate to the defence response but their excess or longer endurance induces tissue damage favouring the worsening of the disease regardless of the cause [46,47]. COX-2 is critical in the inflammatory response process and to be involved in the pathogenesis of influenza virus infection [48]. The same applies to COVID-19 disease for which the induction of a pro-inflammatory cytokine storm is similar to other highly pathogenic human invasive virus [49]."

-Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
-Regional Centre of Pharmacogilance, Campania Region, Naples, Italy
-Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
-Department of Oncology and Onco-Hematology, University of Milan, Milan, Italy
-Clinical Pharmacology Unit, ASST-GOM Niguarda Hospital, Milan, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7189871

Drug repurposing and cytokine management in response to COVID-19: A review

"Coronavirus disease 2019 (COVID-19), the infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an aggressive disease that attacks the respiratory tract and has a higher fatality rate than seasonal influenza. The COVID-19 pandemic is a global health crisis, and no specific therapy or drug has been formally recommended for use against SARS-CoV-2 infection. In this context, it is a rational strategy to investigate the repurposing of existing drugs to use in the treatment of COVID-19 patients. In the meantime, the medical community is trialing several therapies that target various antiviral and

immunomodulating mechanisms to use against the infection. There is no doubt that antiviral and supportive treatments are important in the treatment of COVID-19 patients, but anti-inflammatory therapy also plays a pivotal role in the management COVID-19 patients due to its ability to prevent further injury and organ damage or failure. In this review, we identified drugs that could modulate cytokines levels and play a part in the management of COVID-19. Several drugs that possess an anti-inflammatory profile in others illnesses have been studied in respect of their potential utility in the treatment of the hyperinflammation induced by SAR-COV-2 infection. We highlight a number of antivirals, anti-rheumatic, anti-inflammatory, antineoplastic and antiparasitic drugs that have been found to mitigate cytokine production and consequently attenuate the "cytokine storm" induced by SARS-CoV-2. Reduced hyperinflammation can attenuate multiple organ failure, and even reduce the mortality associated with severe COVID-19. In this context, despite their current unproven clinical efficacy in relation to the current pandemic, the repurposing of drugs with anti-inflammatory activity to use in the treatment of COVID-19 has become a topic of great interest."…

-Laboratory of Neuroscience and Pharmacological Assays (LANEF), São Cristóvão, SE 49100-000 Brazil; Graduate Program of Health Sciences (PPGCS), São Cristóvão, SE, Brazil.

-Graduate Program of Pharmaceutical Sciences (PPGCF). Federal University of Sergipe (UFS), São Cristóvão, SE, Brazil.

-Graduate Program of Health Sciences (PPGCS), São Cristóvão, SE, Brazil.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7457938/

The Management of Cytokine Storm in COVID-19

"Cytokine storm in COVID-19 infection is an excessive immune response to external stimuli where the pathogenesis is complex. The disease progresses rapidly and the mortality is high. Certain evidence shows that the severe deterioration of some patients has been closely related to the strong upregulation of cytokine production in SARS-Co-V2 induced pneumonia with an associated cytokine storm syndrome. Identification of existing approaved therapy with proven safety profile to treat hyperinflammation is critical unmet need in order to reduce COVID-19 associated mortality. To date, no specific therapeutic drugs are available to treat COVID-19 infection. Preliminary studies have shown that immune-modulatory or immune suppressive treatments might be considered as treatment choices for COVID-19, particularly in severe disease. This article review the pathogenesis and treatment strategies of COVID-19 virus-induced inflammatory storm in attempt to provide valuable medication guidance for clinical treatment."

-Division of Respirology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jakarta, Indonesia.

https://pubmed.ncbi.nlm.nih.gov/33020343

SARS-CoV-2 Spike Protein Elicits Cell Signaling in Human Host Cells: Implications for Possible Consequences of COVID-19 Vaccines

..." However, recent observations suggest that the SARS-CoV-2 spike protein can by itself trigger cell signaling that can lead to various biological processes. It is reasonable to assume that such events, in some cases, result in the pathogenesis of certain diseases.

Our laboratory only tested the effects of the SARS-CoV-2 spike protein in lung vascular cells and those implicated in the development of PAH. However, this protein may also affect the cells of systemic and coronary vasculatures, eliciting other cardiovascular diseases such as coronary artery disease, systemic hypertension, and stroke. In addition to cardiovascular cells, other cells that express ACE2 have the potential to be affected by the SARS-CoV-2 spike protein, which may cause adverse pathological events. Thus, it is important to consider the possibility that the SARS-CoV-2 spike protein produced by the new COVID-19 vaccines triggers cell signaling events that promote PAH, other cardiovascular complications, and/or complications in other tissues/organs in certain individuals (Figure 3). "..

-Department of Pharmacology and Physiology, Georgetown University Medical Center, Washington, DC 20007, USA
-Department of Pathological Anatomy N2, Bogomolets National Medical University, 01601 Kiev, Ukraine
https://www.mdpi.com/2076-393X/9/1/36/htm

The following quote pertains to the previous "SARS-CoV" not to be confused with "SARS-CoV-2"

It shows that previous attempts at making a vaccine for it, made the immune system hypersensitive.

Immunization with SARS Coronavirus Vaccines Leads to Pulmonary Immunopathology on Challenge with the SARS Virus

"These SARS-CoV vaccines all induced antibody and protection against infection with SARS-CoV. However, challenge of mice given any of the vaccines led to occurrence of Th2-type immunopathology suggesting hypersensitivity to SARS-CoV components was induced. Caution in proceeding to application of a SARS-CoV vaccine in humans is indicated."

-Department of Microbiology and Immunology, The University of Texas Medical Branch, Galveston, Texas, United States of America.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335060/

Various medical professionals are questioning if this is actually a "viral disease". It is important to note that even with the Spanish Flu of 1918, they could never prove in experiments that it was contagious.[1] If you would like to see more research or discuss this topic further please email inflammation.life@gmail.com

[1]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2862332

Crohn's Disease

…"Although the primary end point of the study (induction of remission) was not achieved, a short course (8 weeks) of THC-rich cannabis produced significant clinical, steroid-free benefits to 10 of 11 patients with active Crohn's disease, compared with placebo, without side effects."

- Department of Gastroenterology and Hepatology, Meir Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Kfar Saba, Israel.

https://www.ncbi.nlm.nih.gov/pubmed/23648372

bit.do/ecscrohns

Role of cannabis in digestive disorders

"Cannabis sativa, a subspecies of the Cannabis plant, contains aromatic hydrocarbon compounds called cannabinoids. Δ9-Tetrahydrocannabinol is the most abundant cannabinoid and is the main psychotropic constituent. Cannabinoids activate two types of G-protein-coupled cannabinoid receptors: cannabinoid type 1 receptor and cannabinoid type 2 receptor. There has been ongoing interest and development in research to explore the therapeutic potential of cannabis. Δ9-Tetrahydrocannabinol exerts biological functions on the gastrointestinal (GI) tract. Cannabis has been used for the treatment of GI disorders such as abdominal pain and diarrhea. **The endocannabinoid system (i.e. endogenous circulating cannabinoids) performs protective activities in the GI tract and presents a promising therapeutic target against various GI conditions such as inflammatory bowel disease (especially Crohn's disease), irritable bowel syndrome, and secretion and motility-related disorders.** The present review sheds light on the role of cannabis in the gut, liver, and pancreas and also on other GI symptoms, such as nausea and vomiting, cannabinoid hyperemesis syndrome, anorexia, weight loss, and chronic abdominal pain. Although the current literature supports the use of marijuana for the treatment of digestive disorders, the clinical efficacy of cannabis and its constituents for various GI disorders remains

unclear."

-Department of Internal Medicine, Mercer University School of Medicine, Macon

-Department of Internal Medicine, Morehouse School of Medicine, Atlanta, Georgia, USA cLU-3, Pitampura, New Delhi, India.

https://pubmed.ncbi.nlm.nih.gov/27792038/

See also Inflammatory Bowel Disease (IBD) , Tumor Necrosis Factor-alpha (TNF-a)

Curcumin

Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs.

https://www.ncbi.nlm.nih.gov/pubmed/20924967

https://www.youtube.com/watch?v=yueIuyoQCX8&

Anti-inflammatory effect of curcumin on mast cell-mediated allergic responses in ovalbumin-induced allergic rhinitis mouse

"Curcumin has commonly been used for the treatment of various allergic diseases. However, its precise anti-allergic rhinitis effect and mechanism remain unknown. In the present study, the effect of curcumin on allergic responses in ovalbumin (OVA)-induced allergic rhinitis mouse was investigated. We explored the effect of curcumin on the release of allergic inflammatory mediators, such as histamine, OVA-specific IgE, and inflammatory cytokines. Also, we found that curcumin improved rhinitis symptoms, inhibited the histopathological changes of nasal mucosa, and decreased the serum levels of histamine, OVA-specific IgE and TNF-α in OVA-induced allergic rhinitis mice. In addition, curcumin suppressed the production of inflammatory cytokines, such as TNF-α, IL-1β, IL-6 and IL-8. Moreover, curcumin significantly inhibited PMA-induced p-ERK, p-p38, p-JNK, p-Iκ-Bα and NF-κB. These findings suggest that curcumin has an anti-allergic effect through modulating mast cell-mediated allergic responses in allergic rhinitis, at least partly by inhibiting MAPK/NF-κB pathway."

-Department of Otolaryngology-Head and Neck Surgery, Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China.

-Department of Microbiology, Key Laboratory for Experimental Teratology, Chinese Ministry of Education, School of Medicine, Shandong University, Jinan, Shandong, China.

-Department of Otolaryngology-Head and Neck Surgery, Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China.

https://pubmed.ncbi.nlm.nih.gov/26507910

Cyclooxygenase (COX)

"Cyclooxygenase (COX) is the main pharmacodynamic target of nonsteroidal anti-inflammatory drugs (NSAIDs)."…

-Department of Physical Medicine and Rehabilitation, Dong-A University College of Medicine, Dong-A University Hospital

-Department of Pharmacology and Clinical Pharmacology, Dong-A University College of Medicine, Dong-A University Hospital, Busan

-Clinical Trials Center, Gachon University Gil Medical Center, Incheon

-Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604555

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…"Any time cyclooxygenase is blocked, arachidonic acid [omega-6] will be forced into the leukotreine pathway, which is a major contributor to "silent Inflammation" and cardiovascular death."…

-Ehlers-Danlos National Foundation

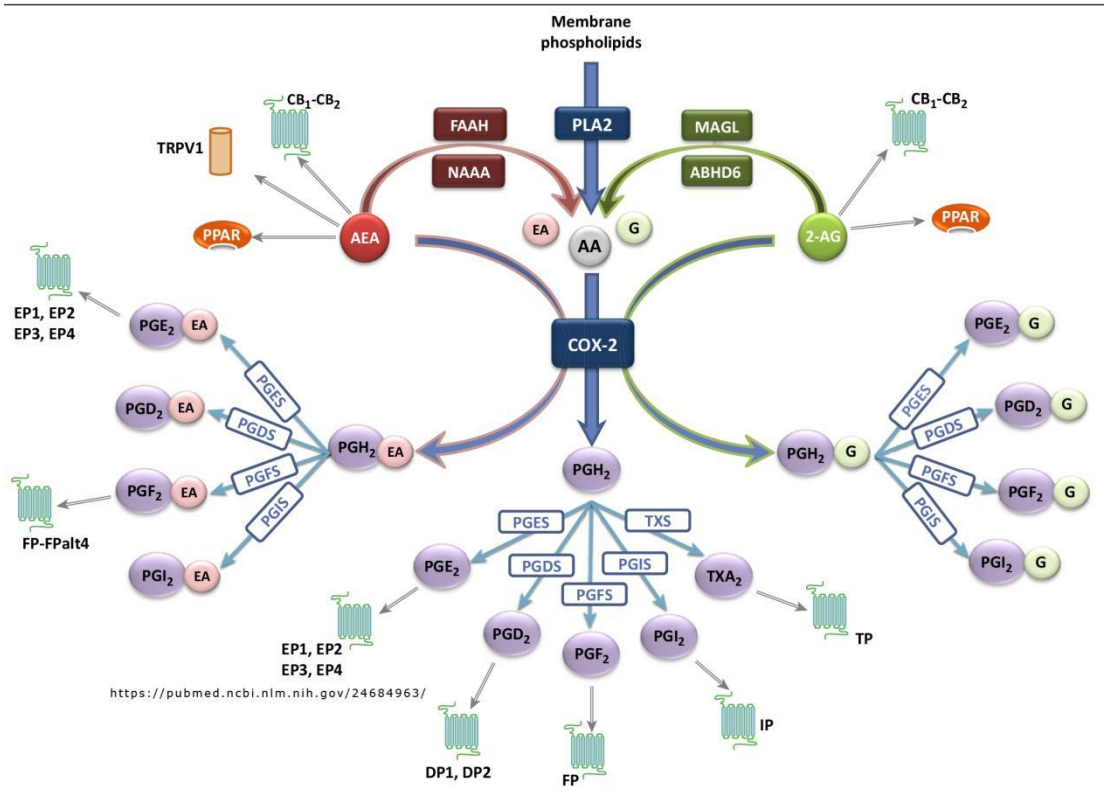
-Dr. Abbas Qutab

https://www.ehlers-danlos.com/2013-annual-conference-files/Qutab_Botanical_Medicine_S.pdf

COX-2-derived endocannabinoid metabolites as novel inflammatory mediators

"Cyclooxygenase-2 (COX-2) is an enzyme that plays a key role in inflammatory processes. Classically, this enzyme is upregulated in inflammatory situations and is responsible for the generation of prostaglandins (PGs) from arachidonic acid (AA). One lesser-known property of COX-2 is its ability to metabolize the endocannabinoids, N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG). Endocannabinoid metabolism by COX-2 is not merely a means to terminate their actions. On the contrary, it generates PG analogs, namely PG-glycerol esters (PG-G) for 2-AG and PG-ethanolamides (PG-EA or prostamides) for AEA. Although the formation of

these COX-2-derived metabolites of the endocannabinoids has been known for a while, their biological effects remain to be fully elucidated. Recently, several studies have focused on the role of these PG-G or PG-EA in vivo. In this review we take a closer look at the literature concerning these novel bioactive lipids and their role in inflammation."



-Bioanalysis and Pharmacology of Bioactive Lipids Research Group, Louvain Drug Research Institute, Université catholique de Louvain, Avenue Emmanuel Mounier 72 (B1.72.01), 1200 Bruxelles, Belgium.
https://pubmed.ncbi.nlm.nih.gov/24684963/

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"It has been known for years that non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and acetaminophen, provide relief from fever, pain, and inflammation through their actions on cyclooxygenase (COX) enzymes.[1] Two COX isozymes, COX-1 and -2, were first identified in the early 1990's as the catalysts for an important step in prostaglandin biosynthesis.[2] Although both enzymes have similar functions, their temporal and spatial expression patterns are very different.[3] COX-1 is constitutively expressed in many somatic cell types and is considered a "housekeeping" enzyme with roles in such processes as vascular hemostasis and gastroprotection.[4] In contrast, COX-2 expression is primarily induced by factors such as endotoxins, cytokines, and growth factors.[5] COX-2 is expressed at sites of inflammation

and produces prostaglandins that mediate inflammatory and pain sensation responses.[6] COX involvement in inflammation, pain, and a variety of diseases has inspired researchers to investigate the actions of NSAIDs on these enzymes. Although many advances have been made over the last 10 years in understanding the pain relief and anti-inflammatory mechanisms of aspirin, ibuprofen, and the new COX-2 inhibitors, the mechanism of acetaminophen action has remained elusive.[7,8]"

- R&D Systems
https://www.rndsystems.com/resources/articles/cox-3-acetaminophen-target-finally-revealed

Life-threatening side effects of selective COX-2 NSAIDs

"in December 1998, celecoxib (Celebrex) was approved by the Food and Drug Administration (FDA) as the first selective COX-2 inhibitor for treatment of arthritis pain.[92,13,22] Rofecoxib (Vioxx) was approved several months later, followed by valdecoxib (Bextra).[92,28,67,79] These NSAIDs were designed to allow continued production of the gastrointestinally protective prostaglandins produced through the COX-1 enzyme system while blocking the COX-2 enzyme that produces the inflammatory prostaglandins.[34,45,51,89]

Celebrex, Vioxx, and Bextra quickly became the mainstay for the treatment of chronic pain conditions related to inflammation.[71] Within a few years, an estimated 15–20 million people in the US were using selective COX-2–inhibiting NSAIDs on a long-term basis. These drugs became the most commonly used pharmaceutical agent with more than 70 million NSAID prescriptions written each year and 30 billion over-the-counter NSAID tablets sold annually. It was estimated that 5–10% of the adult population used NSAIDs, and among the elderly (a group at higher risk of nonselective NSAID-induced gastrointestinal complications), the use of these drugs was as high as 15%. The general acceptance of these drugs was due to the perceived lack of serious gastrointestinal side effects that had been associated with the nonselective class of NSAIDs.[26,119]

On September 30, 2004, Merck Research Laboratories announced the global withdrawal of rofecoxib (Vioxx), its primary selective COX-2–inhibiting NSAID.[52,90,122] Analysis of the results of the Adenomatous Polyps Prevention on Vioxx study (known as the APPROVe study) showed that there was double the risk of serious thromboembolic events, including myocardial infarction, which became apparent after 18 months of Vioxx treatment.[26] Selective COX-2 NSAID's thrombotic mechanism of action is based on COX-1's unopposed action to continued platelet synthesis of thromboxane. Thromboxane is a thrombogenic and atherogenic eicosanoid. Prostacyclin prevents formation of platelet clotting. By inhibiting COX-2 that blocks production of prostacyclin (PGI2) there is unopposed thromboxane which will increase the clotting risk. Thus, inhibiting prostacyclin led to the increased risk of thrombotic cardiovascular and cerebrovascular

events.[5,26,73,123]”

-Department of Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
-Vanderbilt University, Nashville, TN, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3011108/

COX-2-derived endocannabinoid metabolites as novel inflammatory mediators

“Cyclooxygenase-2 (COX-2) is an enzyme that plays a key role in inflammatory processes. Classically, this enzyme is upregulated in inflammatory situations and is responsible for the generation of prostaglandins (PGs) from arachidonic acid (AA). One lesser-known property of COX-2 is its ability to metabolize the endocannabinoids, N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG). Endocannabinoid metabolism by COX-2 is not merely a means to terminate their actions. On the contrary, it generates PG analogs, namely PG-glycerol esters (PG-G) for 2-AG and PG-ethanolamides (PG-EA or prostamides) for AEA. Although the formation of these COX-2-derived metabolites of the endocannabinoids has been known for a while, their biological effects remain to be fully elucidated. Recently, several studies have focused on the role of these PG-G or PG-EA in vivo. In this review we take a closer look at the literature concerning these novel bioactive lipids and their role in inflammation.”

Highlights

- PG-G and PG-EA are COX-2-derived metabolites of endocannabinoids.
- COX-2 is at the center of crosstalk between the endocannabinoid and prostanoid systems.
- PG-G and PG-EA represent novel lipid mediators in inflammation.
- COX-2 substrate-selective inhibitors control PG-G and PG-EA levels and activity.
- Antagonists of their receptors are being characterized.

-Bioanalysis and Pharmacology of Bioactive Lipids Research Group, Louvain Drug Research Institute, Université catholique de Louvain, Avenue Emmanuel Mounier 72 (B1.72.01), 1200 Bruxelles, Belgium
https://embargoed.www.cell.com/trends/pharmacological-sciences/fulltext/S0165-6147(14)00035-2

Oxygenation of the endocannabinoid, 2-arachidonylglycerol, to glyceryl prostaglandins by cyclooxygenase-2

“Cyclooxygenases (COX) play an important role in lipid signaling by oxygenating arachidonic acid to endoperoxide precursors of prostaglandins and thromboxane. Two cyclooxygenases exist which differ in tissue distribution and regulation but otherwise carry out identical chemical

functions. The neutral arachidonate derivative, 2-arachidonylglycerol (2-AG), is one of two described endocannabinoids and appears to be a ligand for both the central (CB1) and peripheral (CB2) cannabinoid receptors. Here we report that 2-AG is a substrate for COX-2 and that it is metabolized as effectively as arachidonic acid. COX-2-mediated 2-AG oxygenation provides the novel lipid, prostaglandin H(2) glycerol ester (PGH(2)-G), in vitro and in cultured macrophages. PGH(2)-G produced by macrophages is a substrate for cellular PGD synthase, affording PGD(2)-G. Pharmacological studies reveal that macrophage production of PGD(2)-G from endogenous sources of 2-AG is calcium-dependent and mediated by diacylglycerol lipase and COX-2. These results identify a distinct function for COX-2 in endocannabinoid metabolism and in the generation of a new family of prostaglandins derived from diacylglycerol and 2-AG."

-Departments of Biochemistry and Chemistry, Vanderbilt-Ingram Cancer Center and Center in Molecular Toxicology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.

https://pubmed.ncbi.nlm.nih.gov/10931854

Cannabinoid system and cyclooxygenases inhibitors

"**Rationale**: The cannabinoid system consists of a complex array of receptors, substances with agonist/antagonist properties for those receptors, biosynthetic machineries and mechanisms for cellular uptake and degradation for endocannabinoids. This system is in interrelation with other systems that comprise lipid mediators like prostaglandins/leukotrienes systems. A clear antagonist, additive or synergic effect of nonsteroidal anti-inflammatory drugs (NSAIDs)-cannabinoid associations was not yet demonstrated. Aim. The present study tried to summarize the existent data on NSAIDS-cannabinoid system interactions.

Conclusions: Some NSAIDs have additional influences on the cannabinoid system either by inhibiting fatty acid amide hydrolase (FAAH) or by inhibiting a possible intracellular transporter of endocannabinoids. All the NSAIDs that inhibit COX2 can influence the cannabinoid system because a possible important degradative pathway for anandamide and 2-arachidonoyl glycerol might involve COX 2. One of the causes for the variety of experimental results presented might be due to pharmacokinetic mechanisms, depending on the route of administration and the dose."

-Department of Pharmacology and Pharmacotheraphy, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

https://pubmed.ncbi.nlm.nih.gov/21505570

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…"Endocannabinoids are further metabolized by eicosanoid-synthesizing enzymes from the

cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 epoxygenase (CYP) pathways to generate complex lipid metabolites with distinct biological functions [17]. Recently it was shown that DHEA is a substrate for enzymes of the LOX and COX pathways to yield metabolites with anti-inflammatory properties [18, 19]. "....

-Department of Comparative Biosciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Medical Scholars Program, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Biochemistry, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Materials Science and Engineering, University of Illinois at Urbana–Champaign, Champaign, IL,
-Department of Pharmacology, University of Michigan, Ann Arbor, MI;
-Division of Nutritional Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-College of Veterinary Medicine, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Animal Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Bioengineering, University of Illinois at Urbana–Champaign, Champaign IL;
-Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI;
-Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana–Champaign, Champaign, IL,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5544256

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..."Prostaglandin synthesis is initiated with the release of arachidonic acid from membrane phospholipids. The subsequent conversion of arachidonic acid to prostaglandin H2 (PGH2) is catalyzed in two steps by cyclooxygenase [4]. Synthase enzymes then convert PGH2 to specific prostaglandins such as PGD2, PGE2, PGF2α, prostacyclin and thromboxane. Thus, cyclooxygenase activity is essential for normal prostaglandin production and is the rate-limiting enzyme in the synthetic pathway. The two recognized forms of this enzyme, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are encoded by two separate genes [5, 6]. COX-1 is constitutively expressed by many tissues and functions as a so-called 'housekeeping' enzyme maintaining homeostatic levels of prostaglandins for the normal function of several organs, in particular the stomach [7]. In contrast, COX-2 is induced by an array of stimuli including inflammation, injury and mechanical stress [8, 9]."...

-Dr. Thomas A Einhorn MD
-Arthritis Research & Therapy
https://arthritis-research.biomedcentral.com/articles/10.1186/ar607

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..."In their studies they used different COX inhibitors (i.e. etodolac, indomethacin and piroxicam), to evaluate prostaglandin production. They found that all these inhibitors not only decreased

prostaglandin production but also decreased the viability of these cells. "…

-Department of Microbial, biochemical and food Biotechnology, University of the Free State, Bloemfontein, South Africa

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3475069/

Metabolism of the endocannabinoids, 2-arachidonylglycerol and anandamide, into prostaglandin, thromboxane, and prostacyclin glycerol esters and ethanolamides

"Cyclooxygenase-2 (COX-2) action on the endocannabinoids, 2-arachidonylglycerol (2-AG) and anandamide (AEA), generates prostaglandin glycerol esters (PG-G) and ethanolamides (PG-EA), respectively. The diversity of PG-Gs and PG-EAs that can be formed enzymatically following COX-2 oxygenation of endocannabinoids was examined in cellular and subcellular systems. In cellular systems, glycerol esters and ethanolamides of PGE(2), PGD(2), and PGF(2alpha) were major products of the endocannabinoid-derived COX-2 products, PGH(2)-G and PGH(2)-EA. The sequential action of purified COX-2 and thromboxane synthase on AEA and 2-AG provided thromboxane A(2) ethanolamide and glycerol ester, respectively. Similarly, bovine prostacyclin synthase catalyzed the isomerization of the intermediate endoperoxides, PGH(2)-G and PGH(2)-EA, to the corresponding prostacyclin derivatives. Quantification of the efficiency of prostaglandin and thromboxane synthase-directed endoperoxide isomerization demonstrated that PGE, PGD, and PGI synthases catalyze the isomerization of PGH(2)-G at rates approaching those observed with PGH(2). In contrast, thromboxane synthase was far more efficient at catalyzing PGH(2) isomerization than at catalyzing the isomerization of PGH(2)-G. These results define the in vitro diversity of endocannabinoid-derived prostanoids and will permit focused investigations into their production and potential biological actions in vivo."

-Department of Biochemistry, Vanderbilt-Ingram Cancer Center, and Center in Molecular Toxicology, Vanderbilt University School of Medicine, USA.

https://pubmed.ncbi.nlm.nih.gov/12244105/

Assay of Endocannabinoid Oxidation by Cyclooxygenase-2

…"The endocannabinoids 2-archidonoylglycerol (2-AG) and arachidonylethanolamide (AEA) are neutral arachidonic acid (AA) derivatives that exert analgesic and anti-inflammatory effects via the activation of cannabinoid receptors, CB1 and CB2 (1,2). Much like arachidonic acid (AA), 2-AG and AEA are oxygenated by the second isoform of the cyclooxygenase enzyme, COX-2. The oxygenation of 2-AG and AEA by COX-2 produces prostaglandin H2-glycerol ester (PGH2-G) and

prostaglandin H2-ethanolamide (PGH2-EA), respectively (3,4). Each PGH2 derivative undergoes further metabolism via prostaglandin synthases to a range of PG-glycerol esters (PG-Gs) and PG-ethanolamides (PG-EAs) that exhibit biological activities such as activation of calcium mobilization in tumor cells and macrophages, modulation of inhibitory synaptic transmission, induction of neurotoxicity by enhancement of excitatory glutamatergic synaptic transmission, and induction of hyperalgesia and anti-inflammatory responses (5–10) (Fig. 1). Additionally, when the macrophage cell line (RAW264.7) is treated with LPS and ionomycin, PG-Gs are produced which stimulate Ca2+ mobilization in the RAW264.7 cells (11,7), suggesting that PG-Gs may exert independent biological activities."…

-A.B. Hancock Jr. Memorial Laboratory for Cancer Research, Vanderbilt Institute of Chemical Biology, Vanderbilt Center in Molecular Toxicology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville TN, USA

-Department of Biochemistry, Vanderbilt Institute of Chemical Biology, Vanderbilt Center in Molecular Toxicology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville TN, USA

-Department of Chemistry, Vanderbilt Institute of Chemical Biology, Vanderbilt Center in Molecular Toxicology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville TN, USA

-Department of Pharmacology, Vanderbilt Institute of Chemical Biology, Vanderbilt Center in Molecular Toxicology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville TN, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5289390/

Non-redundant Functions of Cyclooxygenases: Oxygenation of Endocannabinoids*

.."Cyclooxygenases (COX-1 and COX-2)2 catalyze the committed step in the conversion of AA to PGs, thromboxane, and PGI2 and, in so doing, trigger the biosynthesis of an important family of lipid mediators [1, 2]. Cyclooxygenase activity was first described in 1964 [3], and COX-1 was purified in 1976 [4]. These events occurred concomitantly with the realization that nonsteroidal anti-inflammatory drugs achieve their anti-inflammatory effects primarily by blocking the cyclooxygenase reaction [5]. The discovery of COX-2 generated important insights into inflammation, wound healing, reproduction, renal function, and vascular biology inter alia, leading to a pharmacological strategy for the treatment of inflammation with reduced gastrointestinal toxicity and providing a new target for the prevention of cancer [6, 7]. Despite the rapid pace of these discoveries, our understanding of the physiological roles of the two COX enzymes is incomplete, especially with regard to potential non-redundant functions [8]."..

-A. B. Hancock Jr. Memorial Laboratory for Cancer Research, the Departments of Biochemistry, Chemistry, and Pharmacology, the Vanderbilt Institute of Chemical Biology, the Center in Molecular Toxicology, the Research Center for Pharmacology and Drug Toxicology, and the Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2417164/

See also Anandamide (AEA) & 2-AG (2-Arachidonoyl-glycerol) , Prostaglandins

Cystic Fibrosis (CF)

"Cystic fibrosis is a hereditary disease that affects the lungs and digestive system. The body produces thick and sticky mucus that can clog the lungs and obstruct the pancreas. Cystic fibrosis (CF) can be life-threatening, and people with the condition tend to have a shorter-than-normal life span."

-Medical News Today
https://www.medicalnewstoday.com/articles/147960.php

The endocannabinoid-CB receptor system: Importance for development and in pediatric disease.

…."Therefore, it is suggested that children may respond positively to medicinal applications of cannabinoids without undesirable central effects. Excellent clinical results have previously been reported in pediatric oncology and in case studies of children with severe neurological disease or brain trauma. We suggest cannabinoid treatment for children or young adults with **cystic fibrosis** in order to achieve an improvement of their health condition including improved food intake and reduced inflammatory exacerbations."

-Department of Behavioral Sciences, College of Judea and Samaria, Israel.
https://www.ncbi.nlm.nih.gov/pubmed/15159678

■■■

"Deficiency of the polyunsaturated essential fatty acids linoleic acid (an omega-6 fatty acid) and alpha-linolenic acid (an omega-3 fatty acid) can result from inappropriate parenteral nutrition and malabsorption disorders such as cystic fibrosis. "…

-Baylor College of Medicine, Houston, TX, USA
-Department of Dermatology, Houston Methodist Hospital, Houston, TX, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5315033

Supplementation with fatty acids influences the airway nitric oxide and inflammatory markers in patients with cystic fibrosis.

"To obtain a balance in the fatty acid (FA) metabolism is important for the inflammatory response and of special importance in cystic fibrosis (CF), which is characterized by impaired FA metabolism, chronic inflammation, and infection in the airways. Nitric oxide (NO) has antimicrobial properties and low nasal (nNO) and exhaled NO (FENO), commonly reported in CF that may affect bacterial status. The present study investigates the effect of different FA blends on nNO and FENO and immunological markers in patients with CF."

…"Thirty-five patients in clinically stable condition completed the study. The serum phospholipid FA pattern changed significantly in all 3 groups. An increase of the n-6 FA, arachidonic acid, was associated with a decrease of FENO and nNO. The inflammatory biomarkers, erythrocyte sedimentation rate, and interleukin-8 decreased after supplementation with n-3 FA and erythrocyte sedimentation rate increased after supplementation with n-6 FA."

…"This small pilot study indicated that the composition of dietary n-3 and n-6 FA influenced the inflammatory markers in CF. FENO and nNO were influenced by changes in the arachidonic acid concentration, supporting previous studies suggesting that both the lipid abnormality and the colonization with Pseudomonas influenced NO in the airways."

-Departments of Pediatrics, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.
https://www.ncbi.nlm.nih.gov/pubmed/20639712

It is recommenced to get DHA & EPA omega-3s from diet. See Supplements for related research quotes.

The endocannabinoid-CB receptor system: Importance for development and in pediatric disease

"Endogenous cannabinoids (endocannabinoids) and their cannabinoid CB1 and CB2 receptors, are present from the early stages of gestation and play a number of vital roles for the developing organism. Although most of these data are collected from animal studies, a role for cannabinoid receptors in the developing human brain has been suggested, based on the detection of "atypically" distributed CB1 receptors in several neural pathways of the fetal brain. In addition, a role for the endocannabinoid system for the human infant is likely, since the endocannabinoid 2-arachidonoyl glycerol has been detected in human milk. Animal research indicates that the Endocannabinoid-CB1 Receptor ('ECBR') system fulfills a number of roles in the developing organism: 1. embryonal implantation (requires a temporary and localized reduction in

anandamide); 2. in neural development (by the transient presence of CB1 receptors in white matter areas of the nervous system); 3. as a neuroprotectant (anandamide protects the developing brain from trauma-induced neuronal loss); 4. in the initiation of suckling in the newborn (where activation of the CB1 receptors in the neonatal brain is critical for survival). 5. In addition, subtle but definite deficiencies have been described in memory, motor and addictive behaviors and in higher cognitive ('executive') function in the human offspring as result of prenatal exposure to marihuana. Therefore, the endocanabinoid-CB1 receptor system may play a role in the development of structures which control these functions, including the nigrostriatal pathway and the prefrontal cortex. From the multitude of roles of the endocannabinoids and their receptors in the developing organism, there are two distinct stages of development, during which proper functioning of the endocannabinoid system seems to be critical for survival: embryonal implantation and neonatal milk sucking. We propose that a dysfunctional Endocannabinoid-CB1 Receptor system in infants with growth failure resulting from an inability to ingest food, may resolve the enigma of "non-organic failure-to-thrive" (NOFTT). Developmental observations suggest further that CB1 receptors develop only gradually during the postnatal period, which correlates with an insensitivity to the psychoactive effects of cannabinoid treatment in the young organism. Therefore, it is suggested that children may respond positively to medicinal applications of cannabinoids without undesirable central effects. Excellent clinical results have previously been reported in pediatric oncology and in case studies of children with severe neurological disease or brain trauma. We suggest cannabinoid treatment for children or young adults with cystic fibrosis in order to achieve an improvement of their health condition including improved food intake and reduced inflammatory exacerbations."

-Department of Behavioral Sciences, College of Judea and Samaria, Ariel 44837, Israel.
https://pubmed.ncbi.nlm.nih.gov/15159678

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"Lipid imbalance of essential FAs is believed to be a major contributing factor in the vicious infection-inflammation cycle of cystic fibrosis (Matouk, 2014). The innate variations such as reduced DHA [Docosahexaenoic acid / omega-3] levels, elevated AA [arachidonic acid / omega-6] levels, and raised AA/DHA ratio exacerbate cystic fibrosis infection (Matouk, 2014), which call for proper monitoring and supplementation. For instance, FA supplementation in a clinical study in adults with cystic fibrosis revealed a linear increase in DHA levels and a linear decrease in the AA/DHA ratio (Olveira et al., 2010), suggesting that dietary FA supplementation can modulate the disease."…

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See Supplements for related research quotes.

Cytokine Network

"Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation, hematopoiesis, and many other cellular processes, forming a cytokine network."

-Sino Biological
https://www.sinobiological.com/cytokine-network-a-1312.html

■■■

…"The endocannabinoid system represents a novel therapeutic target for autoimmune and chronic inflammatory diseases due to its anti-inflammatory properties by regulating cytokine network."

…"This suggests that by altering the cytokine network, AEA [anandamide] could indirectly modify the type of immune responses within the CNS. Accordingly, pharmacological modulation of endocannabinoids might be a useful tool for treating neuroinflammatory diseases."

Neuroimmunology Group, Functional and Systems Neurobiology Department, Cajal Institute, CSCI, 28002 Madrid, Spain
https://www.sciencedirect.com/science/article/pii/S088915911100047X

…"Inflammatory pathways impact the pathogenesis of a number of chronic diseases, and involve common inflammatory mediators and regulatory pathways. Inflammatory stimuli activate intracellular signaling pathways that then activate production of inflammatory mediators. Primary inflammatory stimuli, including microbial products and cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), mediate inflammation through interaction with the TLRs, IL-1 receptor (IL-1R), IL-6 receptor (IL-6R), and the TNF receptor (TNFR) [20]. Receptor activation triggers important intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways [21–23]."…

-College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, China
-Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548

Inflammatory cytokines

"Cytokines (Table (Table2)2) are predominantly released from immune cells, including monocytes, macrophages, and lymphocytes. Pro- and anti-inflammatory cytokines facilitate and inhibit inflammation, respectively. Inflammatory cytokines are classified as ILs, colony stimulating factors (CSF), IFNs, TNFs, TGFs, and chemokines, and are produced by cells primarily to recruit leukocytes to the site of infection or injury [58]. Cytokines modulate the immune response to infection or inflammation and regulate inflammation itself via a complex network of interactions. However, excessive inflammatory cytokine production can lead to tissue damage, hemodynamic changes, organ failure, and ultimately death [59, 60]. A better understanding of how to regulate cytokine pathways would allow for more accurate identification of agent-mediated inflammation and the treatment of inflammatory diseases [58]."

Summary of cytokines and their functions

Cytokine	Family	Main sources	Function
IL-1β	IL-1	Macrophages, monocytes	Pro-inflammation, proliferation, apoptosis, differentiation
IL-4	IL-4	Th-cells	Anti-inflammation, T-cell and B-cell proliferation, B-cell differentiation
IL-6	IL-6	Macrophages, T-cells, adipocyte	Pro-inflammation, differentiation, cytokine production
IL-8	CXC	Macrophages, epithelial cells, endothelial cells	Pro-inflammation, chemotaxis, angiogenesis
IL-10	IL-10	Monocytes, T-cells, B-cells	Anti-inflammation, inhibition of the pro-inflammatory cytokines
IL-12	IL-12	Dendritic cells, macrophages, neutrophils	Pro-inflammation, cell differentiation, activates NK cell
IL-11	IL-6	Fibroblasts, neurons, epithelial	Anti-inflammation, differentiation, induces

Cytokine	Family	Main sources	Function
		cells	acute phase protein
TNF-α	TNF	Macrophages, NK cells, CD4+lymphocytes, adipocyte	Pro-inflammation, cytokine production, cell proliferation, apoptosis, anti-infection
IFN-γ	INF	T-cells, NK cells, NKT cells	Pro-inflammation, innate, adaptive immunity anti-viral
GM-CSF	IL-4	T-cells, macrophages, fibroblasts	Pro-inflammation, macrophage activation, increase neutrophil and monocyte function
TGF-β	TGF	Macrophages, T cells	Anti-inflammation, inhibition of pro-inflammatory cytokine production

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548

Cytokine Storm

"Mammalian tissues express at least two cannabinoid receptor types, CB1 and CB2, both G protein coupled. CB1 receptors are found predominantly at nerve terminals where they mediate inhibition of transmitter release. CB2 receptors occur mainly on immune cells, one of their roles being to modulate cytokine release. Endogenous agonists for cannabinoid receptors also exist, and are all eicosanoids."…

-School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK.

https://pubmed.ncbi.nlm.nih.gov/16570099

D

Damage-associated molecular patterns (DAMPs)

"All mammalian cells are equipped with large numbers of sensors for protection from various sorts of invaders, who, in turn, are equipped with molecules containing pathogen-associated molecular patterns (PAMPs). Once these sensors recognize non-self antigens containing PAMPs, various physiological responses including inflammation are induced to eliminate the pathogens. However, the host sometimes suffers from chronic infection or continuous injuries, resulting in production of self-molecules containing damage-associated molecular patterns (DAMPs). DAMPs are also responsible for the elimination of pathogens, but promiscuous recognition of DAMPs through sensors against PAMPs has been reported. **Accumulation of DAMPs leads to massive inflammation and continuous production of DAMPs; that is, a vicious circle leading to the development of autoimmune disease. From a vaccinological point of view, the accurate recognition of both PAMPs and DAMPs is important for vaccine immunogenicity, because vaccine adjuvants are composed of several PAMPs and/or DAMPs, which are also associated with severe adverse events after vaccination**. Here, we review as the roles of PAMPs and DAMPs upon infection with pathogens or inflammation, and the sensors responsible for recognizing them, as well as their relationship with the development of autoimmune disease or the immunogenicity of vaccines."…

-Laboratory of Adjuvant Innovation, National Institute of Biomedical Innovation, Osaka, Japan

-Laboratory of Vaccine Science, WPI Immunology Frontier Research Center, Osaka University, Osaka, Japan

-Edited by: Nelson Gekara, Umea University, Sweden

-Reviewed by: Dario S. Zamboni, Universidade de São Paulo, Brazil; Willem Van Eden, Utrecht University, Netherlands; Yan Shi, University of Calgary, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3539075/

See also Autoimmune Diseases

Dementia

Therapeutic Effects of Cannabis and Cannabinoids

"CB1 receptors are found throughout the central nervous system, and the endogenous cannabinoid system is thought to be important in the regulation of synaptic transmission (Baker et al., 2003), a process that is disordered in patients with dementia. Accumulating evidence suggests that cannabinoids have the potential for neuroprotective effects (Grundy, 2002; Hampson et al., 1998; Shen and Thayer, 1998). This developing understanding of the endogenous cannabinoid system, along with cannabinoids anxiolytic and appetite-stimulating effects, provides a rationale for its study in patients with

dementia."

-National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice;

-Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda.

-Washington (DC): National Academies Press (US); 2017 Jan 12.

https://www.ncbi.nlm.nih.gov/books/NBK425767/

The Role of Peripheral Inflammatory Markers in Dementia and Alzheimer's Disease: A Meta-Analysis

"An increased peripheral level of inflammatory markers is associated with a modest increase in risk of all-cause dementia…"

San Francisco VA Medical Center, 4150 Clement St., VAMC 116H, San Francisco, CA

https://www.ncbi.nlm.nih.gov/pubmed/22982688

Neurohealth Properties of Hericium erinaceus [Lion's Mane mushroom] Mycelia Enriched with Erinacines

"While 1/5 of dementia cases can be reversible in some cases when caused by drugs, alcohol, hormone imbalances, or depression, a significant proportion of individuals suffer from dementias that are irreversible [34]. The most common irreversible dementia types include Alzheimer's disease, vascular dementia, Lewy body dementia, Parkinson's disease, and frontotemporal dementia [35]. Luckily, growing preclinical studies have demonstrated that the risk of dementia and cognitive impairment could be reduced in the early stages by erinacine-enriched H. erinaceus mycelium consumption. Figure 3 illustrates the overall therapeutic mechanism of action of H. erinaceus [Lion's mane mushroom] mycelia enriched with erinacine in dementia."

…"Recent research has highlighted that presbycusis may precede the onset of clinical dementia and may present as an early manifestation of probable Alzheimer's disease [51]. Exogenous application of NGF has been the first to promote nerve fiber regrowth or sprouting in deafened guinea pigs caused by neomycin [52]. Moreover, clinical studies in patients with sensorineural hearing defects have revealed that the amount of circulating NGF is relatively lower compared to the level found in normal patients [53]. Therefore, the otoprotective effect of H. erinaceus mycelia enriched with erinacines in rapidly aging mice has been observed [54]. The results indicated that the H. erinaceus mycelium-treated group had significantly lower hearing thresholds according to auditory brainstem responses measured using click sounds and 8 kHz and 16 kHz tone burst sound stimulation when compared with the control group. These findings suggested that H.

erinaceus mycelium diet supplementation was effective in slowing hearing threshold deterioration.

The beneficial activities of H. erinaceus mycelia on age-associated cognitive change and early dementia are summarized in Table 2. Given the fact that all seven of these studies have provided very encouraging findings, it is also of paramount importance that the daily intake of H. erinaceus mycelia in the context of the entire diet is established before the treatment is administere”

-Grape King Bio Ltd, Zhong-Li Dist., Taoyuan City, Taiwan
-Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei City, Taiwan
-Institute of Food Science and Technology, National Taiwan University, Taipei City, Taiwan
-Department of Food Science, Nutrition and Nutraceutical Biotechnology, Shih Chien University, Taipei City, Taiwan
-Institute of Biotechnology, National Changhua University of Education, Changhua, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987239/

Depression

Omega-3 and omega-6 fatty acid levels in depressive and anxiety disorders.

"Blood levels of polyunsaturated fatty acids (PUFAs) have been associated to current depression. However, it is unclear whether this association extends to remitted depression and to anxiety disorders. This study examined the relationship of PUFAs with the presence and clinical characteristics of depressive and anxiety disorders.”

…”It can be concluded that patients with a current depressive episode (especially the more severe cases with comorbid anxiety) have circulating N-3 [omega-3] PUFA levels lower than those in remission and healthy controls."...

-Department of Psychiatry, Amsterdam Public Health Research Institute and Amsterdam Neuroscience, VU University Medical Centre, A.J. Ernststraat 1187, Amsterdam, The Netherlands.
https://www.ncbi.nlm.nih.gov/pubmed/29040890

Crosstalk between endocannabinoid and immune systems: a potential dysregulation in depression?

“The endocannabinoid (eCB) system, an endogenous lipid signaling system, appears to be dysregulated in depression. The role of endocannabinoids (eCBs) as potent immunomodulators, together with the accumulating support for a chronic low-grade inflammatory profile in depression, suggests a compelling hypothesis for a fundamental impairment in their

intercommunication, in depression."…

"Investigations largely report a hypoactivity of the eCB system and increased inflammatory markers in individuals with depression. Findings depict a multifaceted communication whereby immunocompetent and eCB-related cells can both influence the suppression and enhancement of the other's activity in both the periphery and central nervous system. A dysregulation of the eCB system, as seen in depression, appears to be associated with central and peripheral concentrations of inflammatory agents implicated in the pathophysiology of this illness."…

"The eCB and immune systems have been individually associated with and implicated in pathogenic mechanisms of depression. Both systems tightly regulate the other's activity. As such, a dysregulation in this crosstalk has potential to influence the onset and maintenance of this neuropsychiatric illness. However, few studies have investigated both systems and depression conjointly. This review highlights the demand to consider joint eCB-immune interactions in the pathoetiology of depression."…

-Stress, Psychiatry and Immunology Laboratory, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4828487/

So depression is an inflammatory disease, but where does the inflammation come from?

"We now know that depression is associated with a chronic, low-grade inflammatory response and activation of cell-mediated immunity, as well as activation of the compensatory anti-inflammatory reflex system. It is similarly accompanied by increased oxidative and nitrosative stress (O&NS), which contribute to neuroprogression in the disorder. The obvious question this poses is 'what is the source of this chronic low-grade inflammation?'

Discussion

This review explores the role of inflammation and oxidative and nitrosative stress as possible mediators of known environmental risk factors in depression, and discusses potential implications of these findings. A range of factors appear to increase the risk for the development of depression, and seem to be associated with systemic inflammation; these include psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental cares, sleep and vitamin D deficiency."

Summary

The identification of known sources of inflammation provides support for inflammation as a mediating pathway to both risk and neuroprogression in depression. Critically, most of these

factors are plastic, and potentially amenable to therapeutic and preventative interventions. Most, but not all, of the above mentioned sources of inflammation may play a role in other psychiatric disorders, such as bipolar disorder, schizophrenia, autism and post-traumatic stress disorder."

-IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC, Australia
-Department of Psychiatry, University of Melbourne, Parkville, VIC, Australia
-School of Public health and Preventive Medicine, Monash University, Melbourne, VIC, Australia
-NorthWest Academic Centre, Department of Medicine, The University of Melbourne, St Albans, VIC, Australia
-Melbourne School of Psychological Sciences, University of Melbourne, Parkville, VIC, Australia
-Department of Psychiatry, Chulalongkorn University, Rama Road, Bangkok, Thailand
https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-11-200

Modulation of the Serotonin System by Endocannabinoid Signaling

"The cannabinoid CB1 receptors and their endogenous agonists, endocannabinoids (eCBs), are ubiquitously distributed throughout the central nervous system (CNS), where they play a key role in the regulation of neuronal excitability. As such, CB signaling has been implicated in the regulation of a myriad of physiological functions ranging from feeding homoeostasis to emotional and motivational processes. Ample evidence from behavioral studies also suggests that eCBs are important regulators of stress responses and a deficit in eCB signaling contributes to stress-related disorders such as anxiety and depression. The eCB-induced modulation of stress-related behaviors appears to be mediated, at least in part, through the regulation of the serotoninergic system. In this article, we review the role of eCB signaling in the regulation of the serotoninergic system with special emphasis on the cellular mechanisms by which cannabinoid CB1 receptors modulate the excitability of dorsal raphe serotonin neurons."…

-Research Institute on Addictions, University at Buffalo, State University of New York, Buffalo, New York
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110547/

Arachidonic acid [omega-6] to eicosapentaenoic acid [omega-3] ratio in blood correlates positively with clinical symptoms of depression.

"In this study of 20 moderately to severely depressed patients, diagnosed using current research diagnostic criteria and excluding known bipolar affective disorder and reactive depression, we investigated relationships between severity of depression and levels and ratios of n-3 and n-6 long-chain polyunsaturated fatty acids (PUFA) in plasma and erythrocyte phospholipids (PL). Severity of depression was measured using the 21-item Hamilton depression rating scale (HRS) and a second linear rating scale (LRS) of severity of depressive symptoms that omitted anxiety

symptoms. There was a significant correlation between the ratio of erythrocyte PL arachidonic acid (AA) [omega-6] to eicosapentaenoic acid (EPA) [omega-3] and severity of depression as rated by the HRS ($P < 0.05$) and the LRS for depression ($P < 0.01$). There was also a significant negative correlation between erythrocyte EPA and the LRS ($P < 0.05$). The AA/EPA ratio in plasma PL and the ratio of erythrocyte long-chain (C20 and C22 carbon) n-6 to long-chain n-3 PUFA were also significantly correlated with the LRS ($P < 0.05$). These findings do not appear to be simply explained by differences in dietary intake of EPA. We cannot determine whether the high ratios of AA/EPA in both plasma and erythrocyte PL are the result of depression or whether tissue PUFA change predate the depressive symptoms. We suggest, however, that our findings provide a basis for studying the effect of the nutritional supplementation of depressed subjects, aimed at reducing the AA/EPA ratio in tissues and severity of depression."

-Central Region Mental Health Service, Rockhampton Base Hospital, Queensland, Australia.
https://www.ncbi.nlm.nih.gov/pubmed/8729112/

The potential for military diets to reduce depression, suicide, and impulsive aggression: a review of current evidence for omega-3 and omega-6 fatty acids

"The current burden of psychological distress and illness poses as a significant barrier to optimal force efficacy. Here we assess nutrients in military diets, specifically highly unsaturated essential fatty acids, in the reduction of risk or treatment of psychiatric distress. Moderate to strong evidence from several meta-analyses of prospective cohort trials indicate that Mediterranean diet patterns reduce risk of clinical depressions. Specific nutrients and foods of biological interest in relation to mental health outcomes are then discussed and evaluated. Moderate evidence indicates that when fish consumption decreases and simultaneously omega-6 increases, the risk of clinical depressive symptoms are elevated. One meta-analysis examining tissue compositions provides moderate to strong evidence that higher levels of omega-3 highly unsaturated fatty acids (HUFAs) (eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid) are associated with decreased risk of clinical depressions. Other meta-analytic reviews of randomized placebo-controlled trials provide moderate to strong evidence of significantly improving clinically depressive symptoms when the formulation given was >50% in eicosapentaenoic acid. Finally, a meta-analysis of omega-3 HUFAs provides modest evidence of clinical efficacy for attention-deficit hyperactivity disorder. This article recommends that a rebalancing of the essential fatty acid composition of U.S. military diets, achieve tissue compositions of HUFAs consistent with traditional Mediterranean diets, may help reduce military psychiatric distress and simultaneously increase force efficacy substantially."

-Section of Nutritional Neurosciences, Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD USA.
https://pubmed.ncbi.nlm.nih.gov/25373095/

The role of inflammation in core features of depression: Insights from paradigms using exogenously-induced inflammation

"A wealth of evidence has implicated inflammation in the development of depression. Yet, the heterogeneous nature of depression has impeded efforts to understand, prevent, and treat the disease. The purpose of this integrative review is to summarize the connections between inflammation and established core features of depression that exhibit more homogeneity than the syndrome itself: exaggerated reactivity to negative information, altered reward processing, decreased cognitive control, and somatic syndrome. For each core feature, we first provide a brief overview of its relevance to depression and neurobiological underpinnings, and then review evidence investigating a potential role of inflammation. We focus primarily on findings from experimental paradigms of exogenously-induced inflammation. We conclude that inflammation likely plays a role in exaggerated reactivity to negative information, altered reward reactivity, and somatic symptoms. There is less evidence supporting an effect of inflammation on cognitive control as assessed by standard neuropsychological measures. Finally, we discuss implications for future research and recommendations for how to test the role of inflammation in the pathogenesis of heterogeneous psychiatric disorders."

-SEE Change Institute, Los Angeles, CA 90291 USA
-Department of Psychology & Social Behavior, University of California Irvine, Irvine, CA 92697 USA
-Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience & Human Behavior, University of California Los Angeles, Los Angeles, CA 90095 USA
-Department of Psychology, University of California Los Angeles, Los Angeles, CA 90095 USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6192535

Mast Cells, Astrocytes, Arachidonic Acid: Do They Play a Role in Depression?

"Evidence support that brain membrane fatty acids play a crucial role in psychopathologies such as depression and anxiety disorders. Although the pathogenesis of depression is not still defined, drugs commonly used to reduce arachidonic turnover in the brain can control mood disorders, such as depression. Both astrocytes and mast cells release arachidonic acid during silent inflammation. Here, we hypothesize that arachidonic acid [omega-6] freed from lipid droplets of mast cells, as well as the one released from activated astrocytes, could contribute to characterize a depressive condition, and the fatty acids profile of mast cells, astrocytes and

microglia could also vary, reflecting the pathophysiological depressive state of the subject. Finally, there is evidence that gut microbiota is deeply implicated in mood and behavioral disorders. Human gut microbiota can control nervous system diseases through neuroimmune pathways."…

-Department of Pharmaceutical Sciences, University of Perugia, Italy
-Department of Veterinary Medical Sciences, University of Bologna, Italy
https://www.mdpi.com/2076-3417/10/10/3455/htm

Food for Mood: Relevance of Nutritional Omega-3 Fatty Acids for Depression and Anxiety

"The central nervous system (CNS) has the highest concentration of lipids in the organism after adipose tissue. Among these lipids, the brain is particularly enriched with polyunsaturated fatty acids (PUFAs) represented by the omega-6 (ω6) and omega-3 (ω3) series. These PUFAs include arachidonic acid (AA) and docosahexaenoic acid (DHA), respectively. PUFAs have received substantial attention as being relevant to many brain diseases, including anxiety and depression. This review addresses an important question in the area of nutritional neuroscience regarding the importance of ω3 PUFAs in the prevention and/or treatment of neuropsychiatric diseases, mainly depression and anxiety. In particular, it focuses on clinical and experimental data linking dietary intake of ω3 PUFAs and depression or anxiety. In particular, we will discuss recent experimental data highlighting how ω3 PUFAs can modulate neurobiological processes involved in the pathophysiology of anxiety and depression. Potential mechanisms involved in the neuroprotective and corrective activity of ω3 PUFAs in the brain are discussed, in particular the sensing activity of free fatty acid receptors and the activity of the PUFAs-derived endocannabinoid system and the hypothalamic–pituitary–adrenal axis."

-NutriNeuro: Integrated Nutrition and Neurobiology Laboratory, National Institute of Agronomic Research, University of Bordeaux, Bordeaux, France
-Edited by: Céline Cruciani-Guglielmacci, Paris Diderot University, France
-Reviewed by: Stephanie Fulton, University of Montréal, Canada;
-Ameer Taha, University of California, Davis, United States
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6087749/

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"In the last decade, emerging and persuasive evidence reveals that inflammation may play an important role in the pathogenesis of both clinical depression and chronic pain syndromes.[1,2] This common denominator may partially explain why patients with pain are more prone to develop clinical depression and vice versa."…
-By Michael R. Clark, MD, MPH, MBA

https://www.practicalpainmanagement.com/treatments/pharmacological/chronic-pain-depression-why-antidepressants-treat-both

Mechanisms linking inflammation and depression

…"Inflammation is a key component of the innate immune system's ability to clear infection and repair injured tissue. Inflammation results from the release of proinflammatory cytokines from innate immune cells. In addition to their effects in the periphery, cytokines can communicate with the brain and result in a host of emotional, cognitive, and behavioral changes collectively termed "sickness behaviors" (Dantzer et al., 2008). Of particular relevance for this review, peripheral inflammation has been shown to induce depressive-like behaviors in animal models, including anhedonia (e.g., reduced sucrose consumption), decreases in exploratory, novelty-seeking and social behaviors, reduced food intake; and sleep disturbance (Anisman and Matheson, 2005; De La Garza, 2005; Dunn et al., 2005; Larson and Dunn, 2001; Pecchi et al., 2009). These sickness behaviors are considered an adaptive response intended to reduce the spread of infection and promote healing. However, prolonged inflammatory signaling, such as when the inflammatory response is maintained by ongoing psychosocial stress, can have detrimental effects that include risk for depression and other psychiatric diseases (Dantzer et al., 2008; Miller et al., 2009; Miller and Raison, 2016; Slavich and Irwin, 2014).

Research conducted over the last several decades has elucidated the mechanisms by which peripheral inflammation can access the brain to influence neural processes relevant for depression, including neuroplasticity, neurotransmitter systems, and neuroendocrine function (see Banks and Erickson, 2010; Haroon et al., 2012 for comprehensive reviews on this topic). For example, inflammatory cytokines can alter neuroplasticity by decreasing expression of the brain-derived neuroprotective hormone BDNF (Calabrese et al., 2014). Inflammation can also lead to changes in dopaminergic systems, with relevance for depression (See Felger, 2017 for review). "…

Inflammation and depression in humans: experimental paradigms

"There is a growing body of evidence in humans that inflammation plays a role in the pathogenesis of depression. Markers of inflammation are elevated in depressed individuals (Dowlati et al., 2010; Haapakoski et al., 2015; Howren et al., 2009) and predict increases in depressive symptoms in longitudinal studies (Gimeno et al., 2009; Valkanova et al., 2013; van den Biggelaar et al., 2007; Wium-Andersen et al., 2013).

Similarly, recent data from a study of twin pairs—which holds constant shared genetic and early environmental factors—showed that the twin with higher CRP concentrations at baseline was more likely to develop depression five years later (Huang et al., 2017). Yet, there is also evidence that the inflammation-depression pathway is bidirectional as depressive symptoms predict increases in inflammation in some samples (Huang et al., 2017; Matthews et al., 2010; Stewart et al., 2009). Experimental paradigms,

such as those using exogenously-induced inflammation, are needed to inform our understanding of the directional pathways between inflammation and depression.

Causal evidence in humans supporting a role for inflammation in core features of depression comes from studies administering an inflammatory challenge and examining subsequent changes in cognitive and behavioral functioning. Three predominant models have been used to this end: vaccination, endotoxin, and interferon-α (IFN-α) therapy. The results of studies using these paradigms will be the focus of the present review. Key features and evidence from these three models will be discussed below; Table 1 also provides a summary of the key characteristics of each of these models."

-SEE Change Institute, Los Angeles, CA 90291 USA

-Department of Psychology & Social Behavior, University of California Irvine, Irvine, CA 92697 USA

-Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience & Human Behavior, University of California Los Angeles, Los Angeles, CA 90095 USA

-Department of Psychology, University of California Los Angeles, Los Angeles, CA 90095 USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6192535/

…"Based on the links between depression and inflammation [13-14], it is reasonable to expect that dietary n-3 and n-6 intake could be associated with depression. In fact, epidemiological studies have demonstrated significant inverse relationships between annual fish consumption and major depression—the more fish eaten, the lower the prevalence of serious clinical depression [30]. A number of researchers have shown that depressed patients have, on average, lower plasma levels of n-3 than nondepressed individuals; furthermore, they have found evidence that greater severity of depression is linked to lower levels of n-3 [31]. What is more, a number of well-controlled depression treatment studies have found therapeutic benefits following n-3 supplementation, although there are also exceptions [31]. Thus, these dietary pathways have implications for both behavior and inflammation."…

"Furthermore, another study with older adults suggested that depressive symptoms and n-6:n-3 ratios worked together to enhance inflammation beyond the contribution provided by either variable alone (28). Although predicted cytokine levels were fairly consistent across n-6:n-3 ratios with low depressive symptoms, higher n-6:n-3 ratios were associated with progressively elevated TNF-α and IL-6 levels as depressive symptoms increased. Accordingly, these studies (26, 28) suggest that diet can influence the magnitude of inflammatory responses to stress and depression as well as mood."

-Janice K. Kiecolt-Glaser, Ph.D.

-Department of Psychiatry and The Ohio State Institute for Behavioral Medicine Research, The Ohio State University

College of Medicine, Columbus, Ohio;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2868080

Food for Mood: Relevance of Nutritional Omega-3 Fatty Acids for Depression and Anxiety

"The central nervous system (CNS) has the highest concentration of lipids in the organism after adipose tissue. Among these lipids, the brain is particularly enriched with polyunsaturated fatty acids (PUFAs) represented by the omega-6 (ω6) and omega-3 (ω3) series. These PUFAs include arachidonic acid (AA) and docosahexaenoic acid (DHA), respectively. PUFAs have received substantial attention as being relevant to many brain diseases, including anxiety and depression. This review addresses an important question in the area of nutritional neuroscience regarding the importance of ω3 PUFAs in the prevention and/or treatment of neuropsychiatric diseases, mainly depression and anxiety. In particular, it focuses on clinical and experimental data linking dietary intake of ω3 PUFAs and depression or anxiety. In particular, we will discuss recent experimental data highlighting how ω3 PUFAs can modulate neurobiological processes involved in the pathophysiology of anxiety and depression. Potential mechanisms involved in the neuroprotective and corrective activity of ω3 PUFAs in the brain are discussed, in particular the sensing activity of free fatty acid receptors and the activity of the PUFAs-derived endocannabinoid system and the hypothalamic–pituitary–adrenal axis."

-UMR 1286, NutriNeuro: Integrated Nutrition and Neurobiology Laboratory, National Institute of Agronomic Research, University of Bordeaux, Bordeaux, France
https://www.frontiersin.org/articles/10.3389/fphys.2018.01047/full

■■■

…"There is increasing evidence that DHA specifically plays a significant role in neurological development and disease prevention. DHA is an important component of brain development, and DHA deficiencies have been found in patients with neurological conditions. For example, there is a strong correlation between depression and DHA deficiency (Horrocks and Yeo 1999)."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

See also Glial Cells , Psychiatric Disorders , Sickness Behavior

Depression in the Elderly

The Role of Physical Exercise and Omega-3 Fatty Acids in Depressive Illness in the Elderly.

BACKGROUND: In adulthood, depression is the most common type of mental illness and will be the second leading cause of disease by 2020. Major depression dramatically affects the function of the central nervous system and degrades the quality of life, especially in old age. Several mechanisms underlie the pathophysiology of depressive illness, since it has a multifactorial etiology. Human and animal studies have demonstrated that depression is mainly associated with imbalances in neurotransmitters and neurotrophins, hypothalamic-pituitary-adrenal axis alterations, brain volume changes, neurogenesis dysfunction, and dysregulation of inflammatory pathways. Also the gut microbiota may influence mental health outcomes. Although depression is not a consequence of normal aging, depressive disorders are common in later life, even if often undiagnosed or mis-diagnosed in old age. When untreated, depression reduces life expectancy, worsens medical illnesses, enhances health care costs and is the primary cause of suicide among older people. To date, the underpinnings of depression in the elderly are still to be understood, and the pharmacological treatment is the most commonly used therapy.

OBJECTIVE: Since a sedentary lifestyle and poor eating habits have recently emerged as crucial contributors to the genesis and course of depression, in the present review, we have focused on the effects of physical activity and omega-3 fatty acids on depressive illness in the elderly.

RESULTS: A growing literature indicates that both exercise and dietary interventions can promote mental health throughout one's lifespan.

CONCLUSION: There thus emerges the awareness that an active lifestyle and a balanced diet may constitute valid low-cost prevention strategies to counteract depressive illness in the elderly."

-Institute of Cell Biology and Neurobiology, CNR/Fondazione Santa Lucia, Via del Fosso di Fiorano 64, Rome, Italy.

-Laboratory of Experimental and Behavioral Neurophysiology, Fondazione Santa Lucia, Via del Fosso di Fiorano 64, Rome, Italy.

-Department of Psychology, University Sapienza of Rome, Via dei Marsi 78, Rome, Italy.

https://www.ncbi.nlm.nih.gov/pubmed/28901279

Protection against Depressive Symptoms

…"Depression is the most frequently occurring psychiatric comorbidity, with prevalence in Alzheimer's, Parkinson's, and stroke as high as 87%, 75%, and 79%, respectively [44]. Prior data has shown that levels of NGF are significantly lower in patients with major depressive disorder than

in healthy subjects [45]. H. erinaceus mycelia enriched with erinacines, which are involved in the creation of the neurotrophic factors, are thereby hypothesized to play a role in depression.

In animal models, chronic restraint stress is known to cause decreased BDNF expression in the hippocampus and depression-like behaviors [46]. Hence, alleviation of H. erinaceus mycelia enriched with erinacines in animals subjected to repeated chronic stress was examined [47]. Two weeks of treatment with H. erinaceus mycelia have reduced the immobility time in the tail suspension test and forced swimming test as well as decreased the number of entries and the time spent in the open arm. In addition, restraint-induced low levels of norepinephrine, dopamine, serotonin, high interleukin-6, and tumor necrosis factor-α in the hippocampus were completely reversed by H. erinaceus mycelium administration. Furthermore, H. erinaceus mycelium was shown to activate the BDNF pathways and block NF-κB signals in mice. Hence, these results indicate that H. erinaceus mycelia could be an attractive agent for the treatment of depressive disorders through the modulation of monoamine neurotransmitters and proinflammatory cytokines as well as the regulation of brain-derived neurotrophic factor (BDNF) pathways."

-Grape King Bio Ltd, Zhong-Li Dist., Taoyuan City, Taiwan
-Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei City, Taiwan
-Institute of Food Science and Technology, National Taiwan University, Taipei City, Taiwan
-Department of Food Science, Nutrition and Nutraceutical Biotechnology, Shih Chien University, Taipei City, Taiwan
-Institute of Biotechnology, National Changhua University of Education, Changhua, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987239/

Developmental Disorders

Neuro-Inflammatory Mechanisms in Developmental Disorders Associated with Intellectual Disability and Autism Spectrum Disorder: A Neuro- Immune Perspective

"Intellectual disability (ID) and autism are present in several neurodevelopmental disorders and are often associated in genetic syndromes, such as Fragile X and Rett syndromes. While most evidence indicates that a genetic component plays an important role in the aetiology of both autism and ID, a number of studies suggest that immunological dysfunctions may participate in the pathophysiology of these disorders. Brain-specific autoantibodies have been detected in the sera of many autistic children and autoimmune disorders are increased in families of children with autism. Furthermore, cytokine imbalance has been reported in children with autism. These results may reflect an inappropriate immune response to environmental factors, such as

infectious or toxic exposure. The role of microglia as sensors of pre- and post-natal environmental stimuli and its involvement in the regulation of synaptic connectivity, maturation of brain circuitry and neurogenesis has recently emerged. An abnormal immune response during critical windows of development and consequent abnormal production of neuro-inflammatory mediators may have an impact on the function and structure of brain and can play a role in the pathogenesis of non syndromic autism. Recent evidence suggests an involvement of neuro-inflammation also in syndromic forms of autism and ID. Immune dysregulation has been found in children with Fragile X syndrome and an intrinsic microglia dysfunction has been recently reported in Rett syndrome. The present review summarizes the current literature suggesting that neuro-inflammatory mechanisms may contribute to the pathogenesis of different ID- and autism-associated disorders, thus representing common pathophysiological pathways and potential therapeutic targets."

-Institute of Neurological Science, CNR, Italy.
https://pubmed.ncbi.nlm.nih.gov/26996174/

Diabetes Type 1

Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes.

"Dietary intake of omega-3 fatty acids is associated with reduced risk of IA [islet autoimmunity] in children at increased genetic risk for type 1 diabetes."

Department of Preventive Medicine and Biostatistics, University of Colorado at Denver and Health Sciences Center, Denver, CO

https://www.ncbi.nlm.nih.gov/pubmed/17895458

The "Perfect Storm" for Type 1 Diabetes

"In the case of type 1 diabetes, evidence for a synergism between aberrant intestinal microbiota, a "leaky" intestinal mucosal barrier [leaky gut], and altered mucosal immunity contributing to the disorders pathogenesis has begun to evolve."

Laboratory for Immunobiology, Department of Viral Diseases and Immunology, National Public Health Institute
Department of Clinical and Experimental Medicine, Division of Pediatrics and Diabetes Research Center
Department of Pathology, University of Florida College of Medicine
https://www.ncbi.nlm.nih.gov/pubmed/18820210

■■■

…"Mammalian cells have machinery, the socalled Endocannabinoid system (ECS), to produce and metabolize their own cannabinoids in order to control homeostasis of the gut in a rapidly adapting manner."…

-Division of Gastroenterology, Department of Medicine, University of Calgary
http://www.ncbi.nlm.nih.gov/pubmed/22111567

See also Endocannabinoid System

Diabetes Type 2

Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus

…"Taken together, adipose tissue inflammation is a key factor in the development of insulin resistance and type 2 diabetes in obesity, along with other factors that likely include inflammation and fat accumulation in other metabolically active tissues."…

-Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA
-Departments of Epidemiology
-Departments of Medicine, University of Washington, Seattle, WA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6557583/

■■■

…"We conclude that platelets obtained from some diabetic subjects manifest increased metabolism of arachidonic acid [omega-6] to labile aggregating substances which may contribute to the enhanced platelet aggregation."

- Hormone and Metabolic Research
- P V Halushka, R C Rogers, C B Loadholt, H Wohltman, R Mayfield, S McCoy, J A Colwell
https://pubmed.ncbi.nlm.nih.gov/7033097

Alteration in the balance of prostaglandin and thromboxane synthesis in diabetic rats

…"The changes observed both in platelet and vascular metabolism of arachidonic acid [omega-6] were corrected by islet issue transplantation, suggesting a disease-specific effect. The changes

observed in arachidonic acid metabolism suggest a significant imbalance in thromboxane A2 and PGI2 production in diabetic rats. Such changes might promote the development of the microvascular changes seen in diabetes mellitus."

- The Journal of Laboratory and Clinical Medicine (June 1980)
- J M Gerrard, M J Stuart, G H Rao, M W Steffes, S M Mauer, D M Brown, J G White
https://pubmed.ncbi.nlm.nih.gov/6445927

Insulin and arachidonic acid metabolism in diabetes mellitus

"Vascular prostacyclin synthesis is decreased in both patients and experimental animals with diabetes mellitus. Treatment of experimental animals with insulin reverses the decreased synthesis of prostacyclin. The etiology of the altered arachidonic acid metabolism remains uncertain but appears to be multifactorial and includes alterations in metabolic control and circulating immune complexes. The increased ratio of thromboxane A2 to prostacyclin, which favors an enhanced thrombotic state, may play a role in the accelerated vascular disease of diabetes mellitus."

- Metabolism: Clincal and Experiemental (December 1985)
- P V Halushka, R Mayfield, J A Colwell
https://pubmed.ncbi.nlm.nih.gov/3934501

Prostacyclin is a compound of the prostaglandin type produced in arterial walls, which functions as an anticoagulant and vasodilator. *- Oxford Languages / Google*

Effect of insulin treatment on prostacyclin in experimental diabetes

"Diabetic patients have a high susceptibility to microvascular complications, atherosclerosis and thrombosis. Platelet hyperreactivity possibly related to an imbalance in arachidonic acid metabolism may be involved. Aortic rings or renal cortex produced a potent inhibitor of platelet aggregation, identified as prostacyclin (PGI2). Release of PGI2 by tissues from streptozotocin -- diabetic rats (aorta: 0.07 +/ 0.1 ng/mg wet weight; renal cortex 0.004 +/- 0.001 ng/mg wet weight) was significantly depressed when compared with controls (aorta: 0.26 +/- 0.07 ng/mg wet weight; renal cortex: 0.009 +/- 0.001 ng/mg wet weight). Treatment of diabetic animals with insulin for 8 days restored PGI2 production to normal. The finding that PGI2 is depressed in the

aorta and in the kidney, tissues which develop angiopathy, and that this is normalised by insulin, suggests that impaired PGI2 production, perhaps associated with platelet hyperreactivity may play a role in the vascular complications of diabetes."

- Diabetologia (January 1980)
- H E Harrison, A H Reece, M Johnson
https://pubmed.ncbi.nlm.nih.gov/6988267

Meat Consumption as a Risk Factor for Type 2 Diabetes

"Diabetes prevalence increased as the frequency of meat consumption increased."…
"Meat consumption is consistently associated with diabetes risk. Dietary habits are readily modifiable, but individuals and clinicians will consider dietary changes only if they are aware of the potential benefits of doing so. The foregoing review indicates that the identification of meat consumption as a risk factor for diabetes provides helpful guidance for clinicians and at-risk individuals, and sets the stage for beneficial behavioral changes."

-Physicians Committee for Responsible Medicine,
-The George Washington University School of Medicine
-Nutrition Education, Physicians Committee for Responsible Medicine
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3942738

See also Endocannabinoid System

Diabetes Type 3

…"The modulation of the endocannabinoid system in the development of SAD [sporadic Alzheimer's disease] was not investigated yet, but using STZ [injection of streptozotocin] intraperitoneally as a model for neuropathic diabetes, it was observed an increase in the hippocampal levels and activation of CB1R (Duarte et al., 2007). The endocannabinoid system seems to be involved in cerebral glucose metabolism as well, given that CB2R [cannabinoid 2 receptor] participate in neuronal glucose uptake, mediated by AEA (Köfalvi et al., 2016). In accordance with the tight connection between glucose metabolism and AD [Alzheimer's disease], which is argued to be a type 3 diabetes (De Felice, 2013; Ahmed et al., 2015), this STZ-induced AD-like sporadic dementia model seems suitable to study the endocannabinoid modulation of cognitive and molecular aspects of SAD."…

-Center for Mathematics, Computing and Cognition, Universidade Federal do ABC, São Bernardo do Campo, Brazil
-Center for Natural and Human Sciences, Universidade Federal do ABC, São Bernardo do Campo, Brazil
-Faculty of Medicine, University of Coimbra, Coimbra, Portugal

-Center for Neuroscience and Cell Biology (CNC), University of Coimbra, Coimbra, Portugal

-Edited by: Fabricio A. Pamplona, Entourage Phytolab, Brazil

-Reviewed by: Salim Yalcin Inan, Meram Faculty of Medicine, Turkey; Mychael V. Lourenco, Universidade Federal do Rio de Janeiro, Brazil; Vincenzo Micale, Università di Catania, Italy; Grasielle Clotildes Kincheski, Universidade Federal do Rio de Janeiro, Brazil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6176656

See also Endocannabinoid System

Dialysis

"The clinical purification of blood by dialysis, as a substitute for the normal function of the kidney." *- Oxford Languages / Google*

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"Mortality among long-term hemodialysis patients is high, mostly attributed to cardiovascular events, and may be related to chronic inflammation. We hypothesized that the anti-inflammatory benefits of higher dietary omega-3, compared to omega-6, poly-unsaturated fatty acids may modulate the inflammatory processes and reduce death risk."….

"**Conclusions:** Higher dietary omega-6 to omega-3 ratio appears associated with both worsening inflammation over time and a trend towards higher death risk in hemodialysis patients. Additional studies including interventional trials are needed to examine the association of dietary fatty acids with clinical outcomes in these patients."…

-Nazanin Noori, MD, PhD, Ramanath Dukkipati, MD, Csaba P. Kovesdy, MD, John J. Sim, MD, Usama Feroze, MD, Sameer B. Murali, MD, Rachelle Bross, RD, PhD, Debbie Benner, RD, Joel D Kopple, MD, and Kamyar Kalantar-Zadeh, MD, MPH, PhD

-Harold Simmons Center for Chronic Disease Research and Epidemiology

-Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA 90502

-David Geffen School of Medicine at UCLA and the UCLA School of Public Health, Los Angeles, CA

-Salem Veterans Affairs Medical Center, Salem, VA

-DaVita Inc, El Segundo, CA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3144295

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…"Omega-3 fatty acids relatively improved systemic inflammation of chronic HD [hemodialysis] patients without any prominent benefits on anemia. However, future well-designed studies on

larger number of patients may determine utility of omega-3 fatty acids in HD patients with respect to inflammation and anemia."…

…"On the other hand, **dialysis patients have a chronic inflammatory state** which may contribute to iron-restricted erythropoiesis via decreasing the mobilization of iron from the reticulo-endothelial system to circulating transferrin, a situation which is associated with the reduced response to ESA therapy and IV iron supplementation [1,3,6]. "…

-Resident of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
-Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran
-Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
-Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran
-Department of Epidemiology, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran , Iran
-Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3922959

Blood Fatty Acid Status and Clinical Outcomes in Dialysis Patients: A Systematic Review

…"Dialysis patients having altered blood FA [fatty acids] profiles present with increased MUFA and reduced PUFA levels. The available evidence suggests that low levels of circulating PUFAs were associated with increased risks of CV events and mortality in dialysis patients. Therefore, it is necessary to establish a reference range for blood PUFA profile in these patients, which can be used as a biomarker for risk assessment. As the FA composition in blood is influenced by dietary intakes, medical nutrition therapy for dialysis patients should also include dietary modifications that ensure adequate consumptions of essential FA, particularly n-3 PUFA. Most studies available have focused on HD patients and only a few included PD patients, suggesting that more research related to blood FA profiles in PD patients is warranted."

-Dietetics Program, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia;
-School of Biosciences, Faculty of Health and Medical Sciences, Taylor's University, Subang Jaya , Malaysia;
-School of Medicine, Faculty of Health and Medical Sciences, Taylor's University, Subang Jaya, Malaysia;
-Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia;
-Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia;
-Department of Nutrition and Food Science, Wayne State University, Detroit, MI, USA
-Malaysian Palm Oil Council, Kelana Jaya, Malaysia;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6213187/

Diarrhea

"Diarrhea kills 2,195 children every day—more than AIDS, malaria, and measles combined. Diarrheal diseases account for 1 in 9 child deaths worldwide, making diarrhea the second leading cause of death among children under the age of 5."

-*Center for Disease Control (CDC)*

https://www.cdc.gov/healthywater/pdf/global/programs/Globaldiarrhea508c.pdf

Infants fed formula with added long chain polyunsaturated fatty acids have reduced incidence of respiratory illnesses and diarrhea during the first year of life.

"Long chain polyunsaturated fatty acids (LCPUFAs) may influence the immune system. Our objective was to compare the frequency of common illnesses in infants who received formula with or without added LCPUFAs."

…"In healthy infants, formula with DHA/ARA [docosahexaenoic acid / arachidonic acid] was associated with lower incidence of common respiratory symptoms and illnesses, as well as diarrhea."

-Department of Medical Affairs, Clinical Research, Mead Johnson Nutrition, Evansville, USA.
https://www.ncbi.nlm.nih.gov/pubmed/24989353

Inhibiting fatty acid amide hydrolase normalizes endotoxin-induced enhanced gastrointestinal motility in mice.

"Inhibiting FAAH normalizes various parameters of GI dysmotility in intestinal pathophysiology. Inhibition of FAAH represents a new approach to the treatment of disordered intestinal motility."

-Hotchkiss Brain Institute and Snyder Institute of Infection, Immunity & Inflammation, Department of Physiology & Pharmacology, University Calgary, Calgary, AB, Canada.
https://www.ncbi.nlm.nih.gov/pubmed/21883147

Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome.

"In patients with IBS with diarrhea or alternating, dronabinol [synthetic THC] reduces fasting

colonic motility; FAAH and CNR1 variants could influence the effects of this drug on colonic motility."

-Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER)
-College of Medicine, Mayo Clinic, Rochester, Minnesota, USA.
https://www.ncbi.nlm.nih.gov/pubmed/21803011

Diet

Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases

"Anthropological and epidemiological studies and studies at the molecular level indicate that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of approximately 1 whereas in Western diets the ratio is 15/1 to 16.7/1. A high omega-6/omega-3 ratio, as is found in today's Western diets, promotes the pathogenesis of many diseases, including cardiovascular disease, cancer, osteoporosis, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 polyunsaturated fatty acids (PUFA) (a lower omega-6/omega-3 ratio), exert suppressive effects. Increased dietary intake of linoleic acid (LA) leads to oxidation of low-density lipoprotein (LDL), platelet aggregation, and interferes with the incorporation of EFA in cell membrane phospholipids. Both omega-6 and omega-3 fatty acids influence gene expression. Omega-3 fatty acids have anti-inflammatory effects, suppress interleukin 1beta (IL-1beta), tumor necrosis factor-alpha (TNFalpha) and interleukin-6 (IL-6), whereas omega-6 fatty acids do not. Because inflammation is at the base of many chronic diseases, dietary intake of omega-3 fatty acids plays an important role in the manifestation of disease, particularly in persons with genetic variation, as for example in individuals with genetic variants at the 5-lipoxygenase (5-LO). Carotid intima media thickness (IMT) taken as a marker of the atherosclerotic burden is significantly increased, by 80%, in the variant group compared to carriers with the common allele, suggesting increased 5-LO promoter activity associated with the (variant) allele. Dietary arachidonic acid (AA) and LA increase the risk for cardiovascular disease in those with the variants, whereas dietary intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) decrease the risk. A lower ratio of omega-6/omega-3 fatty acids is needed for the prevention and management of chronic diseases. Because of genetic variation, the optimal omega-6/omega-3 fatty acid ratio would vary with the disease under consideration."

- Dr. Artemis P. Simopoulos M.D
-The Center for Genetics, Nutrition and Health, 4330 Klingle Street NW, 20016 Washington DC, United States
https://pubmed.ncbi.nlm.nih.gov/26950145

Anti-inflammatory Diets

"Chronic disease is driven by inflammation. This article will provide an overview on how the balance of macronutrients and omega-6 and omega-3 fatty acids in the diet can alter the expression of inflammatory genes. In particular, how the balance of the protein to glycemic load of a meal can alter the generation of insulin and glucagon and the how the balance of omega-6 and omega-3 fatty acids can effect eicosanoid formation. Clinical results on the reduction of inflammation following anti-inflammatory diets are discussed as well as the molecular targets of anti-inflammatory nutrition. To overcome silent inflammation requires an anti-inflammatory diet (with omega-3s and polyphenols, in particular those of Maqui). The most important aspect of such an anti-inflammatory diet is the stabilization of insulin and reduced intake of omega-6 fatty acids."…

-Dr Barry Sears
-Inflammation Research Foundation , Marblehead , Massachusetts.
https://pubmed.ncbi.nlm.nih.gov/26400429/

■■■

…"The typical diet that has become widely adopted in many countries over the past 40 years is relatively low in fruits, vegetables and other fiber- and prebiotic-rich foods[66,123–125] and high in refined grains[124], alcohol[126] and ultra-processed foods[125], particularly those containing emulsifiers[127]. These dietary factors can alter the gut microbiota composition and function[123,127–130] and are linked to increased intestinal permeability[129–131] and epigenetic changes in the immune system[129] that ultimately cause low-grade endotoxemia and SCI [Systemic Chronic Inflammation][129–131]. The influence of diet on inflammation is not confined to these effects, though. For example, orally absorbed advanced glycation and lipoxidation end-products that are formed during the processing of foods or when foods are cooked at high temperatures and in low-humidity conditions are appetite increasing and are linked to overnutrition and hence obesity and inflammation[132]. Furthermore, high-glycemic-load foods, such as isolated sugars and refined grains, which are common ingredients in most ultra-processed foods, can cause increased oxidative stress that activates inflammatory genes[133].

Other dietary components that are thought to influence inflammation include trans fatty acids[134] and dietary salt. For example, salt has been shown to skew macrophages toward a pro-inflammatory phenotype characterized by the increased differentiation of naive CD4+ T cells into

T helper (TH)-17 cells, which are highly inflammatory, and decreased expression and anti-inflammatory activity of T regulatory cells[135]. In addition, high salt intake can cause adverse changes in gut microbiota composition, as exemplified by the reduced Lactobacillus population observed in animals and humans fed high-salt diets[135]. This specific population is critical for health as it regulates TH17 cells and enhances the integrity of the intestinal epithelial barrier, thus reducing systemic inflammation[135]. Consistent with the expected health-damaging effects of consuming foods that are high in trans fats and salt, a recent cohort study of [44,551] French adults who were followed for a median of 7.1 years found that a 10% increase in the proportion of ultra-processed food consumption was associated with a 14% greater risk of all-cause mortality[136].

Several other nutritional factors can also promote inflammation and potentially contribute to the development of SCI. These factors include deficiencies in micronutrients, including zinc[137] and magnesium[], which are caused by eating processed or refined foods that are low in vitamins and minerals, and having suboptimal omega-3 levels[139], which impacts the resolution phase of inflammation. Longchain omega-3 fatty acids—especially eicosapentaenoic acid and docosahexaenoic acid—modulate the expression of genes involved in metabolism and inflammation[139]. More importantly, they are precursors to molecules such as resolvins, maresins and protectins that are involved in the resolution of inflammation[28,29]. The main contributors to the growing worldwide incidence of low omega-3 status are a low intake of fish and high intake of vegetable oils that are high in linoleic acid, which displaces omega-3 fatty acids in cell membrane phospholipids[140,141]. In turn, various RCTs have shown that omega-3 fatty acid supplementation reduces inflammation[142–144] and may thus have health-promoting effects[141–144].

Evidence linking diet and mortality is robust. For example, an analysis of nationally representative health surveys and diseasespecific mortality statistics from the National Center for Health Statistics in the United States showed that the dietary risk factors associated with the greatest mortality among American adults in 2005 were high dietary trans fatty acids, low dietary omega-3 fatty acids, and high dietary salt[145]. In addition, a recent systematic analysis of dietary data from [195] different countries identified poor diet as the main risk factor for death in 2017, with excessive sodium intake being responsible for more than half of diet-related deaths[146].

Finally, when combined with low physical activity, consuming hyperpalatable processed foods that are high in fat, sugar, salt and flavor additives[147] can cause major changes in cell metabolism and lead to the increased production (and defective disposal) of dysfunctional organelles such as mitochondria, as well as to misplaced, misfolded and oxidized endogenous molecules[30,60,148]. These altered molecules, which increase with age[19,30], can be recognized as DAMPs by innate immune cells, which in turn activate the inflammasome machinery, amplify the inflammatory

response[1,30,60] and contribute to a biological state that has been called "inflammaging," defined as the "the long-term result of the chronic physiological stimulation of the innate immune system" that occurs in later life[30]. As proposed, inflammaging involves changes in numerous organ systems, such as the brain, gut, liver, kidney, adipose tissue and muscle[19], and it is driven by a variety of molecular-age-related mechanisms that have been called the "Seven Pillars of Aging"[55]—namely, adaptation to stress, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis and stem cells and regeneration."…

-Buck Institute for Research on Aging, Novato, CA, USA.

-Stanford 1000 Immunomes Project, Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, CA, USA.

-Institute for Research in Translational Medicine, Universidad Austral, CONICET, Pilar, Buenos Aires, Argentina.

-Iuve Inc., San Mateo, CA, USA.

-Lawrence Berkeley National Laboratory, Berkeley, CA, USA.

-Center for Primary Health Care Research, Lund University/Region Skåne, Skåne University Hospital, Malmö, Sweden.

-Medical Scientist Training Program, University of California, San Francisco, San Francisco, CA, USA.

-IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy.

-Department of Applied Mathematics and Laboratory of Systems Biology of Aging, Lobachevsky University, Nizhny Novgorod, Russia.

-Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA.

-Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, University College London, London, UK.

-MassGeneral Hospital for Children, Harvard Medical School, Boston, MA, USA.

-Department of Environmental Health Sciences, School of Public Health, Columbia University Medical Center, New York, NY, USA.

-Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA.

-Humanitas Clinical and Research Center, Rozzano, Milan, Italy.

-Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy.

-William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University, London, UK.

-Division of Immunology and Rheumatology, Department of Medicine, Stanford University, Stanford, CA, USA.

-Departments of Medicine and Genetics, Albert Einstein College of Medicine, New York, NY, USA.

-Paul F. Glenn Center for the Biology of Aging, Stanford University School of Medicine, Stanford, CA, USA.

-Center for Tissue Regeneration, Repair and Restoration, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA.

-Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA.

-Department of Pathology, University of California, Los Angeles, Los Angeles, CA, USA.

-Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain.

-Research Institute of the Hospital 12 de Octubre (i+12), Madrid, Spain.

-Biostatistics and Computational Biology Branch, Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA.

-NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA.

-Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147972/

■■■

"The relationship between diet and disease has long been established, with epidemiological and clinical evidence affirming the role of certain dietary fatty acid classes in disease pathogenesis. Within the same class, different fatty acids may exhibit beneficial or deleterious effects, with implications on disease progression or prevention. In conjunction with other fatty acids and lipids, the omega-3, -6 and -9 fatty acids make up the lipidome, and with the conversion and storage of excess carbohydrates into fats, transcendence of the glycome into the lipidome occurs. The essential omega-3 fatty acids are typically associated with initiating anti-inflammatory responses, while omega-6 fatty acids are associated with pro-inflammatory responses. Non-essential, omega-9 fatty acids serve as necessary components for other metabolic pathways, which may affect disease risk. These fatty acids which act as independent, yet synergistic lipid moieties that interact with other biomolecules within the cellular ecosystem epitomize the critical role of these fatty acids in homeostasis and overall health. This review focuses on the functional roles and potential mechanisms of omega-3, omega-6 and omega-9 fatty acids in regard to inflammation and disease pathogenesis. A particular emphasis is placed on cardiovascular disease, the leading cause of morbidity and mortality in the United States."…

-College of Agriculture, Environment and Nutrition Sciences, Tuskegee University, Tuskegee, Alabama, USA
-Department of Biology, Tuskegee University, Tuskegee, Alabama, USA
https://www.longdom.org/open-access/omega-omega-and-omega-fatty-acids-implications-for-cardiovascular-and-other-diseases-2153-0637.1000123.pdf

http://bit.do/diet369

A systemic review of the roles of n-3 fatty acids in health and disease

"Attention to the role of n-3 long-chain fatty acids in human health and disease has been continuously increased during recent decades. Many clinical and epidemiologic studies have shown positive roles for n-3 fatty acids in infant development; cancer; cardiovascular diseases; and more recently, in various mental illnesses, including depression, attention-deficit hyperactivity disorder, and dementia. These fatty acids are known to have pleiotropic effects, including effects against inflammation, platelet aggregation, hypertension, and hyperlipidemia. These beneficial effects may be mediated through several distinct mechanisms, including alterations in cell membrane composition and function, gene expression, or eicosanoid production. A number of authorities have recently recommended increases in intakes of n-3

fatty acids by the general population. To comply with this recommendation a variety of food products, most notably eggs, yogurt, milk, and spreads have been enriched with these fatty acids. Ongoing research will further determine the tissue distribution, biological effects, cost-effectiveness, and consumer acceptability of such enriched products. Furthermore, additional controlled clinical trials are needed to document whether long-term consumption or supplementation with eicosapentaenoic acid/docosahexaenoic acid or the plant-derived counterpart (alpha-linolenic acid) results in better quality of life."

-Department of Human Nutritional Sciences, University of Manitoba and Canadian Centre for Agri-Food Research in Medicine, St. Boniface Hospital Research Centre, Winnipeg, MB, Canada.

https://pubmed.ncbi.nlm.nih.gov/19328262

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See supplements for related research quotes.

Diseases of Civilizations

"Nutrition and food are one of the most complex aspects of human lives, being influenced by biochemical, psychological, social and cultural factors. The Western diet is the prototype of modern dietary pattern and is mainly characterized by the intake of large amounts of red meat, dairy products, refined grains and sugar. **Large amounts of scientific evidence positively correlate Western diet to acne, obesity, diabetes, heart disease and cancer, the so-called "diseases of civilization"**. The pathophysiological common ground of all these pathologies is the IGF-1 and mTORC pathways, which will be disscussed further in this paper."

-Victor Gabriel CLATICI, Dermalife Medical Centre, Bucharest, Romania;

-Cristiana VOICU, Dermalife Medical Centre, Bucharest, Romania;

-Catalina VOAIDES, UASVM Bucharest, Faculty of Biotechnologies, Bucharest, Romania;

-Anca ROSEANU, Department of Ligand-Receptor Interaction, Institute of Biochemistry of the Romanian Academy, Bucharest, Romania;

-Madalina ICRIVERZI, Department of Ligand-Receptor Interaction, Institute of Biochemistry of the Romanian Academy, Bucharest, Romania;

-Stefana JURCOANE, UASVM Bucharest, Faculty of Biotechnologies, Bucharest, Romania;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6362881/

Polyunsaturated Fatty Acids and Their Potential Therapeutic Role in

Cardiovascular System Disorders—A Review

“It has been established that PUFAs are required for the normal development and functioning of the brain and heart, and also for the equilibrium of all tissues and organs. Studies concerning the nutritional deficiency of omega-3 fatty acids as well as the particular roles of omega-6 and omega-3 have become the focus of numerous research groups around the world [22,23,24,25,26]. Deficit of omega-6 linoleic acid leads to poor growth, fatty liver, skin lesions, and reproductive failure, while the symptoms of omega-3 fatty acids deficiency include reduced vision or abnormal electroretinogram results. Studies in rodents have revealed significant effects of n-3 PUFAs deficiency on learning, memory, cognition, and behavior [27]. **The literature reports highlight how the increment of the omega-6/omega-3 ratio corresponds to an increase in the occurrence of pro-inflammatory conditions. It is crucial to maintain a proper balance of omega-3 in our bodies, since an excess of omega-6 leads to low grade chronic systemic inflammation—recognized as the leading cause of the so-called civilizational diseases [28,29,30,31,32].**”

-The Lumina Cordis Foundation, Szymanowskiego Street 2/a, 51-609 Wroclaw, Poland; ti.orebil@alokos

-FLC Pharma Ltd., Wroclaw Technology Park Muchoborska Street 18, 54-424 Wroclaw, Poland; -Department of Bioorganic Chemistry, Faculty of Chemistry, University of Technology, Wybrzeze Wyspianskiego Street 27, 50-370 Wroclaw, Poland;

-Institute of Animal Breeding, Faculty of Biology and Animal Sciences, Wroclaw University of Environmental and Life Sciences, Chelmonskiego Street 38c, 50-001 Wroclaw, Poland;

-Institute of Cosmetology, Wroclaw College of Physiotherapy, Kosciuszki 4 Street, 50-038 Wroclaw, Poland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6213446/

How Western Diet And Lifestyle Drive The Pandemic Of Obesity And Civilization Diseases

”Westernized populations are plagued by a plethora of chronic non-infectious degenerative diseases, termed as "civilization diseases", like obesity, diabetes, cardiovascular diseases, cancer, autoimmune diseases, Alzheimer's disease and many more, diseases which are rare or virtually absent in hunter-gatherers and other non-westernized populations. There is a growing awareness that the cause of this amazing discrepancy lies in the profound changes in diet and lifestyle during recent human history. This paper shows that the transition from Paleolithic nutrition to Western diets, along with lack of corresponding genetic adaptations, cause significant distortions of the fine-tuned metabolism that has evolved over millions of years of human evolution in adaptation to Paleolithic diets. With the increasing spread of Western diet and lifestyle worldwide, overweight and civilization diseases are also rapidly increasing in developing countries. It is suggested that the diet-related key changes in the developmental process include an increased production of reactive oxygen species and oxidative stress,

development of hyperinsulinemia and insulin resistance, low-grade inflammation and an abnormal activation of the sympathetic nervous system and the renin-angiotensin system, all of which play pivotal roles in the development of diseases of civilization. In addition, diet-related epigenetic changes and fetal programming play an important role. The suggested pathomechanism is also able to explain the well-known but not completely understood close relationship between obesity and the wide range of comorbidities, like type 2 diabetes mellitus, cardiovascular disease, etc., as diseases of the same etiopathology. Changing our lifestyle in accordance with our genetic makeup, including diet and physical activity, may help prevent or limit the development of these diseases."

Wolfgang Kopp
-Retired Head, Diagnostikzentrum Graz, Austria.
https://pubmed.ncbi.nlm.nih.gov/31695465/

Origins and evolution of the Western diet: health implications for the 21st century

There is growing awareness that the profound changes in the environment (eg, in diet and other lifestyle conditions) that began with the introduction of agriculture and animal husbandry approximately 10000 y ago occurred too recently on an evolutionary time scale for the human genome to adjust. In conjunction with this discordance between our ancient, genetically determined biology and the nutritional, cultural, and activity patterns of contemporary Western populations, many of the so-called diseases of civilization have emerged. In particular, food staples and food-processing procedures introduced during the Neolithic and Industrial Periods have fundamentally altered 7 crucial nutritional characteristics of ancestral hominin diets: 1) glycemic load, 2) fatty acid composition, 3) macronutrient composition, 4) micronutrient density, 5) acid-base balance, 6) sodium-potassium ratio, and 7) fiber content. The evolutionary collision of our ancient genome with the nutritional qualities of recently introduced foods may underlie many of the chronic diseases of Western civilization.

Department of Health and Exercise Science, Colorado State University
https://pubmed.ncbi.nlm.nih.gov/15699220/

Food Diversity and Indigenous Food Systems to Combat Diet-Linked Chronic Diseases

Improving food and nutritional diversity based on the diversity of traditional plant-based foods is

an important dietary strategy to address the challenges of rapidly emerging diet- and lifestyle-linked noncommunicable chronic diseases (NCDs) of indigenous communities worldwide. Restoration of native ecosystems, revival of traditional food crop cultivation, and revival of traditional knowledge of food preparation, processing, and preservation are important steps to build dietary support strategies against an NCD epidemic of contemporary indigenous communities. Recent studies have indicated that many traditional plant-based foods of Native Americans provide a rich source of human health–relevant bioactive compounds with diverse health benefits. Based on this rationale of health benefits of traditional plant-based foods, the objective of this review is to present a state-of-the-art comprehensive framework for ecologically and culturally relevant sustainable strategies to restore and integrate the traditional plant food diversity of Native Americans to address the NCD challenges of indigenous and wider nonindigenous communities worldwide.

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https://doi.org/10.1093/cdn/nzz099

How Western Diet And Lifestyle Drive The Pandemic Of Obesity And Civilization Diseases

“Westernized populations are plagued by a plethora of chronic non-infectious degenerative diseases, termed as “civilization diseases”, like obesity, diabetes, cardiovascular diseases, cancer, autoimmune diseases, Alzheimer's disease and many more, diseases which are rare or virtually absent in hunter-gatherers and other non-westernized populations. There is a growing awareness that the cause of this amazing discrepancy lies in the profound changes in diet and lifestyle during recent human history. This paper shows that the transition from Paleolithic nutrition to Western diets, along with lack of corresponding genetic adaptations, cause significant distortions of the fine-tuned metabolism that has evolved over millions of years of human evolution in adaptation to Paleolithic diets. With the increasing spread of Western diet and lifestyle worldwide, overweight and civilization diseases are also rapidly increasing in developing countries. It is suggested that the diet-related key changes in the developmental process include an increased production of reactive oxygen species and oxidative stress, development of hyperinsulinemia and insulin resistance, low-grade inflammation and an abnormal activation of the sympathetic nervous system and the renin-angiotensin system, all of which play pivotal roles in the development of diseases of civilization. In addition, diet-related epigenetic changes and fetal programming play an important role. The suggested pathomechanism is also able to explain the well-known but not completely understood close relationship between obesity and the wide range of comorbidities, like type 2 diabetes mellitus,

cardiovascular disease, etc., as diseases of the same etiopathology. Changing our lifestyle in accordance with our genetic makeup, including diet and physical activity, may help prevent or limit the development of these diseases."…

"Furthermore, due to agribusiness and modern agriculture, WDs contain excessive amounts of omega-6 polyunsaturated fatty acids (PUFAs) and only small amounts of omega-3 PUFAs, resulting in an unhealthy omega-6/omega-3 ratio of 20: 1 compared to a balanced ratio during the Paleolithic period. The consumption of the omega-6 PUFAs has dramatically increased in the western world primarily in the form of vegetable oils. A diet rich in omega-6 fatty acids is proinflammatory and prothrombotic, and has been implicated in the development of various degenerative diseases, including T2DM, CVD, cancer, obesity inflammatory bowel disease, major depression, Alzheimer's disease and other more."

-Retired Head, Diagnostikzentrum Graz, Austria
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6817492/

Disease Prevention

The role of the ω-3 [omega-3] fatty acid DHA in the human life cycle

"Dietary consumption of the essential fatty acids linoleic acid (LA; ω-6) and α-linolenic acid (ALA; ω-3) is necessary for human growth and development. In the past 150 years, the average Western diet has changed dramatically such that humans today consume a much higher proportion of ω-6 fatty acids relative to ω-3 fatty acids than ever before. The importance of ω-3 fatty acids in human development has been well established in fetal and neonatal development, with brain and retinal tissues highly dependent on ω-3 fatty acids, specifically docosahexaenoic acid (DHA) for membrane fluidity and signal transduction. In childhood, ω-3s have been shown to contribute to ongoing cognitive development and may be involved in metabolic programming of bone turnover and adipogenesis. ω-3s may also play important roles in adult neurophysiology and disease prevention."

-Department of Surgery and the Vascular Biology Program, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA.
https://pubmed.ncbi.nlm.nih.gov/23192455/

DNA (Deoxyribonucleic Acid)

Fish oil omega-3 polyunsaturated fatty acids attenuate oxidative stress-induced DNA damage in vascular endothelial cells

"Our results suggested that EPA and DHA attenuate oxidative stress-induced DNA damage in vascular endothelial cells through upregulation of NRF2-mediated antioxidant response. Therefore omega-3 fatty acids likely help prevent cardiovascular disease, at least in part, by their genome protective properties."

- Department of Cardiovascular Physiology and Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

- Department of Cardiovascular Medicine, Fukushima Medical University, Fukushima, Japan

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5679535/

Metabolism of the Endocannabinoid Anandamide: Open Questions after 25 Years

…"In addition, accumulating evidence points to AEA [anandamide] as a unique natural repressor of gene transcription, via epigenetic mechanisms that include increased DNA methylation (Paradisi et al., 2008), reduced histone acetylation and microRNA (D'Addario et al., 2013). It should be recalled that DNA methylation is a fundamental epigenetic modification of the genome that is involved in a large number of cellular processes, like embryonic development, transcription, chromatin structure, X chromosome inactivation, and genomic imprinting and chromosome stability. Among many other diseases, a role for altered methylation has been established in cancer, for which DNA hypomethylation is a hallmark (Paradisi et al., 2008). Against this background, the potential of AEA as a natural anti-cancer agent appears very promising, and certainly worth of urgent investigations."

-Department of Medicine, Campus Bio-Medico University of Rome, Rome, Italy

-European Center for Brain Research, IRCCS Santa Lucia Foundation, Rome, Italy

-Edited by: Ildikó Ràcz, University Hospital Bonn, Germany

-Reviewed by: John J. Woodward, Medical University of South Carolina, United States

-Meliha Karsak, University Medical Center Hamburg-Eppendorf, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5447297/

See also Cancer & Inflammation

Docosahexaenoic acid (DHA)

docosahexaenoic acid [DHA] - is an omega-3 fatty acid and primary structural component of the human brain, cerebral cortex, skin, and retina thus plays an important role in their development and function.

- U.S National Library of Medicine
https://pubchem.ncbi.nlm.nih.gov/compound/Docosahexaenoic-acid

■■■

..."Thus, DHA is quantitatively the most important omega-3 PUFA in the brain."...
-Faculty of Health and Social Sciences, Bournemouth University, Bournemouth, UK

https://www.frontiersin.org/articles/10.3389/fnagi.2015.00052/full

DHA Effects in Brain Development and Function

"Docosahexaenoic acid (DHA) is a structural constituent of membranes specifically in the central nervous system. Its accumulation in the fetal brain takes place mainly during the last trimester of pregnancy and continues at very high rates up to the end of the second year of life. Since the endogenous formation of DHA seems to be relatively low, DHA intake may contribute to optimal conditions for brain development. We performed a narrative review on research on the associations between DHA levels and brain development and function throughout the lifespan. Data from cell and animal studies justify the indication of DHA in relation to brain function for neuronal cell growth and differentiation as well as in relation to neuronal signaling. Most data from human studies concern the contribution of DHA to optimal visual acuity development. Accumulating data indicate that DHA may have effects on the brain in infancy, and recent studies indicate that the effect of DHA may depend on gender and genotype of genes involved in the endogenous synthesis of DHA. While DHA levels may affect early development, potential effects are also increasingly recognized during childhood and adult life, suggesting a role of DHA in cognitive decline and in relation to major psychiatric disorders."

-Department of Nutrition Exercise and Sports, University of Copenhagen, Denmark;

-Psychiatric Clinic, Department of Neurosciences and Mental Health, Fondazione IRCCS Ospedale Cà Granda-Ospedale Maggiore Policlinico, University of Milan, Italy;

-Department of Psychiatry and Behavioural Neurosciences, University of Texas at Houston, Way, Houston, TX , USA

-Pediatric Clinic, Fondazione IRCCS Ospedale Cà Granda-Ospedale Maggiore Policlinico, Department of Clinical Sciences and Community Health, University of Milan, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728620/

"Modern humans have evolved with a staple source of preformed docosahexaenoic acid (DHA) in the diet. An important turning point in human evolution was the discovery of high-quality, easily digested nutrients from coastal seafood and inland freshwater sources. Multi-generational exploitation of seafood by shore-based dwellers coincided with the rapid expansion of grey matter in the cerebral cortex, which characterizes the modern human brain. The DHA molecule has unique structural properties that appear to provide optimal conditions for a wide range of cell membrane functions. This has particular implications for grey matter, which is membrane-rich tissue. An important metabolic role for DHA has recently been identified as the precursor for resolvins and protectins. The rudimentary source of DHA is marine algae; therefore it is found concentrated in fish and marine oils. Unlike the photosynthetic cells in algae and higher plants, mammalian cells lack the specific enzymes required for the de novo synthesis of alpha-linolenic acid (ALA), the precursor for all omega-3 fatty acid syntheses. Endogenous synthesis of DHA from ALA in humans is much lower and more limited than previously assumed. The excessive consumption of omega-6 fatty acids in the modern Western diet further displaces DHA from membrane phospholipids. An emerging body of research is exploring a unique role for DHA in neurodevelopment and the prevention of neuropsychiatric and neurodegenerative disorders. DHA is increasingly being added back into the food supply as fish oil or algal oil supplementation."…

"A new picture is emerging which places nutrition, and docosahexaenoic acid (DHA) in particular, in an integral role in the evolution of human intelligence. The creation of a new database of the fossil record, which catalogues fossils at the level of individual collections, has been analyzed to demonstrate that a turning point in human evolution coincides with the inclusion of seafood in the diet [1,2]. "

-Centre for Occupational and Health Psychology, School of Psychology, Cardiff University
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257695/

Docosahexaenoic acid (DHA), a fundamental fatty acid for the brain: New dietary sources

"Docosahexaenoic acid (C22: 6n-3, DHA) is a long-chain polyunsaturated fatty acid of marine origin fundamental for the formation and function of the nervous system, particularly the brain and the retina of humans. It has been proposed a remarkable role of DHA during human evolution, mainly on the growth and development of the brain. Currently, DHA is considered a critical nutrient during pregnancy and breastfeeding due their active participation in the development of the nervous system in early life. DHA and specifically one of its derivatives

known as neuroprotectin D-1 (NPD-1), has neuroprotective properties against brain aging, neurodegenerative diseases and injury caused after brain ischemia-reperfusion episodes. This paper discusses the importance of DHA in the human brain given its relevance in the development of the tissue and as neuroprotective agent. It is also included a critical view about the ways to supply this noble fatty acid to the population."

-Nutrition Department, Faculty of Medicine, University of Chile, Santiago, Chile.

-Lipid Center, Institute of Nutrition and Food Technology (INTA), University of Chile and Faculty of Medicine,, University de Los Andes, Santiago, Chile.

https://pubmed.ncbi.nlm.nih.gov/28870371

Health benefits of docosahexaenoic acid (DHA)

"Docosahexaenoic acid (DHA) is essential for the growth and functional development of the brain in infants. DHA is also required for maintenance of normal brain function in adults. The inclusion of plentiful DHA in the diet improves learning ability, whereas deficiencies of DHA are associated with deficits in learning. DHA is taken up by the brain in preference to other fatty acids. The turnover of DHA in the brain is very fast, more so than is generally realized. The visual acuity of healthy, full-term, formula-fed infants is increased when their formula includes DHA. During the last 50 years, many infants have been fed formula diets lacking DHA and other omega-3 fatty acids. DHA deficiencies are associated with foetal alcohol syndrome, attention deficit hyperactivity disorder, cystic fibrosis, phenylketonuria, unipolar depression, aggressive hostility, and adrenoleukodystrophy. Decreases in DHA in the brain are associated with cognitive decline during aging and with onset of sporadic Alzheimer disease. The leading cause of death in western nations is cardiovascular disease. Epidemiological studies have shown a strong correlation between fish consumption and reduction in sudden death from myocardial infarction. The reduction is approximately 50% with 200 mg day(-1)of DHA from fish. DHA is the active component in fish. Not only does fish oil reduce triglycerides in the blood and decrease thrombosis, but it also prevents cardiac arrhythmias. The association of DHA deficiency with depression is the reason for the robust positive correlation between depression and myocardial infarction. Patients with cardiovascular disease or Type II diabetes are often advised to adopt a low-fat diet with a high proportion of carbohydrate. A study with women shows that this type of diet increases plasma triglycerides and the severity of Type II diabetes and coronary heart disease. DHA is present in fatty fish (salmon, tuna, mackerel) and mother's milk. DHA is present at low levels in meat and eggs, but is not usually present in infant formulas. EPA, another long-chain n-3 fatty acid, is also present in fatty fish. The shorter chain n-3 fatty acid, alpha-linolenic

acid, is not converted very well to DHA in man. These longchain n-3 fatty acids (also known as omega-3 fatty acids) are now becoming available in some foods, especially infant formula and eggs in Europe and Japan. Fish oil decreases the proliferation of tumour cells, whereas arachidonic acid, a longchain n-6 fatty acid, increases their proliferation. These opposite effects are also seen with inflammation, particularly with rheumatoid arthritis, and with asthma. DHA has a positive effect on diseases such as hypertension, arthritis, atherosclerosis, depression, adult-onset diabetes mellitus, myocardial infarction, thrombosis, and some cancers."

-L A Horrocks , Y K Yeo
-Docosa Foods Ltd, Columbus, OH, USA
https://pubmed.ncbi.nlm.nih.gov/10479465

Docosahexaenoic Acid and Cognition throughout the Lifespan

"Docosahexaenoic acid (DHA) is the predominant omega-3 (n-3) polyunsaturated fatty acid (PUFA) found in the brain and can affect neurological function by modulating signal transduction pathways, neurotransmission, neurogenesis, myelination, membrane receptor function, synaptic plasticity, neuroinflammation, membrane integrity and membrane organization. DHA is rapidly accumulated in the brain during gestation and early infancy, and the availability of DHA via transfer from maternal stores impacts the degree of DHA incorporation into neural tissues. The consumption of DHA leads to many positive physiological and behavioral effects, including those on cognition. Advanced cognitive function is uniquely human, and the optimal development and aging of cognitive abilities has profound impacts on quality of life, productivity, and advancement of society in general. However, the modern diet typically lacks appreciable amounts of DHA. Therefore, in modern populations, maintaining optimal levels of DHA in the brain throughout the lifespan likely requires obtaining preformed DHA via dietary or supplemental sources. In this review, we examine the role of DHA in optimal cognition during development, adulthood, and aging with a focus on human evidence and putative mechanisms of action."…

-DSM Nutritional Products, R&D Human Nutrition and Health, Boulder, CO, USA
-DSM Nutritional Products, R&D Human Nutrition and Health, Basel, Switzerland;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772061/

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See supplements for related research quotes.

…"The human brain is predominantly composed of lipids, and a large proportion of the polyunsaturated fatty acids (PUFA) are n-3 PUFA, specifically docosahexaenoic acid (DHA) [18]. "…

-Department of Agriculture, Nutrition, and Food Systems, University of New Hampshire,USA

-USDA Jean Mayer Human Nutrition Research Center on Aging, Tufts University, USA

-Medicine, Sanford School of Medicine, University of South Dakota, USA

-Department of Biomedical and Nutritional Sciences, University of Massachusetts Lowell, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164488/

…"In terms of the n–3 FAs, DHA predominates, with only docosapentaenoic acid (22:5n–3) contributing as a minor component. Because only trace amounts of α-linolenic acid and EPA are present in the brain [4–6], most reports of brain FA analyses do not even list these components. DHA is concentrated in the GM, and very small amounts are found in purified myelin [4–6]. Within the GM, the amino-phospholipids PE and especially PS have very high concentrations of DHA and PC has a lower concentration [4–6]. The observation that DHA can be 37% of GM PS [4], coupled with the positional distribution exclusively within the sn-2 position of the brain phospholipids [7], indicates that >73% of GM PS molecules contain DHA. The amino-phospholipid DHA is found at a high concentration across several brain subcellular fractions, including nerve terminals, microsomes, synaptic vesicles [7], and synaptosomal plasma membranes [8]."…

-Clinical Nutrition and Metabolism, Uppsala University, and Department of Geriatric Medicine, Uppsala University Hospital, Sweden

-Nutritional Lipids, DSM Nutritional Products, Columbia, MD; and

-Department of Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

-Presented at the symposium "Nutritional Prevention of Cognitive Decline" held 25 April 2012 at the American Society of Nutrition Scientific Sessions and Annual Meeting at Experimental Biology 2012 in San Diego, CA. The symposium was sponsored by the American Society for Nutrition, Nutrition Epidemiology RIS, and a grant from the Office of Dietary Supplements at NIH.

-A summary of the symposium "Nutritional Prevention of Cognitive Decline" was published in the September 2012 issue of Advances in Nutrition.

- Author disclosures: T. Cederholm and J. Palmblad, no conflicts of interest. N. Salem is employed by a company that produces and sells essential fatty acids, including the n–3 fatty acids EPA and DHA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3823515

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See supplements for related

research quotes.

Neuroprotectin D1 (NPD1): a DHA-derived mediator that protects brain and retina against cell injury-induced oxidative stress

“The biosynthesis of oxygenated arachidonic acid messengers triggered by cerebral ischemia-reperfusion is preceded by an early and rapid phospholipase A2 activation reflected in free arachidonic and docosahexaenoic acid (DHA) accumulation. These fatty acids are released from membrane phospholipids. Both fatty acids are derived from dietary essential fatty acids; however, only DHA, the omega-3 polyunsaturated fatty acyl chain, is concentrated in phospholipids of various cells of brain and retina. Synaptic membranes and photoreceptors share the highest content of DHA of all cell membranes. DHA is involved in memory formation, excitable membrane function, photoreceptor cell biogenesis and function, and neuronal signaling, and has been implicated in neuroprotection. In addition, this fatty acid is required for retinal pigment epithelium cell (RPE) functional integrity. Here we provide an overview of the recent elucidation of a specific mediator generated from DHA that contributes at least in part to its biological significance. In oxidative stress-challenged human RPE cells and rat brain undergoing ischemia-reperfusion, 10,17S-docosatriene (neuroprotectin D1, NPD1) synthesis evolves. In addition, calcium ionophore A23187, IL-1beta, or the supply of DHA enhances NPD1 synthesis. A time-dependent release of endogenous free DHA followed by NPD1 formation occurs, suggesting that a phospholipase A2 releases the mediator's precursor. When NPD1 is infused during ischemia-reperfusion or added to RPE cells during oxidative stress, apoptotic DNA damage is down-regulated. NPD1 also up-regulates the anti-apoptotic Bcl-2 proteins Bcl-2 and BclxL and decreases pro-apoptotic Bax and Bad expression. Moreover, NPD1 inhibits oxidative stress-induced caspase-3 activation. NPD1 also inhibits IL-1beta-stimulated expression of COX-2. Overall, NPD1 protects cells from oxidative stress-induced apoptosis. Because photoreceptors are progressively impaired after RPE cell damage in retinal degenerative diseases, understanding of how these signals contribute to retinal cell survival may lead to the development of new therapeutic strategies. Moreover, NPD1 bioactivity demonstrates that DHA is not only a target of lipid peroxidation, but rather is the precursor to a neuroprotective signaling response to ischemia-reperfusion, thus opening newer avenues of therapeutic exploration in stroke, neurotrauma, spinal cord injury, and neurodegenerative diseases, such as Alzheimer disease, aiming to up-regulate this novel cell-survival signaling.”

-LSU Neuroscience Center and Department of Opthamology, Louisiana State University Health Sciences Center School of Medicine, New Orleans, USA.

https://pubmed.ncbi.nlm.nih.gov/15912889/

How does high DHA fish oil affect health? A systematic review of evidence

"The health benefits of fish oil, and its omega-3 long chain polyunsaturated fatty acid content, have attracted much scientific attention in the last four decades. Fish oils that contain higher amounts of eicosapentaenoic acid (EPA; 20:5n-3) than docosahexaenoic acid (DHA; 22:6n-3), in a distinctive ratio of 18/12, are typically the most abundantly available and are commonly studied. Although the two fatty acids have traditionally been considered together, as though they were one entity, different physiological effects of EPA and DHA have recently been reported. New oils containing a higher quantity of DHA compared with EPA, such as fractionated and concentrated fish oil, tuna oil, calamari oil and microalgae oil, are increasingly becoming available on the market, and other oils, including those extracted from genetically modified oilseed crops, soon to come. This systematic review focuses on the effects of high DHA fish oils on various human health conditions, such as the heart and cardiovascular system, the brain and visual function, inflammation and immune function and growth/Body Mass Index. Although inconclusive results were reported in several instances, and inconsistent outcomes observed in others, current data provides substantiated evidence in support of DHA being a beneficial bioactive compound for heart, cardiovascular and brain function, with different, and at times complementary, effects compared with EPA. DHA has also been reported to be effective in slowing the rate of cognitive decline, while its possible effects on depression disorders are still unclear. Interestingly, gender- and age- specific divergent roles for DHA have also been reported. This review provides a comprehensive collection of evidence and a critical summary of the documented physiological effects of high DHA fish oils for human health."

-School of Medicine, Deakin University , Geelong , Australia.
-Nu-Mega Ingredients Pty Ltd , Altona North , Melbourne , Australia.
-Department of Food Science and Nutrition , Zhejiang University , Hangzhou , China.
-Department of Nutrition , Dietetics and Food, Monash University , Clayton , Australia.
-School of Life and Environmental Sciences , Deakin University , Geelong , Australia.
https://pubmed.ncbi.nlm.nih.gov/29494205/

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…"DHA-EA has been shown to be anti-inflammatory in several different inflammation models."….

-Department of Comparative Biosciences, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Department of Biochemistry, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Division of Nutritional Sciences, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Beckman Institute for Advanced Science, Neuroscience Program, Center for Biophysics and Quantitative Biology,

Department of Bioengineering, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6685292

DHA is mentioned throughout this book in most topics.

See also Omega-3

Dreams

The Endocannabinoid System Modulating Levels of Consciousness, Emotions and Likely Dream Contents.

…"In this regard, an accumulative body of evidence in human and animal models has been reported regarding the role of the endocannabinoid system in the control of emotional states and dreams. Moreover, preliminary studies in humans have indicated that treatment with cannabinoids may decrease post-traumatic stress disorder symptoms, including nightmares.

CONCLUSION:

Thus, based on a review of the literature available in PubMed, this article hypothesizes a conceptual framework within which the endocannabinoid system might influence the generation of dream experiences."

-Laboratory of Molecular and Integrative Neurosciences, School of Medicine, Health Sciences Division,Anáhuac Mayab University, Mérida-Progreso Highway

-Aging Research Group, Health Sciences Division, Anahuac Mayab University
-Intercontinental Neuroscience Research Group, Mérida, Yucatán, Mexico.
https://www.ncbi.nlm.nih.gov/pubmed/28240187

Drugs of Abuse

Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors.

..."Accumulating evidence also implicates brain endocannabinoid signaling in the etiology of drug addiction which is characterized by compulsive drug seeking,"...

Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, USA.
http://www.ncbi.nlm.nih.gov/pubmed/21798285

An endocannabinoid hypothesis of drug reward and drug addiction

…"Cannabinoids and endocannabinoids appear to be involved in adding to the rewarding effects of addictive substances, including, nicotine, opiates, alcohol, cocaine, and BDZs. The results suggest that the EPCS may be an important natural regulatory mechanism for drug rewardand a target for the treatment of addictive disorders."

-Department of Biology, William Paterson University, Wayne, New Jersey, USA.
https://pubmed.ncbi.nlm.nih.gov/18991888/

Cannabinoid Regulation of Brain Reward Processing with an Emphasis on the Role of CB1 Receptors: A Step Back into the Future.

"Over the last decades, the endocannabinoid system has been implicated in a large variety of functions, including a crucial modulation of brain-reward circuits and the regulation of motivational processes. Importantly, behavioral studies have shown that cannabinoid compounds activate brain reward mechanisms and circuits in a similar manner to other drugs of abuse, such as nicotine, alcohol, cocaine, and heroin, although the conditions under which cannabinoids exert their rewarding effects may be more limited. Furthermore, there is evidence on the involvement of the endocannabinoid system in the regulation of cue- and drug-induced relapsing phenomena in animal models. The aim of this review is to briefly present the available data obtained using diverse behavioral experimental approaches in experimental animals, namely, the intracranial self-stimulation paradigm, the self-administration procedure, the conditioned place preference procedure, and the reinstatement of drug-seeking behavior procedure, to provide a comprehensive picture of the current status of what is known about the endocannabinoid system mechanisms that underlie modification of brain-reward processes. Emphasis is placed on the effects of cannabinoid 1 (CB1) receptor agonists, antagonists, and endocannabinoid modulators. Further, the role of CB1 receptors in reward processes is investigated through presentation of respective genetic ablation studies in mice. The vast majority of studies in the existing literature suggest that the endocannabinoid system plays a major role in modulating motivation and reward processes. However, much remains to be done before we fully understand these interactions. Further research in the future will shed more light on these processes and, thus, could lead to the development of potential pharmacotherapies designed to treat reward-dysfunction-related disorders."

-Laboratory of Behavioral Neuroscience, Department of Psychology, School of Social Sciences, University of Crete, Greece

-Laboratory of Behavioural Neuroscience, School of Nursing and Human Sciences, Faculty of Science and Health, Dublin City University, Ireland

http://www.ncbi.nlm.nih.gov/pubmed/25132823

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”The endocannabinoid system regulates neurotransmission in brain regions relevant to neurobiological and behavioral actions of addicting drugs.”…

-B.B.Brodie Department of Neuroscience, University of Cagliari, 09042, Monserrato, Italy

-CNR Neuroscience Institute-Cagliari, University of Cagliari, 09042, Monserrato, Italy

-Center of Excellence for the Neurobiology of Addiction, University of Cagliari, 09042, Monserrato, Italy

-Division of Geriatric Medicine and Gerontology, Department of Medicine, John Hopkins University School of Medicine, Baltimore, Maryland 21224

-Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, Intramural Research Program, Department of Health and Human Services,

-National Institute on Drug Abuse,National Institutes of Health, Baltimore, Maryland, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3167063/

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…”Importantly, behavioral studies have shown that cannabinoid compounds activate brain reward mechanisms and circuits in a similar manner to other drugs of abuse, such as nicotine, alcohol, cocaine, and heroin.”

-B.B.Brodie Department of Neuroscience, University of Cagliari, Monserrato, Italy

-CNR Neuroscience Institute-Cagliari, University of Cagliari, Monserrato, Italy

-Center of Excellence for the Neurobiology of Addiction, University of Cagliari, Monserrato, Italy

-Division of Geriatric Medicine and Gerontology, Department of Medicine, John Hopkins University School of Medicine, Baltimore, Maryland

-Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, Intramural Research -Program, Department of Health and Human Services, National Institute on Drug Abuse-National Institutes of Health, Baltimore, Maryland

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3167063/pdf/nihms318810.pdf

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…”This suggests that both endogenous cannabinoid (anandamide) and non cannabinoid (OEA and PEA) fatty acid ethanolamides, which are all substrates for FAAH, participate in the fine tuning of neurophysiological and behavioral effects of addicting drugs. “

-Preclinical Pharmacology Section, Behavioral Neuroscience Branch, Intramural Research Program

-National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, USA

http://www.ncbi.nlm.nih.gov/pubmed/15870833

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"Accumulating evidence suggests that the endogenous cannabinoid system is involved in the reinforcing effects of heroin."..

-Department of Biology, William Paterson University, Wayne, New Jersey, USA.
http://www.ncbi.nlm.nih.gov/pubmed/18991888

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..."These data indicate that AEA [anandamide] and 2-AG [2-arachidonoylglycerol] signaling pathways interact to regulate specific behavioral processes in vivo, including those relevant to drug abuse, thus providing a potential mechanistic basis for the distinct pharmacological profiles of direct CB1 agonists and inhibitors of individual endocannabinoid degradative enzymes."...

-The Skaggs Institute for Chemical Biology and Department of Chemical Physiology, The Scripps Research Institute, La Jolla, CA, USA
https://pubmed.ncbi.nlm.nih.gov/19918051/

Methamphetamine-seeking behavior is due to inhibition of nicotinic cholinergic transmission by activation of cannabinoid CB1 receptors

-Department of Pharmacology, Faculty of Pharmaceutical Sciences, Nagasaki International University
https://pubmed.ncbi.nlm.nih.gov/18782581/

Drug Allergies

The role of cannabinoids in inflammatory modulation of allergic respiratory disorders, inflammatory pain and ischemic stroke

"This review is intended to offer updated information on the involvement of cannabinoids in the process of inflammation, focusing on immune/allergic reactions, inflammatory pain and neuroinflammation and discussing the interactions among endocannabinoid metabolism, prostanoids and nitric oxide. Two types of cannabinoid receptors, CB1 and CB2, which belong to the G protein-coupled receptor family, have been identified and are targeted by numerous exogenous and endogenous ligands. The activation of CB2 receptors on mast cells has direct antiinflammatory effects, causing decreased release of pro-inflammatory mediators by these cells. The activation of CB1 receptors on bronchial nerve endings has bronchodilator effects by acting on the airway smooth muscle and may be beneficial in airway hyperreactivity and asthma. Moreover, pharmacologic interference with endocannabinoid metabolism has been

demonstrated to result in anti-nociceptive activity, mediated by CB1 and CB2 receptors, in animal models of inflammatory pain. The presence of endocannabinoid machinery in the central nervous system, together with high levels of CB1 expression, suggests that the endocannabinoid system is an important modulator of neuroinflammation and a possible drug target. In selected conditions, the activation of CB1 receptors in cerebral blood vessels can have beneficial antiischemic effects. However, as endocannabinoids can also bind to vanilloid receptors, they may also mediate neurotoxic effects."

-Department of Preclinical and Clinical Pharmacology, University of Florence
https://pubmed.ncbi.nlm.nih.gov/22420307/

Dry Eyes

Topical omega-3 and omega-6 fatty acids for treatment of dry eye.

"Topical application of ALA omega-3 fatty acid may be a novel therapy to treat the clinical signs and inflammatory changes accompanying dry eye syndrome."

-Schepens Eye Research Institute, 20 Staniford St, Boston, MA 02114, USA.
https://www.ncbi.nlm.nih.gov/pubmed/18268213

Dupuytren's Contracture

https://www.keep-healthy.com/dupuytrens-contracture/

Dyslexia

"a general term for disorders that involve difficulty in learning to read or interpret words, letters, and other symbols, but that do not affect general intelligence." *- Oxford Languages / Google*

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…"Long-term studies testing the efficacy of pharmacologic intervention in dyslexia are lacking, and side effects of pharmacologic intervention (such as methylphenidate or amphetamines) last

even after treatment completion. As a result, use of nonpharmacologic management has become common.[12]

In 1997, Richardson et al found elevated levels of phosphomonoesters among 12 adults with dyslexia compared with a control group of 10 healthy adults. High levels of phosphomonoesters indicated a deficiency in the biosynthesis of phospholipids or their incorporation into membranes. Because the metabolism of membrane phospholipids is heavily influenced by their essential fatty acid composition,[2] there might be potential for HUFA dietary supplementation as therapy for children with dyslexia.

In a case study of a grade 6 boy with dyslexia, fatty acid supplementation with omega-3 (α-linolenic acid) and a reduction of saturated fat from the diet improved his reading skills and reduced physical findings of fatty acid deficiency.[10]

In 2002, Richardson and Puri conducted a 2-stage randomized, placebo-controlled study on the effects of supplementation with HUFAs on ADHD-related symptoms in children with learning disabilities. In the first stage, 41 children 8 to 12 years old were randomized to either taking daily dietary supplementation (186 mg of EPA, 480 mg of DHA, 96 mg of γ-linolenic acid, 42 mg of arachidonic acid, vitamin E, conjugated linoleic acid, and 8 mg of thyme oil) or receiving placebo for a period of 3 months. Results showed statistically significant reductions in ADHD symptoms, dyslexia-related symptoms (eg, inattention, learning and memory problems), and anxiety.[13] In the second stage of the study, the children who had initially received placebo were switched to the fatty acid supplement and were followed for a further 3 months. Among this group, the improvements in ADHD symptoms, dyslexia-related symptoms, and anxiety were statistically significant as they were in the initial treatment group.[14]

A larger randomized, placebo-controlled study of children with dyslexia revealed substantial improvements in reading skills among 102 children 8 to 12 years of age treated for 6 months with 186 mg of EPA, 480 mg of DHA, 96 mg of γ-linolenic acid, 42 mg of arachidonic acid, vitamin E, conjugated linoleic acid, and 8 mg of thyme oil. The difference was especially noticeable among children with symptomatic fatty acid deficiency at baseline.[15]

***However, in another randomized, placebo-controlled study, investigators asked teachers to assess 61 children for dyslexia; 31 of the children with dyslexia were treated for 90 days with 500 mg of EPA and 400 mg of carnosine (ie, an amino acid presumed to interact positively with cognitive functions), while 30 of the children with dyslexia received placebo. There was no statistically significant improvement documented in any of the cognitive measures, including reading and spelling skills.[16]"...

Visual function in dyslexia

"There is evidence of visual and central processing deficits in dyslexia.[17] The magnocellular layer of the thalamus, which is responsible for processing rapid visual stimuli, is dependent on a high content of unsaturated fatty acids.

Stordy[17] found that use of 480 mg/d of DHA supplementation for a month among young adults with dyslexia normalized dark adaptation compared with a control group; this finding contributes to the growing body of evidence for the benefits of omega-3 HUFA supplementation for those with dyslexia."…

Conclusion

"The benefit of omega-3 supplementation for children with dyslexia has been studied, but evidence is limited. Larger, systematic, and well controlled studies are needed in order to provide definitive evidence. Objective measures of fatty acid deficiency, closer monitoring of dietary intake throughout the study, and systematic diagnosis of dyslexia are some of the required measures to improve current evidence. Optimal dosing should also be determined."

-Michal Zelcer, MSc
-Ran D. Goldman, MD FRCPC
-Canadian Family Physician
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4569108/

*** NOTE: It should be noted that the effectiveness of DHA given in research is largely depending on the source as some fish oil supplements convert in the body and do not significantly raise DHA levels.

"Docosahexaenoic acid (DHA) is uniquely concentrated in the brain, and is essential for its function, but must be mostly acquired from diet. Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol, whereas the transporter at blood brain barrier is specific for phospholipid form of DHA."…

-Department of Medicine, University of Illinois at Chicago, Chicago, IL USA
-Department of Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, IL USA
-Jesse Brown VA Medical Center, Chicago, IL USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5596017

Evidence for fatty acid deficiency in Dyslexia

"Visual function in dyslexia improved by fatty acid treatment

Stordy (1995) proposed that fatty acid treatment may help in the management of dyslexia. She

had first observed an apparent association between breastfeeding (and its duration) in relation to the severity of dyslexia, as well as poor night vision in dyslexic individuals. She therefore tested dyslexic adults and found they showed impaired dark adaptation, but this visual problem normalised after just 4 weeks of supplementation with the omega-3 fatty acids EPA and DHA.

The role of omega-3 fatty acids in visual function is well recognised, and the evidence for visual problems in dyslexia is now substantial. Stordy's 1995 findings not only suggested a possible biochemical basis for these which might also help to explain other features of dyslexia, but also suggested new treatment possibilities.

Abnormal brain lipid metabolism in dyslexia revealed by brain imaging

To investigate the proposal that membrane lipid metabolism in dyslexia may be abnormal, a study was carried out at the MRI Unit at Hammersmith Hospital (Richardson et al., 1997). MR imaging is a safe and non-invasive technique involving the use of radiowaves within a very strong magnetic field. It can be used to obtain either structural images (the well-known MRI) or information on the chemical composition of tissues (magnetic resonance spectroscopy, or MRS). To study membrane lipid metabolism in the living brain, 31-phosphorus MRS is the best available technique. From 31- phosphorus MRS spectra, seven different phosphorus metabolites can be clearly identified, and their concentrations measured. Two of these provide information on membrane lipid turnover: phosphomonoesters (PMEs) include the precursors of membrane phospholipids, while phosphodiesters (PDEs) index their breakdown products.

Results showed a clear excess of PMEs in dyslexic adults compared with controls, suggesting a problem in the synthesis of membrane phospholipids in dyslexia, while PDE levels were normal. These results are also compatible with deficiency in certain HUFA in dyslexia. (PMEs have to combine with diacylglycerols - molecules with two fatty acids - to form membrane phospholipids. If these molecules do not contain the 'right' fatty acids, then this process could be impaired, resulting in an accumulation of the PME precursors.)

Blood biochemical abnormalities in dyslexia

In a single case report, Baker (1985) found fatty acid deficiencies on biochemical testing of a dyslexic boy who also showed overt clinical signs such as rough, dry skin and hair. More recently, MacDonell et al (2000) found that dyslexic adults showed increased levels of a PLA2 enzyme that removes HUFA from membranes.

Clinical signs of fatty acid deficiency in dyslexia

In a large sample of dyslexic and non-dyslexic adults, clinical signs of fatty acid deficiency were significantly higher in the dyslexic group (Taylor et al., 2000). These signs were assessed using the same

scale as was used in recent studies of ADHD (Stevens et al., 1995), where fatty acid deficiency scores were also related to blood biochemical measures of fatty acid deficiency. Within dyslexic children, those with more clinical signs of fatty acid deficiency had more severe difficulties in reading, spelling and working memory (Richardson et al, 2000a). However, there was no evidence that fatty acid deficiency was confined to any particular subgroup as defined by psychometric tests.

Double-blind treatment trials in dyslexia - preliminary results

In view of the mounting evidence for fatty acid abnormalities in dyslexia, several double-blind clinical trials were set up to assess whether treatment with fatty acids can be of benefit in this condition (Richardson et al, 1999). These studies are now approaching completion, and some preliminary results are already available.

Trial 1: In a school-based study, 41 dyslexic children with ADHD features took either a fatty acid supplement (mainly fish oil with some evening primrose, supplying EPA, DHA, GLA and some AA) or a placebo (containing olive oil) for three months. They were assessed before and after treatment on standard parent ratings of ADHD symptoms (Richardson et al, 2000b; Richardson and Puri 2002).

- Compared with the placebo-treated group, those dyslexic children who had received the fatty acid supplement showed significant reductions in a range of ADHD symptoms, particularly cognitive problems (inattention, learning and memory problems) and anxiety.
- In a second stage of the study, those children who had received the placebo treatment were then switched to the fatty acid supplement under single-blind conditions and followed for a further 3 months. In these children, significant improvements were observed for a wide range of ADHD measures, in striking contrast to the lack of improvement they had shown on placebo treatment.

Numbers in this study were small, so these results need to be confirmed in larger double-blind trials still underway. However, they provide promising evidence that dietary supplementation with HUFA can be of some benefit in the management of ADHD-related symptoms in dyslexia.

Trial 2: In a larger clinic-based study, 102 dyslexic children took either the same fatty acid supplement or placebo for six months under double-blind conditions. Supplementation was associated with significant improvements in reading, especially for children with fatty acid deficiency signs or visual symptoms at baseline (Richardson et al, in preparation).”

-Alexandra J. Richardson
-Senior Research Fellow in Neuroscience, Mansfield College and University Lab. of Physiology, Oxford.
https://www.fabresearch.org/uploads/itemUploads/6700/2002%20AJR%20Handout%20-%20FAs%20in%20DDA.pdf

Dark adaptation, motor skills, docosahexaenoic acid, and dyslexia

"Dyslexia is a widespread condition characterized by difficulty with learning and movement skills. It is frequently comorbid with dyspraxia (developmental coordination disorder), the chief characteristic of which is impaired movement skills, indicating that there may be some common biological basis to the conditions. Visual and central processing deficits have been found. The long-chain polyunsaturated fatty acids (LCPUFAs) are important components of retinal and brain membranes. In the preliminary studies reported here, dark adaptation was shown to be impaired in 10 dyslexic young adults when compared with a similar control group ($P < 0.05$, repeated-measures analysis of variance); dark adaptation improved in 5 dyslexia patients after supplementation with a docosahexaenoic acid (DHA)-rich fish oil for 1 mo ($P < 0.05$, paired t test on final rod threshold); and movement skills in a group of 15 dyspraxic children improved after 4 mo of supplementation with a mixture of high-DHA fish oil, evening primrose oil, and thyme oil ($P < 0.007$ for manual dexterity, $P < 0.02$ for ball skills, and $P < 0.03$ for static and dynamic balance; paired t tests). The studies were small and had designs that did not allow firm conclusions to be made. However, when considered with other evidence from another closely related condition, attention-deficit hyperactivity disorder, for which reduced ability to elongate and desaturate the essential fatty acids linoleic acid and alpha-linolenic acid to arachidonic acid and DHA, respectively, has been proposed, the studies suggest that more research, including double-blind, placebo-controlled studies, would be useful to clarify the benefits of LCPUFAs in dyslexia and other closely related conditions."

-School of Biological Sciences, University of Surrey, Guildford, United Kingdom.
https://pubmed.ncbi.nlm.nih.gov/10617990/

A 5-month open study with long-chain polyunsaturated fatty acids in dyslexia

"This open pilot study investigated effects of a docosahexaenoic acid (DHA)-rich supplement on learning ability in a group of 20 dyslexic children in Sweden. Children formally diagnosed as dyslexic took eight capsules per day of a long-chain polyunsaturated fatty acid (LC-PUFA) supplement containing high-DHA fish oil and evening primrose oil. Subjective assessments by the children and their parents were completed at baseline and 6, 12, and 20 weeks after supplementation. Quantitative evaluation by word-chain test was completed before and after 4 months of supplementation to measure word decoding (speed of reading) and letter decoding (motoric-perceptual speed). Subjective parent and child assessments showed increasing numbers of positive responders over time in reading speed, general schoolwork, and overall perceived benefit. Significant improvements were observed in reading speed and motor-perceptual velocity. Thirteen of 17 children had a significant improvement on the word-chain

test (P < .04). Reading speed improved by 60% from 1.76 +/- 0.29 before the study to 2.82 +/- 0.36 after supplementation (P < .01 by Wilcoxon sign test). Motoric-perceptual velocity improved by 23% from a stanine value of 3.76 +/- 0.42 to 4.65 +/- 0.66 after supplementation (P < .05 by Wilcoxon sign test). Thus LC-PUFA supplementation for 5 months provides positive and clear beneficial effect on variables usually impaired by dyslexia."

-Journal of Medicinal Food
-Lars Lindmark & Peter Clough
https://pubmed.ncbi.nlm.nih.gov/18158838/

Dysmenorrhea

"Dysmenorrhea is the medical term for menstrual cramps, which are caused by uterine contractions. Primary dysmenorrhea refers to common menstrual cramps, while secondary dysmenorrhea results from a disorder in the reproductive organs."

-Cleveland Clinic
https://my.clevelandclinic.org/health/diseases/4148-dysmenorrhea

Painful menstruation and low intake of n-3 [omega-3] fatty acids

"Menstrual pain, dysmenorrhea, which is known to be prostaglandin mediated, can possibly be influenced by the dietary ratio of omega-3 and omega-6 polyunsaturated fatty acids. The prostaglandins derived from marine omega-3 fatty acids are normally less aggressive and therefore expected to be associated with milder menstrual symptoms. This hypothesis was surveyed in an epidemiological study in Danish women based upon self administered questionnaires concerning menstrual history, present symptoms, general health, socio-economic factors, and general dietary habits. Two prospective four-day dietary records were used to estimate average daily nutrient intake. The subjects were recruited by advertising, they were 20-45 years of age, not pregnant, and did not use oral contraceptives. No correlations were found between socioeconomic or anthropometric data and menstrual problems. However, certain dietary habits e.g. low intakes of animal and fish products, and low intakes of specific nutrients (omega-3 PUFA, B12 and omega-3/omega-6 ratio) were correlated with menstrual pain. The other nutrients in the diet were not significantly related to menstrual pain. The results were highly significant and mutually consistent and supported the hypothesis that a higher intake of marine, omega-3 fatty acids correlate with milder menstrual symptoms."

-Specialkursus i Husholdning, Aarhus Universitet.

https://www.ncbi.nlm.nih.gov/pubmed/8701537

Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents.

"The purpose of the study was to examine whether dietary supplementation with omega-3 fatty acids can relieve symptoms of dysmenorrhea in adolescents."

…"This study suggests that dietary supplementation with omega-3 fatty acids has a beneficial effect on symptoms of dysmenorrhea in adolescents."

-Division of Adolescent Medicine, Children's Hospital Medical Center, Cincinnati, OH 45229, USA.
https://www.ncbi.nlm.nih.gov/pubmed/8623866

The effect of cinnamon on menstrual bleeding and systemic symptoms with primary dysmenorrhea.

"Primary dysmenorrhea with interferes in daily activities can have adverse effects on quality of life of women."

…"The mean amount of menstrual bleeding in the cinnamon group was significantly lower than the placebo group ($P < 0.05$ and $P < 0.001$, respectively). The mean pain severity score in the cinnamon group was less than the placebo group at various intervals (4.1 ± 0.5 vs. 6.1 ± 0.4 at 24 hours, 3.2 ± 0.6 vs. 6.1 ± 0.4 at 48 hours, and 1.8 ± 0.4 vs. 4.0 ± 0.3 at 72 hours, respectively) ($P < 0.001$). The mean severity of nausea and the frequencies of vomiting significantly decreased in the cinnamon group compared with the placebo group at various intervals ($P < 0.001$, $P < 0.05$)."

…"Regarding the significant effect of cinnamon on reduction of pain, menstrual bleeding, nausea and vomiting with primary dysmenorrhea without side effects, it can be regarded as a safe and effective treatment for dysmenorrhea in young women."

-Department of Midwifery, Nursing and Midwifery Faculty, Ilam University of Medical Sciences, Ilam, IR Iran.
-Department of Neurosurgery, Medicine Faculty, Ilam University of Medical Sciences, Ilam, IR Iran.
-Department of Nursing, Nursing and Midwifery Faculty, Ilam University of Medical Sciences, Ilam, IR Iran.
-Department of Anesthesiology, Medicine Faculty, Ilam University of Medical Sciences, Ilam, IR Iran.
https://www.ncbi.nlm.nih.gov/pubmed/26023350

Women and omega-3 Fatty acids

"Omega-3 fatty acids (omega-3 FA) are constituents of the membranes of all cells in the body

and are precursors of locally produced hormones, eicosanoids, which are important in the prevention and treatment of various diseases, especially in women. Omega-3 FA are of interest in some of the most common conditions affecting women. One mechanism underlying dysmenorrhea is a disturbed balance between antiinflammatory, vasodilator eicosanoids derived from omega-3 FA and proinflammatory, vasoconstrictor eicosanoids derived from omega-6 FA. Increased intake of omega-3 FA can reverse the symptoms in this condition by decreasing the amount of omega-6 FA in cell membranes. An increased prostacyclin/thromboxane ratio induced by omega-3 FA can facilitate pregnancy in women with infertility problems by increasing uterine blood flow. Supplementation with omega-3 FA during pregnancy lowers the risk of premature birth and can increase the length of pregnancy and birth weight by altering the balance of eicosanoids involved in labor and promote fetal growth by improving placental blood flow. Intake of omega-3 FA during pregnancy and breast feeding may facilitate the child's brain development. There is also some evidence that supplementation with omega-3 FA might help to prevent preeclampsia, postpartum depression, menopausal problems, postmenopausal osteoporosis, and breast cancer. Furthermore, because elevated triglyceride levels are associated with cardiovascular disease, especially in women; and because omega-3 FA have powerful effects on triglycerides, women in particular gain from an increased intake of these fatty acids. This is especially important in women receiving hormone therapy, which can increase triglyceride levels. The quality of the omega-3 FA preparation is important. It should have an appropriate antioxidant content not to induce lipid peroxidation, and its content of dioxin and polychlorinated biphenyls (PCBs) should be well below the established safe limit."

-Department of Obstetrics and Gynecology, Malmö University Hospital, University of Lund, Sweden.
https://pubmed.ncbi.nlm.nih.gov/15385858

Dyspepsia

"Dyspepsia, also known as indigestion, is a term that describes discomfort or pain in the upper abdomen. It is not a disease. The term refers to a group of symptoms that often include bloating, discomfort, nausea, and burping. In the majority of cases, indigestion is linked to eating or drinking."

https://www.medicalnewstoday.com/articles/163484.php

Dyspraxia

"Dyspraxia is a brain-based motor disorder. It affects fine and gross motor skills, motor planning, and coordination. It's not related to intelligence, but it can sometimes affect cognitive skills. Dyspraxia is sometimes used interchangeably with developmental coordination disorder."

-Healthline
https://www.healthline.com/health/dyspraxia

Evidence for fatty acid deficiency in Dyspraxia

"In children with dyspraxia, so far only 'open' trials of fatty acid supplementation have been carried out (Stordy, 1997), 15 children whose poor motor skills initially placed them in the bottom 1% of the population were treated with an omega-3/omega-6 fatty acid supplement, and retested after 12 weeks. Improvements were found on objective measures of manual dexterity, ball skills, and balance, as well as on parental ratings of the children's dyspraxic and ADHD symptoms. However, open studies can never be regarded as reliable because expectations can influence the results, and the first randomised, double-blind plabebo-controlled trial in dyspraxia is now underway."

-Alexandra J. Richardson
-Senior Research Fellow in Neuroscience, Mansfield College and University Lab. of Physiology, Oxford.
https://www.fabresearch.org/uploads/itemUploads/6700/2002%20AJR%20Handout%20-%20FAs%20in%20DDA.pdf

Use of arachidonic acid and/or docosahexanoic acid for the manufacture of a medicament for the treatment of dyspraxia

…"Dyspraxia is now recognised to be caused by an immaturity of brain development associated with poor synaptic transmission and possibly poor arborisation of neurones, that is to say a disorder with an organic basis.

In practical terms dyspraxics are poorly co-ordinated, disorganised, have problems of ideation, motor planning and execution so that written work and ball games are extremely difficult for them. Handwriting is poor. Poor memory, restlessness .and impulsiveness may be features of the condition. Poor peer relations as a consequence of their clumsiness and slow learning of games lead to low self esteem. "…

"The invention is discussed in general terms later herein but broadly we have found dyspraxia to be due to inadequate supplies of the long chain polyunsaturated fatty acids docosahexaenoic

acid (DHA) [omega-3] and arachidonic acid (AA) [omega-6]. Dyspraxia may thus be treated by providing DHA and AA, the earlier the better. LA and especially GLA and DGLA are metabolic precursors of AA, and may be used in its stead. Likewise ALA and especially SA and EPA .are precursors of DHA and may be used in its stead. Antioxidants may optionally be provided as well since they protect the highly polyunsaturated fatty acids and increase their incorporation into cell membranes.

DHA and AA are major constituents of the retina, of nerve tissue .and of the brain. DHA is found in high concentrations at synapses and AA is important for cell signalling. Recent work has shown that their provision to children is important in the normal development of visual acuity, dark adaptation and cognitive function and is of particular benefit for dyslexics. However to our knowledge no one has previously suggested that dyspraxic individuals might also benefit from this treatment approach.

We first found a dramatic response to treatment with AA, DHA and GLA in a boy with dyspraxia. The subject was a 5 year old boy with severe dyspraxia. He exhibited all the classic signs of dyspraxia, he was clumsy, had poor balance and consequently bumped into objects and was accident prone. His drinks were always provided in a cup with a lid and a straw because of spillage. He did not enjoy and avoided drawing or learning to write because of poor fine motor skills and the difficulty of holding a pencil and physically drawing the lines as he wished. He had similar difficulty with scissors and cutting out. Clumsiness in ball games and difficulty with catching and hitting a ball lead to poor self esteem and difficulties in playing with friends. Characteristically at school he avoided the tasks which involved reading and writing and was easily distracted in class.

After supplementation with essential fatty acids and antioxidant for two months, his fine and gross motor skills and balance had improved so much that he rarely tripped over, he could carry liquid in an uncovered cup, and could catch a ball and hit a ball with a baseball bat. All these skills were absent before supplementation.

His language skills had also improved with more desire to read, fewer errors and faster reading. The social disruption in school caused by clumsiness and impulsiveness had also lessened. His teacher, unaware of the supplementation, reported that he was working well and was less disruptive. Overall the boy was calmer, happier and more willing to do things."….

-Patent WO1998008501A1
-Scotia Holdings Plc (Health Care / Biotech & Pharmaceuticals)
https://patents.google.com/patent/WO1998008501A1/en

E

E. Coli

"Human peripheral-type cannabinoid receptor (CB2) was expressed in Escherichia coli as a fusion with the maltose-binding protein, thioredoxin, and a deca-histidine tag. Functional activity and structural integrity of the receptor in bacterial protoplast membranes was confirmed by extensive binding studies with a variety of natural and synthetic cannabinoid ligands. E. coli membranes expressing CB2 also activated cognate G-proteins in an in vitro coupled assay."…

-Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2253291/

Eczema

"Eczema" and "dermatitis" are both generic terms for "skin inflammation" and are often used interchangeably. There are a number of types of eczema and dermatitis that have different causes and symptoms, but most can be managed with a good skin care regimen and by avoiding irritants that cause flare-ups."

-Healthline

https://www.healthline.com/health/difference-between-eczema-and-dermatitis

Do long-chain omega-3 fatty acids protect from atopic dermatitis?

"Long-chain polyunsaturated fatty acids are essential for human nutrition. The number of double bonds determines whether a given fatty acid is termed two, three, or x times unsaturated. Depending on the distance of the first double bond from the fatty acid's methyl group, one distinguishes omega-3 fatty acids from omega-6 fatty acids. While the use of gamma linolenic acid, a long-chain fatty acid of the omega-6 family, has proven unsuccessful in the prevention or treatment of atopic dermatitis, supplementation of long-chain omega-3 fatty acids may represent a promising approach in the prevention of allergic disorders, especially atopic dermatitis. Whether the concept of long-chain omega-3 fatty acid administration will also become established in a therapeutic setting, depends on whether the beneficial effects observed so far can be substantiated in randomized controlled intervention studies."

-Nutrition Counseling and Therapy with Special Focus on Allergology, Munich, Germany.

-Division of Immunodermatology and Experimental Allergology, Department of Dermatology, Allergology, and Venereology, Medical University Hanover, Hanover, Germany.
https://pubmed.ncbi.nlm.nih.gov/26882378/

Eicosanoids in skin inflammation

"Eicosanoids play an integral part in homeostatic mechanisms related to skin health and structural integrity. They also mediate inflammatory events developed in response to environmental factors, such as exposure to ultraviolet radiation, and inflammatory and allergic disorders, including psoriasis and atopic dermatitis. This review article discusses biochemical aspects related to cutaneous eicosanoid metabolism, the contribution of these potent autacoids to skin inflammation and related conditions, and considers the importance of nutritional supplementation with bioactives such as omega-3 and omega-6 polyunsaturated fatty acids and plant-derived antioxidants as means of addressing skin health issues."

-School of Pharmacy and Centre for Skin Sciences, School of Life Sciences, University of Bradford, Richmond Road, UK
https://pubmed.ncbi.nlm.nih.gov/22521864/

Eicosanoids

eicosanoid - "any of a class of compounds (such as the prostaglandins) derived from polyunsaturated fatty acids (such as arachidonic acid) and involved in cellular activity."

-Merriam-Webster
https://www.merriam-webster.com/dictionary/eicosanoid

■■■

…"Eicosanoids are powerful lipid mediators of inflammation and are known to regulate multiple aspects of inflammatory processes."…

-Department of Veterinary Pathobiology, University of Missouri, Columbia, MO, USA
-Departments of Chemistry/Biochemistry and Pharmacology, University of California, San Diego, La Jolla, CA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5610093/

■■■

…"Endogenous ligands for CB receptors discovered until now are eicosanoids: N–arachidonoylethanolamide (anandamide), 2–arachidonoyl glycerol, noladin ether, O–arachidonoylethanolamine (virodhamide) and N–arachidonoyldopamine."…

-Department of Pharmacology and Pharmacotherapy, 'Carol Davila' University of Medicine and Pharmacy, Romania
-Department of Physiology, 'Carol Davila' University of Medicine and Pharmacy, Romania
-Department of Dermatology, 'Carol Davila' University of Medicine and Pharmacy, Romania
-Department of Anatomy, 'Carol Davila' University of Medicine and Pharmacy, Romania
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056416

Eicosanoid Storm in Infection and Inflammation

"Controlled immune responses to infection and injury involve complex molecular signalling networks with coordinated and often opposing actions. Eicosanoids and related bioactive lipid mediators derived from polyunsaturated fatty acids constitute a major bioactive lipid network that is among the most complex and challenging pathways to map in a physiological context. Eicosanoid signalling, similar to cytokine signalling and inflammasome formation, has primarily been viewed as a pro-inflammatory component of the innate immune response; however, recent advances in lipidomics have helped to elucidate unique eicosanoids and related docosanoids with anti-inflammatory and pro-resolution functions. This has advanced our overall understanding of the inflammatory response and its therapeutic implications. The induction of a pro-inflammatory and anti-inflammatory eicosanoid storm through the activation of inflammatory receptors by infectious agents is reviewed.

Eicosanoids are locally acting bioactive signaling lipids derived from arachidonic acid and related polyunsaturated fatty acids (PUFAs) that regulate a diverse set of homeostatic and inflammatory processes [1,2] linked to numerous diseases. Inhibiting the formation or receptor-mediated actions of classical eicosanoids (that is prostaglandins and leukotrienes) by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), by the leukotriene inhibitor zileuton, and by leukotriene receptor antagonists during inflammation remains a prevailing strategy to alleviate pain, swelling, fever and asthmatic conditions. However, pleiotropic effects are becoming increasingly appreciated for most eicosanoids and their related docosanoids.

Hundreds of structurally and stereochemically distinct eicosanoid species can be made from arachidonic acid and other ω6-derived PUFAs such as dihomo-γ-linolenic acid (DGLA) whose origin is the 18-carbon essential fatty acid linoleic acid as well as ω3-derived PUFAs from α-linolenic acid (ALA) including eicosapentaenoic acid (EPA) which can be further elongated to docosapentaenoic acid (DPA) and further desaturated to docosahexaenoic acid (DHA). Although the physiological roles of only a few of the eicosanoid and related docosanoid species are well understood, some of the agonists and receptors that activate inflammasome formation and the cytokine storm that accompanies infection[3,4] appear to also initiate the release of arachidonic acid and related PUFAs, resulting in an eicosanoid storm[5]."

-Department of Chemistry and Biochemistry and Department of Pharmacology, School of Medicine, University of California at San Diego, La Jolla, California, USA
https://www.nature.com/articles/nri3859

■■■

"Mammalian tissues express at least two cannabinoid receptor types, CB1 and CB2, both G protein coupled. CB1 receptors are found predominantly at nerve terminals where they mediate inhibition of transmitter release. CB2 receptors occur mainly on immune cells, one of their roles being to modulate cytokine release. Endogenous agonists for cannabinoid receptors also exist, and are all eicosanoids."….

-School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK
https://pubmed.ncbi.nlm.nih.gov/16570099

Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids

"Omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFA) are precursors of potent lipid mediators, termed eicosanoids, which play an important role in the regulation of inflammation. Eicosanoids derived from n-6 PUFAs (e.g., arachidonic acid) have proinflammatory and immunoactive functions, whereas eicosanoids derived from n-3 PUFAs [e.g., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] have anti-inflammatory properties, traditionally attributed to their ability to inhibit the formation of n-6 PUFA-derived eicosanoids. While the typical Western diet has a much greater ratio of n-6 PUFAs compared with n-3 PUFAs, research has shown that by increasing the ratio of n-3 to n-6 fatty acids in the diet, and consequently favoring the production of EPA in the body, or by increasing the dietary intake of EPA and DHA through consumption of fatty fish or fish-oil supplements, reductions may be achieved in the incidence of many chronic diseases that involve inflammatory processes; most notably, these include cardiovascular diseases, inflammatory bowel disease (IBD), cancer, and rheumatoid arthritis, but psychiatric and neurodegenerative illnesses are other examples."

-Alimentary Pharmabiotic Centre (APC), County Cork, Ireland.
https://pubmed.ncbi.nlm.nih.gov/20500789/

Proinflammatory effects of n-6 fatty-acid-derived eicosanoids and anti-inflammatory effects of the n-3 fatty-acid-derived eicosanoids.

Proinflammatory effects of the n-6 fatty-acid-derived eicosanoids

Arachidonic acid (n-6) derived eicosanoids		Physiological effects	Organs or cells
Prostaglandins	PGD2	Bronchoconstriction Proinflammatory	Bronchi Activation of eosinophils
	PGE2	Proarrhythmic Induces fever Causes pain Increases production of IL-6	Vessels Nociceptor sensory neurons
	PGF2	Bronchoconstriction	Bronchi
	PGI2	Proarrhythmic	Vessels
		Causes pain	Nociceptor sensory neurons
Thromboxanes	TXA2	Proaggregation Vasoconstriction Bronchoconstriction	Platelets Vessels Bronchi
	TXB2	Proaggregation Vasoconstriction Bronchoconstriction	Platelets Vessels Bronchi
Leukotrienes	LTA4		
	LTB4	Proinflammatory Chemotaxis Release of reactive oxygen species	Leukocytes Leukocytes Granulocytes
	LTC4		
	LTD4		

	LTE4		
Anti-inflammatory effects of the n-3 fatty-acid-derived eicosanoids			
	EPA and DHA (n-3) derived eicosanoids	Physiological effects	Organs or cells
Prostaglandins	PGD3		
	PGE3	Antiarrhythmic	Vessels
	PGF3		
	PGI3	Antiarrhythmic	Vessels
Thromboxanes	TXA3	Antiaggregation	Platelets
	TXB3	Antiaggregation	Platelets
Leukotrienes	LTA5		
	LTB5	Anti-inflammatory	Leukocytes
	LTC5		
	LTD5		
	LTE5		
Resolvins	RVE1	Antiaggregation Anti-inflammatory	Platelets Dendritic cells
	RVD	Anti-inflammatory	
Neuroprotectin	NPD1	Anti-inflammatory Antiapoptotic Decreases oxidative stress	Retina (photoreceptor cells) and brain

Data elaborated from [21, 37–39]

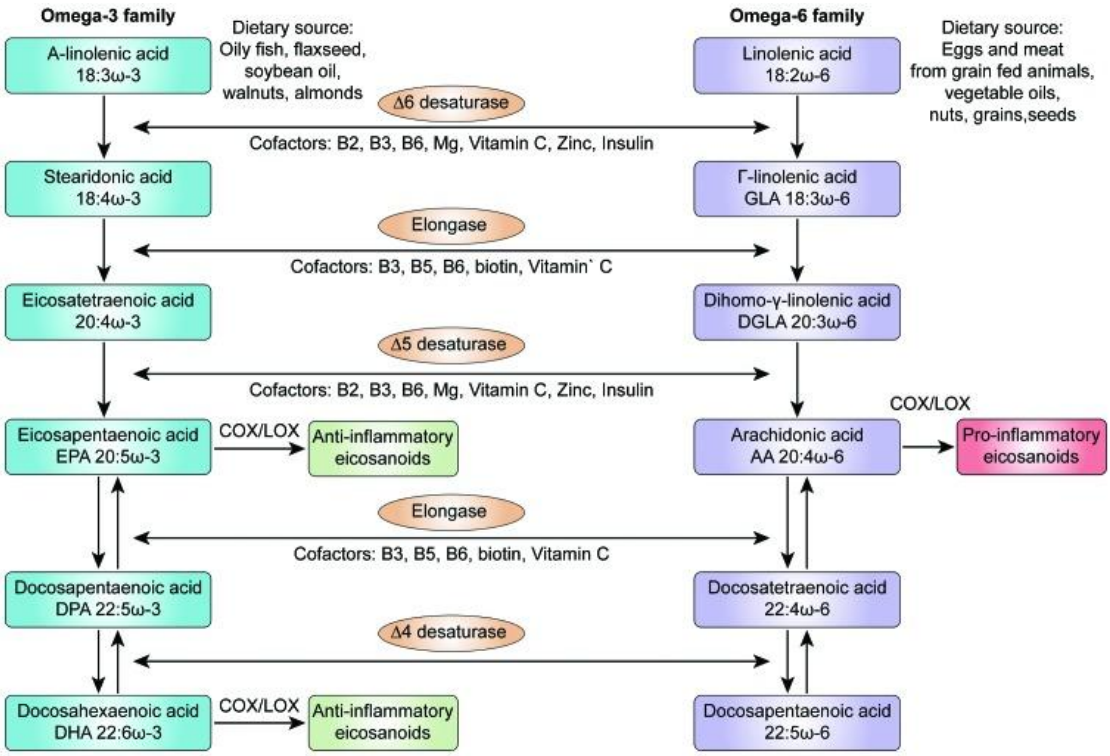
-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland
-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

Application of metabolomics part II: Focus on fatty acids and their metabolites in healthy adults

"Fatty acids (FAs) are major constituents of lipids and play essential roles in the diverse biological functions of the human body. They are key components of the cell membrane, provide an essential source of cellular fuel and energy storage and are involved in critical signal transduction pathways. Depending on the chemical structure, an FA can be a saturated FA (SFA), a monounsaturated FA (MUFA), or a polyunsaturated FA (PUFA). Apart from the essential PUFAs [i.e., linoleic acid (LA) and alpha-linolenic acid (ALA)], the human body can synthesize the majority of FAs. LA and ALA are precursors for omega-3 and omega-6 FAs, respectively, and can only be obtained from the diet. LA is metabolized to arachidonic acid (AA) and is mainly found in meat and eggs from grain-fed animals, vegetable oils, nuts and seeds [(1)]. ALA and its derivatives,

Figure 1

"Eicosanoid synthesis pathway. Lipid mediators are generated from omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) in the lipoxygenase (LOX) and cyclooxygenase (COX) pathways. Conversion of precursor omega-3 and omega-6 PUFAs to their derivatives is facilitated by desaturase and elongase in the presence of cofactors. Pro-inflammatory 4-series leukotrienes, 2-series prostaglandins, and thromboxane A2 are derived from AA, and eicosapentaenoic acid (EPA) derived 3-series prostaglandins, and 5-series leukotrienes have reduced inflammatory properties. Pro-resolving lipoxins derive from AA; resolvins, protectins, and maresins are generated from DHA and EPA."



…"eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found in fish oil, flaxseeds, walnuts, and seeds [2]. Eicosanoids are metabolites produced from AA, EPA and DHA under the activity of cyclooxygenases (COXs), lipoxygenases (LOXs) and cytochrome P450s (CYPs). Eicosanoids play critical roles in the inflammation process [Fig. 1]. The Western diet now provides a 15:1 ratio of omega-6/omega-3 ratio that is markedly higher compared with such levels a century ago [3]. The consumption of a Westernized diet is associated with a higher risk of the onset of chronic disease [4,5]. An unbalanced omega-6 to omega-3 ratio results in an increased production of AA and pro-inflammatory eicosanoids [6]. Due to the enzyme competition, the production of anti-inflammatory EPA/DHA-derived eicosanoids is reduced. Overall, therefore, this imbalance promotes a pro-inflammatory profile [7]. It is already known that type-2 diabetes and its complications are associated with lipid metabolism disorder and Farnesoid X receptor (FXR) plays an important role in regulating lipid and glucose metabolism. Liu et al demonstrated that the activation of FXR in mice induced the activation of the AMPK-ACC-CPT1 pathway, a signaling pathway promoting fatty acid oxidation and achieving its lipid-lowering effect [8]. Additionally, it has been established that in individuals with high-fat diet-induced type 2 diabetes, monounsaturated free fatty acids (FFAs) can serve as a predictive indicator of vascular restenosis following interventional therapy [9]. Chronic diseases often occur when inflammation is persistent or has not been effectively resolved [10]."

-Laboratory of Toxicology and Forensic Sciences, Medical School, University of Crete, Heraklion
-Metabolomic Medicine Clinic, Athens, Greece
-European Institute of Nutritional Medicine, E.I.Nu.M, Rome, Italy
-Toxplus Spin-Off S.A., Heraklion
-Laboratory of Anatomy-Histology-Embryology and
-Laboratory of Clinical Virology, School of Medicine, University of Crete, Heraklion, Greece
-Correspondence to: Professor Aristides Tsatsakis, Laboratory of Toxicology and Forensic Sciences, Medical School, University of Crete, Heraklion,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6257830/

See also Arachidonic Acid (Omega-6) , Prostaglandins

Eicosapentaenoic acid (EPA)

…"EPA is elongated to DPAn-3 (22:5n-3 or docosapentaenoic acid). DPAn-3 is then metabolized to DHA in several relatively more complex steps. Firstly it is elongated then desaturated via delta-6desaturase to form the intermediate molecule 24:6n-3. It must then be taken into the peroxisomes to undergo limited β-oxidation to remove two carbon atoms in a process known as

retro-conversion or the "Sprecher" pathway [12]. Interestingly, microalgae seem to be more efficient at synthesizing DHA by bypassing the last three steps and simply metabolizing DHA in one step from DPA with delta 4 desaturase [12]."...

-Centre for Occupational and Health Psychology, School of Psychology, Cardiff University
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257695

Emotional States

"The endocannabinoid system regulates a wide range of physiological processes including pain, inflammation, and cognitive/emotional states."

-Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA 92037, USA.
https://www.ncbi.nlm.nih.gov/pubmed/20493882

Endocannabinoid system and synaptic plasticity: implications for emotional responses

"The endocannabinoid system has been involved in the regulation of anxiety, and proposed as an inhibitory modulator of neuronal, behavioral and adrenocortical responses to stressful stimuli. Brain regions such as the amygdala, hippocampus and cortex, which are directly involved in the regulation of emotional behavior, contain high densities of cannabinoid CB1 receptors. Mutant mice lacking CB1 receptors show anxiogenic and depressive-like behaviors as well as an altered hypothalamus pituitary adrenal axis activity, whereas enhancement of endocannabinoid signaling produces anxiolytic and antidepressant-like effects. Genetic and pharmacological approaches also support an involvement of endocannabinoids in extinction of aversive memories. Thus, the endocannabinoid system appears to play a pivotal role in the regulation of emotional states. Endocannabinoids have emerged as mediators of short- and long-term synaptic plasticity in diverse brain structures. Despite the fact that most of the studies on this field have been performed using in vitro models, endocannabinoid-mediated plasticity might be considered as a plausible candidate underlying some of the diverse physiological functions of the endogenous cannabinoid system, including developmental, affective and cognitive processes. In this paper, we will focus on the functional relevance of endocannabinoid-mediated plasticity within the framework of emotional responses. Alterations of the endocannabinoid system may constitute an important factor in the aetiology of certain neuropsychiatric disorders, and, in turn, enhancers of endocannabinoid signaling could represent a potential therapeutical tool in the treatment of both anxiety and depressive symptoms."

-Departamento de Fisiología Fisiología Animal II, Facultad de Biología, Universidad Complutense, Madrid, Spain
https://pubmed.ncbi.nlm.nih.gov/17641734/

Functional role of the endocannabinoid system in emotional homeostasis

…"Taken together, present data reinforce the involvement of the endocannabinoid system in the control of emotional homeostasis and further suggest the pharmacological manipulation of the endocannabinoid system as a potential therapeutic tool in the management of anxiety-related disorders."

-Departamento de Fisiología, Universidad Complutense, Madrid, España.
https://pubmed.ncbi.nlm.nih.gov/19145562/

Endocannabinoid system and stress and anxiety responses

"Cannabinoid agonists induce complex and often contradictory effects on anxiety in humans and experimental animals. The data from animal tests provide evidence of dose-dependent bidirectional modulation of anxiety by the cannabinoid system and the importance of environmental context. The mechanisms mediating the effects of cannabinoids on anxiety-related responses appear to involve CB1 and non-CB1 cannabinoid receptors. In addition, the CRH, GABA(A), cholecystokinin, opioid and serotonergic systems have also been implicated. Brain regions such as the amygdala, hippocampus and cortex, directly involved in the regulation of emotional behavior, contain high densities of CB1 receptors. Mutant mice lacking CB1 receptors show anxiogenic-like and depressive-like phenotypes in several tests, as well as profound alterations in their adrenocortical activity. Pharmacological blockade of CB1 receptors induces anxiety in rats, and inhibition of anandamide metabolism produces anxiolytic-like effects. Thus, the endocannabinoid system appears to play a pivotal role in the regulation of emotional states and may constitute a novel pharmacological target for anti-anxiety therapy."

-Department of Physiology (Animal Physiology II), Faculty of Biology, Complutense University
https://pubmed.ncbi.nlm.nih.gov/15927244/

Encephalomyelitis

Encephalomyelitis is inflammation of the brain and spinal cord, typically due to acute viral infection. - *(Oxford / Google)*

Combination of cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), mitigates experimental autoimmune encephalomyelitis (EAE) by altering the gut microbiome

"Currently, a combination of marijuana cannabinoids including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) is used as a drug to treat muscle spasticity in patients with Multiple Sclerosis (MS). Because these cannabinoids can also suppress inflammation, it is unclear whether such patients benefit from suppression of neuroinflammation and if so, what is the mechanism through which cannabinoids act. In the currently study, we used a murine model of MS, experimental autoimmune encephalomyelitis (EAE), to study the role of gut microbiota in the attenuation of clinical signs of paralysis and inflammation caused by cannabinoids. THC + CBD treatment attenuated EAE and caused significant decrease in inflammatory cytokines such as IL-17 and IFN-γ while promoting the induction of anti-inflammatory cytokines such as IL-10 and TGF-β. Use of 16S rRNA sequencing on bacterial DNA extracted from the gut revealed that EAE mice showed high abundance of mucin degrading bacterial species, such as Akkermansia muciniphila (A. muc), which was significantly reduced after THC + CBD treatment. Fecal Material Transfer (FMT) experiments confirmed that THC + CBD-mediated changes in the microbiome play a critical role in attenuating EAE. In silico computational metabolomics revealed that LPS biosynthesis, a key component in gram-negative bacteria such as A. muc, was found to be elevated in EAE mice which was confirmed by demonstrating higher levels of LPS in the brain, while treatment with THC + CBD reversed this trend. EAE mice treated with THC + CBD also had significantly higher levels of short chain fatty acids such as butyric, isovaleric, and valeric acids compared to naïve or disease controls. Collectively, our data suggest that cannabinoids may attenuate EAE and suppress neuroinflammation by preventing microbial dysbiosis seen during EAE and promoting healthy gut microbiota."

-Department of Pathology, Microbiology and Immunology. University of South Carolina School of Medicine, Columbia, SC, USA

https://www.sciencedirect.com/science/article/pii/S0889159119306476

Endocrine system

The effects of cannabinoids on the endocrine system.

"Cannabinoids are the derivatives of the cannabis plant, the most potent bioactive component of which is tetrahydrocannabinol (THC). The most commonly used drugs containing cannabinoids are marijuana, hashish, and hashish oil. These compounds exert their effects via interaction with the cannabinoid receptors CB1 and CB2. Type 1 receptors (CB1) are localised mostly in the

central nervous system and in the adipose tissue and many visceral organs, including most endocrine organs. Type 2 cannabinoid receptors (CB2) are positioned in the peripheral nervous system (peripheral nerve endings) and on the surface of the immune system cells. Recently, more and more attention has been paid to the role that endogenous ligands play for these receptors, as well as to the role of the receptors themselves. So far, endogenous cannabinoids have been confirmed to participate in the regulation of food intake and energy homeostasis of the body, and have a significant impact on the endocrine system, including the activity of the pituitary gland, adrenal cortex, thyroid gland, pancreas, and gonads. Interrelations between the endocannabinoid system and the activity of the endocrine system may be a therapeutic target for a number of drugs that have been proved effective in the treatment of infertility, obesity, diabetes, and even prevention of diseases associated with the cardiovascular system. So far, endogenous cannabinoids have been confirmed to participate in the regulation of food intake and energy homeostasis of the body, and have a significant impact on the endocrine system, including the activity of the pituitary gland, adrenal cortex, thyroid gland, pancreas, and gonads. Interrelations between the endocannabinoid system and the activity of the endocrine system may be a therapeutic target for a number of drugs that have been proved effective in the treatment of infertility, obesity, diabetes, and even prevention of diseases associated with the cardiovascular system."

-Chair and Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poland.

https://www.ncbi.nlm.nih.gov/pubmed/30618031

Endocannabinoid System

..."The Endocannabinoid System [is] a lipid-derived neurotransmitter system consisting of cannabinoid receptors, endocannabinoid signaling messengers, and regulatory biosynthetic and degradative enzymes."...

-Dept. of Anatomy and Neurobiology, University of California, Irvine

-School of Medicine, University of California, Irvine

-Dept. of Brain and Cognitive Sciences, Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA, USA

-Harvard Medical School, Harvard University, Boston, MA, USA

*-*Author for correspondence: Daniele Piomelli, Department of Anatomy and Neurobiology,*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5699224

An Introduction to the Endogenous Cannabinoid System.

"The endocannabinoid system (ECS) is a widespread neuromodulatory system that plays important roles in central nervous system development, synaptic plasticity, and the response to endogenous and environmental insults. The ECS comprises cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids. The most abundant cannabinoid receptors are the CB1 cannabinoid receptors; however, CB2 cannabinoid receptors, transient receptor potential channels, and peroxisome proliferator activated receptors are also engaged by some cannabinoids. Exogenous cannabinoids, such as tetrahydrocannabinol, produce their biological effects through their interactions with cannabinoid receptors. The best-studied endogenous cannabinoids are 2-arachidonoyl glycerol and arachidonoyl ethanolamide (anandamide). Despite similarities in chemical structure, 2-arachidonoyl glycerol and anandamide are synthesized and degraded by distinct enzymatic pathways, which impart fundamentally different physiologic and pathophysiologic roles to these two endocannabinoids. As a result of the pervasive social use of cannabis and the involvement of endocannabinoids in a multitude of biological processes, much has been learned about the physiologic and pathophysiologic roles of the ECS. This review provides an introduction to the ECS with an emphasis on its role in synaptic plasticity and how the ECS is perturbed in schizophrenia."

-Department of Psychological and Brain Sciences and Linda and Jack Gill Center for Biomolecular Science
https://www.ncbi.nlm.nih.gov/pubmed/26698193

Getting High on the Endocannabinoid System

"The endogenous cannabinoid system—named for the plant [cannabis] that led to its discovery—is one of the most important physiologic systems involved in establishing and maintaining human health. Endocannabinoids and their receptors are found throughout the body: in the brain, organs, connective tissues, glands, and immune cells. With its complex actions in our immune system, nervous system, and virtually all of the body's organs, the endocannabinoids are literally a bridge between body and mind. By understanding this system, we begin to see a mechanism that could connect brain activity and states of physical health and disease."

-Bradley E. Alger, Ph.D.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3997295/

The effects of cannabinoids on the endocrine system.

“Cannabinoids are the derivatives of the cannabis plant, the most potent bioactive component of which is tetrahydrocannabinol (THC). The most commonly used drugs containing cannabinoids are marijuana, hashish, and hashish oil. These compounds exert their effects via interaction with the cannabinoid receptors CB1 and CB2. Type 1 receptors (CB1) are localised mostly in the central nervous system and in the adipose tissue and many visceral organs, including most endocrine organs. Type 2 cannabinoid receptors (CB2) are positioned in the peripheral nervous system (peripheral nerve endings) and on the surface of the immune system cells. Recently, more and more attention has been paid to the role that endogenous ligands play for these receptors, as well as to the role of the receptors themselves. So far, endogenous cannabinoids have been confirmed to participate in the regulation of food intake and energy homeostasis of the body, and have a significant impact on the endocrine system, including the activity of the pituitary gland, adrenal cortex, thyroid gland, pancreas, and gonads. Interrelations between the endocannabinoid system and the activity of the endocrine system may be a therapeutic target for a number of drugs that have been proved effective in the treatment of infertility, obesity, diabetes, and even prevention of diseases associated with the cardiovascular system.”

Chair and Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poland.

https://www.ncbi.nlm.nih.gov/pubmed/30618031

Supply and demand for endocannabinoids

“The endocannabinoid system consists of G-protein coupled cannabinoid receptors that can be activated by cannabis-derived drugs and small lipids called endocannabinoids, plus associated biochemical machinery (precursors, synthetic and degradative enzymes, transporters). The endocannabinoid system in the brain primarily influences neuronal synaptic communication, and affects biological – functions including eating, anxiety, learning and memory, growth and development – via an array of actions throughout the nervous system. While many aspects of synaptic regulation by endocannabinoids are becoming clear, details of the subcellular organization and regulation of the endocannabinoid system are less well understood. This review focuses on recent investigations that illuminate fundamental issues of endocannabinoid storage, release, and functional roles.”…

- Department of Physiology, University of Maryland School of Medicine, 655 W. Baltimore St., Baltimore, MD, USA
- Program in Neuroscience, University of Maryland School of Medicine, 655 W. Baltimore St., Baltimore, MD, USA
- Institute of Molecular Medicine and Genetics, Medical College of Georgia, Georgia Health Sciences University, GA
- Graduate Program in Neuroscience, Medical College of Georgia, Georgia Health Sciences University, Augusta, GA
- Department of Neurology, Medical College of Georgia, Georgia Health Sciences University, Augusta, GA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3106144

The Endocannabinoid System and Pain

"The therapeutic potential of cannabinoids has been the topic of extensive investigation following the discovery of cannabinoid receptors and their endogenous ligands. Cannabinoid receptors and their endogenous ligands are present at supraspinal, spinal and peripheral levels. Cannabinoids suppress behavioral responses to noxious stimulation and suppress nociceptive processing through activation of cannabinoid CB1 and CB2 receptor subtypes. Endocannabinoids, the brains own cannabis-like substances, share the same molecular target as Δ9-tetrahydrocannabinol, the main psychoactive component in cannabis. Endocannabinoids serve as synaptic circuit breakers and regulate multiple physiological and pathological conditions, e.g. regulation of food intake, immunomodulation, inflammation, analgesia, cancer, addictive behavior, epilepsy and others. This review will focus on uncovering the roles of anandamide and 2-arachidonoylglycerol, the two best characterized endocannabinoids identified to date, in controlling nociceptive responding. The roles of anandamide and 2-arachidonoylglycerol, released under physiological conditions, in modulating nociceptive responding at different levels of the neuraxis will be emphasized in this review. Effects of modulation of endocannabinoid levels through inhibition of endocannabinoid hydrolysis and uptake is also compared with effects of exogenous administration of synthetic endocannabinoids in acute, inflammatory and neuropathic pain models. Finally, the therapeutic potential of the endocannabinoid signaling system is discussed in the context of identifying novel pharmacotherapies for the treatment of pain."

-Neuroscience and Behavior Program, Department of Psychology, University of Georgia, Athens, GA, USA
http://www.eurekaselect.com/93567/article

The Endocannabinoid System (ECS), The universal regulator

"The endocannabinoid system (ECS) plays a very important role in the human body for our survival. This is due to its ability to play a critical role in maintaining the homeostasis of the human body, which encompasses the brain, endocrine, and immune system, to name a few. ECS is a unique system in multiple dimensions. To begin with, it is a retrograde system functioning post- to pre-synapse, allowing it to be a "master regulator" in the body. Secondly, it has a very wide scope of influence due to an abundance of cannabinoid receptors located anywhere from immune cells to neurons. Finally, cannabinoids are rapidly synthesized and degraded, so they do not stay in the body for very long in high amounts, possibly enabling cannabinoid therapy to be a

safer alternative to opioids or benzodiazepines. This paper will discuss how ECS functions through the regulation of neurotransmitter function, apoptosis, mitochondrial function, and ion-gated channels. The practical applications of the ECS, as well as the avenues for diseases such as epilepsy, cancer, amyotrophic lateral sclerosis (ALS), and autism, which have no known cure as of now, will be explored."

-Department of Biochemistry and Molecular Biology, Colorado State University, USA
-Nova Southeastern University, 3301 College Ave, Fort Lauderdale, FL, USA
https://www.jyi.org/2018-june/2018/6/1/the-endocannabinoid-system-our-universal-regulator

Endocannabinoid system: An overview of its potential in current medical practice

“The endocannabinoid system (ECS) is a lipid signalling system, comprising of the endogenous cannabis-like ligands (endocannabinoids) anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which derive from arachidonic acid. These bind to a family of G-protein-coupled receptors, called CB1 and CB2. The cannabinoid receptor 1 (CB1R) is distributed in brain areas associated with motor control, emotional responses, motivated behaviour and energy homeostasis. In the periphery, the same receptor is expressed in the adipose tissue, pancreas, liver, GI tract, skeletal muscles, heart and the reproduction system. The CB2R is mainly expressed in the immune system regulating its functions. Endocannabinoids are synthesized and released upon demand in a receptor-dependent way. They act as retrograde signalling messengers in GABAergic and glutamatergic synapses and as modulators of postsynaptic transmission, interacting with other neurotransmitters. Endocannabinoids are transported into cells by a specific uptake system and degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). The ECS is involved in various pathophysiological conditions in central and peripheral tissues. It is implicated in the hormonal regulation of food intake, cardiovascular, gastrointestinal, immune, behavioral, antiproliferative and mammalian reproduction functions. Recent advances have correlated the ECS with drug addiction and alcoholism. The growing number of preclinical and clinical data on ECS modulators is bound to result in novel therapeutic approaches for a number of diseases currently treated inadequately. The ECS dysregulation has been correlated to obesity and metabolic syndrome pathogenesis. Rimonabant is the first CB1 blocker launched to treat cardiometabolic risk factors in obese and overweight patients. Phase III clinical trials showed the drug's ability to regulate intra-abdominal fat tissue levels, lipidemic, glycemic and inflammatory parameters. However, safety conerns have led to its withrawal. The role of endocannabinoids in mammalian reproduction is an emerging research area given their

implication in fertilization, preimplantation embryo and spermatogenesis. The relevant preclinical data on endocannabinoid signalling open up new perspectives as a target to improve infertility and reproductive health in humans."

-1st Department of Internal Medicine Clinic, AHEPA University Hospital, Aristotle University, Thessaloniki, Greece.
https://pubmed.ncbi.nlm.nih.gov/19675519/

The peripheral cannabinoid receptor knockout mice: an update

"This review gives an overview of the CB2 [cannabinoid 2] receptor (CB2R) knockout (CB2R−/−) mice phenotype and the work that has been carried out using this mutant mouse. Using the CB2R−/− mice, investigators have discovered the involvement of CB2R [cannabinoid 2 receptor] on immune cell function and development, infection, embryonic development, bone loss, liver disorders, pain, autoimmune inflammation, allergic dermatitis, atherosclerosis, apoptosis and chemotaxis."

-Department of Biological Sciences, California State Polytechnic University
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2219525/

The Endocannabinoid [EC] /Endovanilloid System [EV] in Bone: From Osteoporosis to Osteosarcoma

…"The EC/EV system is proven to be involved in the regulation of several physiological processes, such as appetite control, energy balance [11], pain perception [12], and immune response [13]. Moreover, it has been proposed as an anticancer target by several studies [14,15]. The CB1 receptor is more expressed in the central nervous system (CNS), whereas the CB2 receptor can be found predominantly in peripheral tissues [16], even though there is growing evidences indicating that it is also present in the brain [17,18]."…

-Department of Women, Child, and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy;
-Department of Experimental Medicine, University of Campania Luigi Vanvitelli, Naples, Italy;
-Department of Gynecology, Obstetrics and Reproductive Sciences, University of Campania Luigi Vanvitelli, Naples, Italy;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6514542/

Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities.

…"This review mentions several possible additional therapeutic targets for cannabinoid receptor

agonists. These include other kinds of pain, epilepsy, anxiety, depression, Parkinson's and Huntington's diseases, amyotrophic lateral sclerosis, stroke, cancer, drug dependence, glaucoma, autoimmune uveitis, osteoporosis, sepsis, and hepatic, renal, intestinal and cardiovascular disorders. It also describes potential strategies for improving the efficacy and/or benefit-to-risk ratio of these agonists in the clinic. These are strategies that involve (i) targeting cannabinoid receptors located outside the blood-brain barrier, (ii) targeting cannabinoid receptors expressed by a particular tissue, (iii) targeting upregulated cannabinoid receptors, (iv) selectively targeting cannabinoid CB(2) receptors, and/or (v) adjunctive 'multi-targeting'."

School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK.
https://www.ncbi.nlm.nih.gov/pubmed/23108552

Human Endocannabinoid System

"In the 1990's, scientists discovered endocannabinoids, the natural cannabis-like molecules produced by the human body. Scientists began to realize cannabis exerted its effects, in part, by mimicking our endocannabinoids. It appears the main function of the endocannabinoid system is to maintain bodily homeostasis—biological harmony in response to changes in the environment.[9] Taxonomic investigation pevealed that the endocannabinoid system is incredibly old, having evolved over 500 million years ago. Moreover, it is present in all vertebrates—mammals, bird, reptiles, amphibians, fish, etc, all produce endocannabinoids![10]

Research initially suggested endocannabinoid receptors were only present in the brain and nerves, but scientists later found that the receptors are present throughout the body, including our skin, immune cells, bone, fat tissue, liver, pancreas, skeletal muscle, heart, blood vessels, kidney, and gastrointestinal tract.[11] We now know the endocannabinoid system is involved in a wide variety of processes, including pain, memory, mood, appetite, stress, sleep, metabolism, immune function, and reproductive function.[12,13] Endocannabinoids are arguably one of the most widespread and versatile signaling molecules known to man." **[sic]**

-University of California (UCLA Health)
~~https://www.uclahealth.org/cannabis/human-endocannabinoid-system~~

https://archive.is/mVbCc

The Endocannabinoid System and Plant-Derived Cannabinoids in Diabetes and Diabetic Complications

"Oxidative stress and inflammation play critical roles in the development of diabetes and its complications. Recent studies provided compelling evidence that the newly discovered lipid

signaling system (ie, the endocannabinoid system) may significantly influence reactive oxygen species production, inflammation, and subsequent tissue injury, in addition to its well-known metabolic effects and functions. The modulation of the activity of this system holds tremendous therapeutic potential in a wide range of diseases, ranging from cancer, pain, neurodegenerative, and cardiovascular diseases to obesity and metabolic syndrome, diabetes, and diabetic complications. This review focuses on the role of the endocannabinoid system in primary diabetes and its effects on various diabetic complications, such as diabetic cardiovascular dysfunction, nephropathy, retinopathy, and neuropathy, particularly highlighting the mechanisms beyond the metabolic consequences of the activation of the endocannabinoid system. The therapeutic potential of targeting the endocannabinoid system and certain plant-derived cannabinoids, such as cannabidiol and Δ9-tetrahydrocannabivarin, which are devoid of psychotropic effects and possess potent anti-inflammatory and/or antioxidant properties, in diabetes and diabetic complications is also discussed."

-Section on Oxidative Stress and Tissue Injury, Laboratory of Physiological Studies, National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

-Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest, Hungary

-Department of Surgery, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3349875/

Cannabinoid Delivery Systems for Pain and Inflammation Treatment

"There is a growing body of evidence to suggest that cannabinoids are beneficial for a range of clinical conditions, including pain, inflammation, epilepsy, sleep disorders, the symptoms of multiple sclerosis, anorexia, schizophrenia and other conditions. The transformation of cannabinoids from herbal preparations into highly regulated prescription drugs is therefore progressing rapidly. The development of such drugs requires well-controlled clinical trials to be carried out in order to objectively establish therapeutic efficacy, dose ranges and safety. The low oral bioavailability of cannabinoids has led to feasible methods of administration, such as the transdermal route, intranasal administration and transmucosal adsorption, being proposed. The highly lipophilic nature of cannabinoids means that they are seen as suitable candidates for advanced nanosized drug delivery systems, which can be applied via a range of routes. Nanotechnology-based drug delivery strategies have flourished in several therapeutic fields in recent years and numerous drugs have reached the market. This review explores the most recent developments, from preclinical to advanced clinical trials, in the cannabinoid delivery field, and focuses particularly on pain and inflammation treatment. Likely future directions are also considered and reported."

-Istituto Farmaceutico Candioli, Beinasco, Italy;
-Department of Drug Science and Technology, University of Turin, Turin, Italy;
-Department of Life Sciences and Systems Biology, University of Turin, Turin, Italy;
-Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6222489/

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“Hello, my name is Dr. David Allen. I'm a retired cardiac surgeon and member of the International Cannabinoid Research Society - ICRS. That means I'm a cannabinoid research scientist. And I'm here to tell you about the discovery of the endocannabinoid system, the ECS. And the significance and how it was we'll change medicine. And we discovered the endocannabinoid system about 30 years ago. And we really didn't understand the significance of its discovery. And so we, we found out that this is a chemical communication that your body has, it's not electrical, it's chemical. And it's kind of like the hormone systems that that people are familiar with. And your body makes these cannabinoids, they're endogenous, so they're endocannabinoids. And they perform some miraculous functions in the body. And we're just learning the significance of these of these functions. And basically, the endocannabinoid system is responsible for homeostasis. Most people don't understand what that really means. But it's, it's the body's ability to maintain itself and function in the proper environment. And so it's it's critically important that the doctors in the future understand this control mechanism. And we're finding out that they, that manipulation of this endocannabinoid system will control diabetes, it controls cancer it controls whether you can survive a heart attack or stroke. And so this is critically important for doctors to understand this new science. And the discovery of the endocannabinoid system is the single most important medical scientific discovery ever. And will will save more lives than the discovery and application of sterile surgical technique. And I'm a heart surgeon saying that so more people will be saved by manipulation of the endocannabinoid system, then are currently saved by by surgery. And so we found out there studies that if you use cannabis for for 20 years or more just smoking cannabis, that it decreases the incidence of diabetes by 66%. There are studies that show when they specifically stress beta cells of the pancreas to try to kill them by oxidative techniques, that if you use cannabinoids, it, it protects the cells from this oxidation. And so, so really what this means is you can use cannabis and decrease the incidence of diabetes by 66%. Or more maybe if you use it if you use it other ways if you eat it, and your doctor currently can't give you any medicine at all, that decreases the incidence of diabetes by even 2%. So this is a miracle that cannabis does this. And it means that your use of cannabis will protect the beta cells of your pancreas from oxidation. That means basically all cannabis use is medical, regardless of whether you understand the science behind

this or not."

- Dr. David Allen M.D, Retired Cardiac Surgeon & Cannabinoid Research Scientist
- Member of the International Cannabinoid Research Society (ICRS)
http://bit.do/drdavidallen

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"Our Endocannabinoid System regulates everything in our body. Our Immune system, digestive system, cardiovascular system, nervous system, endocrine system, skin, skeleton, everything in our body is homeostatically regulated by our Endocannabinoid System. And yet it's not taught in medical school? There's something a little flawed here..."

- Dr. Bob Melamede
https://www.youtube.com/watch?v=3qkhwaETnjw (http://bit.do/drbobm)

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"Even if you've never smoked a joint in your life, you have sort of internal cannabis in your body. You have an endocannabinoid system endo meanings inside, you've got cannabinoid receptors in your brain and in your liver and your spleen and your bladder and your immune system cells. You've got receptors all over your body for this plant. And so when you smoke, you're sort of stimulating working within the endocannabinoid system and you're stimulating your cannabinoid receptors that helps to regulate your immune system, your energy, your metabolism, your blood sugar, it's sort of tamps down inflammation, your endocannabinoid system does a lot to maintain homeostasis in your body. So there's at least two types of cannabinoid receptors that we know about so far. There's CB1 and CB2. So the CB1 receptors are located all over your brain, and it's actually the most plentiful g coupled receptor in your brain. Although there aren't any in your brainstem, which means that you can't overdose from cannabis. It won't stop you from breathing, the way that you could say overdose from pain medicines. When people ask me like so what's the most important thing you learned? By far the most important thing I learned was that THC and CBD can kill cancer cells that they can kill cancer cells while leaving healthy cells intact. They trigger a programmed cell death, which is called apoptosis. And not only do they trigger apoptosis, but they prevent the cancer cells from being invasive from metastasizing. They prevent the growing tumor from signaling that it needs more blood supply, which is called angiogenesis. So cannabinoids, not just as a treatment for nausea and decreased appetite that happens because of chemotherapy but cannabinoids actually being chemotherapy actually treating cancer. That's really exciting to me."

-Dr. Julie Holland
https://www.youtube.com/watch?v=3qkhwaETnjw&t=29 (29s+)

…"Considerable data support the notion that endocannabinoid signaling has three broad and overlapping functions in mammals. The first is a stress recovery role, operating in a feedback loop in which endocannabinoid signaling is activated by stress and functions to return endocrine, nervous and behavioral systems to homeostatic balance (Hill et al., 2010b). The second function is to control energy balance through regulation of the intake, storage and utilization of food (Di Marzo et al., 2009b). The third function involves immune regulation; endocannabinoid signaling is activated by tissue injury (Pacher and Mechoulam, 2011) and modulates immune and inflammatory responses (Klein and Cabral, 2006). In light of these vital functions, it is not surprising that alterations in endocannabinoid signaling have important biological effects.

Based upon thousands of years of human experience with cannabis sativa as well as compelling preclinical data, it is reasonable to hypothesize that endogenous cannabinoid signaling is: (1) heterogenous in humans; (2) dysfunctional in some diseases or disorders; and (3) a potential target for therapeutic development. The purpose of this review is to summarize the available data supporting the first two hypotheses, and the corollary hypothesis that heterogeneity in endocannabinoid signaling contributes to variability among humans in the susceptibility to disease or disorders. In part one, two well-studied proteins of the endocannabinoid signaling system, the CB1 cannabinoid receptor (CB1R) and fatty acid amide hydrolase (FAAH), are introduced and evidence for their heterogeneity in humans is summarized. In part two, current understanding of mechanisms that regulate endocannabinoid ligand concentrations in the circulation is presented. Part three summarizes the data pertinent to the hypothesis that heterogeneity in the genes for CB1R (CNR1) and FAAH (FAAH) or differences in circulating endocannabinoids associate with the symptoms and/or diagnoses of substance use disorders, depression, anxiety and eating disorders, schizophrenia and attention deficit disorder."…

-Department of Pharmacology and Neuroscience Research Center, Medical College of Wisconsin
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288440

"The endocannabinoid system is found in most, if not all, mammalian organs and is involved in a variety of physiological functions, ranging from the control of synaptic plasticity in the brain to the modulation of smooth muscle motility in the gastrointestinal tract. This signaling complex consists of G protein-coupled cannabinoid receptors, endogenous ligands for those receptors (endocannabinoids) and enzymes/transporters responsible for the formation and deactivation of these ligands. There are two subtypes of cannabinoid receptors, CB1 and CB2, and two major endocannabinoids, arachidonoylethanolamide (anandamide) and 2-arachidonoyl-sn-glycerol (2-AG), which are produced upon demand through cleavage of distinct phospholipid precursors."…

-Department of Anatomy and Neurobiology, University of California, Irvine, Irvine, CA, USA.
-Department of Pharmacology, University of California, Irvine, Irvine, CA, USA.
-Department of Biological Chemistry, University of California, Irvine, Irvine, CA, USA.
https://pubmed.ncbi.nlm.nih.gov/33387286

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…"Chronic state of inflammation plays an important role in the onset of classic inflammatory diseases (e.g., arthritis) but also of various diseases, including cardiovascular and neurodegenerative diseases, diabetes, cancer, asthma. The suppression or inhibition of inflammatory/pro-inflammatory mediators using synthetic anti-inflammatory compounds (both steroidal and non-steroidal) is one of the major routes for the treatment of inflammatory disorders. However, several common side effects, including gastric irritation and ulceration, renal and hepatic failure, haemolytic anaemia, asthma exacerbation, skin rashes, are often associated with the use of synthetic anti-inflammatory drugs [25]. Increasing amounts of evidence demonstrate that the endocannabinoid system actively participates in the pathophysiology of osteoarthritis-associated joint pain. Production and release of endocannabinoids are mediated, during inflammatory-joint disease, by the generation of pro inflammatory cytokines (interferon [IFN]-c, interleukin (IL-12, IL-15, IL-17, IL-18), chemokines, chemical mediators, such as nitric oxide synthetase (NOS)-2, cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs) and various other arachidonic acid metabolic by-products [7]. Overall, preclinical and clinical data support the potentially effective anti-inflammatory properties of endocannabinoid agonists that target CB2 receptors."…

-Istituto Farmaceutico Candioli, Beinasco, Italy;
-Department of Drug Science and Technology, University of Turin, Turin, Italy;
-Department of Life Sciences and Systems Biology, University of Turin, Turin, Italy;
-Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6222489/

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"The endocannabinoid system plays a key role in regulating a variety of physiological processes such as appetite control and energy balance, pain perception, and immune responses."

-Bone and Cancer Group, Edinburgh Cancer Research Centre, The University of Edinburgh, Edinburgh, UK
-Rheumatic Disease Unit, The Centre for Molecular Medicine, The University of Edinburgh, Edinburgh, UK
-Edited by: Vicky E. MacRae, The University of Edinburgh, UK
-Reviewed by: Paula H. Stern, Northwestern University Feinberg School of Medicine, USA; Alun Hughes, University of St Andrews, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499879/

…"The endocannabinoid system is involved in inflammation, pain, and metabolic disorders, and the modulation of CB receptors is a promising strategy for pharmacotherapy (6, 7). "…

-Institute of Biochemistry and Molecular Medicine, National Center of Competence in Research TransCure, University of Bern, Bern, Switzerland,

-Swiss Tropical and Public Health Institute, Socinstrasse 57, Basel, Switzerland, the University of Basel, Petersplatz 1, Basel, Switzerland,

-Natural and Medical Sciences Institute at the University of Tuebingen, Reutlingen, Germany, and

-Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481297/

"Is there a place for cannabinoid-based medicines in psychiatry? Evidence from animal and human studies points to the endocannabinoid system as an important regulator of emotionality, but how can we exploit this knowledge for therapy? This review article offers a critical assessment of the evidence, focused on obsessive compulsive disorder, and clues to future research."

-Daniele Piomelli, PhD, Editor-in-Chief, University of California-Irvine, School of Medicine

https://www.news-medical.net/news/20190603/Bodys-endocannabinoid-system-appears-to-be-new-target-for-drug-development-against-OCD.aspx

http://bit.do/201906

"The endocannabinoid system regulates a wide range of physiological processes including pain, inflammation, and cognitive/emotional states."

-Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA 92037, USA.

https://www.ncbi.nlm.nih.gov/pubmed/20493882

"The eCB [endocannabinoid] system was initially described in the late 1980s after the identification of specific receptors (83). It now comprises the cannabinoid receptor types 1 (CB1) and 2 (CB2), their endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and the enzymes responsible for their synthesis and degradation (84–86)."

-Department of Pharmacology, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

-Center of Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Ribeirão Preto, Brazil

-Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA

-Edited by: Frank Kirchhoff, University of Saarland, Germany
-Reviewed by: Eng-Ang Ling, National University of Singapore, Singapore;
-Aviva Jane Symes
-Uniformed Services University of the Health Sciences, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4729885/

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"Endocannabinoids are important retrograde modulators of synaptic transmission throughout the nervous system. Cannabinoid receptors are seven transmembrane G-protein coupled receptors favoring protein. They are known to play an important role in various processes, including metabolic regulation, craving, pain, anxiety, and immune function. "…

-Laboratoire de Neuropharmacologie, École d'optométrie, Université de Montréal, C.P. Succursale Centre-Ville, Montréal, QC, Canada H3C 3J7
https://www.hindawi.com/journals/np/2016/9247057/

■■■

"The endocannabinoid system is up-regulated in numerous pathophysiological states such as inflammatory, neurodegenerative, gastrointestinal, metabolic and cardiovascular diseases, pain, and cancer. It has been suggested that this phenomenon primarily serves an autoprotective role in inhibiting disease progression and/or diminishing signs and symptoms. Accordingly, enhancement of endogenous endocannabinoid tone by inhibition of endocannabinoid degradation represents a promising therapeutic approach for the treatment of many diseases."

-Department of Experimental Physiology and Pathophysiology, Medical University of Białystok, Mickiewicz str, Białystok, Poland.
-Department of Experimental Physiology and Pathophysiology, Medical University of Białystok, Mickiewicz str., Białystok, Poland.
https://www.ncbi.nlm.nih.gov/pubmed/29729263

■■■

"In the last 25 years a good deal of information has been accumulated on the main components of the "endocannabinoid (eCB) system", a rather complex ensemble of lipid signals ("endocannabinoids"), their target receptors, purported transporters, and metabolic enzymes. It has been clearly documented that eCB signaling plays a key role in many human health and disease conditions of the central nervous system, thus opening the avenue to the therapeutic exploitation of eCB-oriented drugs for the treatment of psychiatric, neurodegenerative, and neuroinflammatory disorders."

- Centre for Integrative Neuroscience and Neurodynamics, School of Psychology and Clinical Language Sciences,

University of Reading, Reading, UK.

- Center of Integrated Research and School of Medicine, Campus Bio-Medico University of Rome.

- Mafalda Luce Center for Pervasive Developmental Disorders, Milan, Italy.

- Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Teramo, Italy.

- Center of Integrated Research and School of Medicine, Campus Bio-Medico University of Rome, - European Center for Brain Research (CERC)/Santa Lucia Foundation, Rome, Italy.

https://www.ncbi.nlm.nih.gov/m/pubmed/26216231/

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…"The endocannabinoid system is an important neuromodulatory system involved in a plethora of physiological functions (De Petrocellis et al., 2004; Freund et al., 2003; Piomelli, 2003). "…

-Department of Physiological Chemistry, Johannes Gutenberg University, Duesbergweg 6, 55099 Mainz, Germany.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1769341/

■■■

"The Endocannabinoid System (ECS) is one of the largest homeostatic systems in the human body, with elements throughout the brain and in every major organ. Scientific research has shown that changes in ECS activity may correlate with a wide range of disease states."

-PHYTECS, Los Angeles CA, USA.

http://www.phytecs.com/

The thrifty lipids: Endocannabinoids and the neural control of energy conservation

"The "thrifty gene hypothesis" posits that evolution preferentially selects physiological mechanisms that optimize energy storage to increase survival under alternating conditions of abundance and scarcity of food. Recent experiments suggest that endocannabinoids – a class of lipid-derived mediators that activate cannabinoid receptors in many cells of the body – are key agents of energy conservation. The new evidence indicates that these compounds increase energy intake and decrease energy expenditure by controlling the activity of peripheral and central neural pathways involved in the sensing and hedonic processing of sweet and fatty foods, as well as in the storage of their energy content for future use."

…"The endocannabinoid system plays a critical role in monitoring energy needs and maintaining metabolic balance in mammals [2]. This signaling complex is found in most mammalian organs and tissues, and comprises a set of lipid-derived messengers (i.e., endocannabinoids) [3], as well as proteins that control their formation and deactivation [4–12] and cell-surface receptors that

transduce their actions (CB1 and CB2 cannabinoid receptors) [13, 14]. One of the best-understood endocannabinoids, the fatty acyl ester 2-arachidonoyl-sn-glycerol (2-AG), is produced in the brain and spinal cord through the consecutive activation of two receptor-operated lipases, phospholipase C-β (PLC-β) and diacylglycerol lipase-α (DGL-α). After release into the extracellular space, 2-AG diffuses to presynaptic nerve terminals, where it reduces neurotransmitter release by recruiting Gi/o protein-coupled CB1 receptors (CB1Rs), to be finally eliminated through enzyme-mediated hydrolysis [6, 8, 9, 15] (see Figure 1). Less is known on the workings of another important endocannabinoid, anandamide (arachidonoylethanolamide), though it is generally assumed that, like 2-AG, this compound acts in the brain as a local modulator of synaptic activity [3] (see Box 1)."

…"The central nervous system (CNS) has long been recognized as a site of endocannabinoid control of feeding behavior [16, 17]. There is substantial evidence, however, that endocannabinoid signaling in peripheral tissues also plays an important role in energy homeostasis [18–21]. In the present review, we highlight recent findings suggesting that an overarching function of the endocannabinoids, and particularly of 2-AG, both inside and outside the CNS might be to regulate the sensing and seeking of sweet and fatty foods, when these are available, and promote the storage of their energy content to allow for its utilization during periods of scarcity. According to this view, endocannabinoid signaling is a key molecular instantiation of the "thrifty gene hypothesis", which states that evolution selects physiological mechanisms that maximize energy storage to increase survival under alternating conditions of feast and famine [1]."

-Departments of Pharmacology, University of California, Irvine, School of Medicine, Irvine, CA, USA
-Biological Chemistry, University of California, Irvine, School of Medicine, Irvine, CA, USA
-Unit of Drug Discovery and Development, Italian Institute of Technology, Genoa, Italy
-Corresponding author: Daniele Piomelli, University of California, Irvine, Department of Pharmacology, 3101
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3744874/

Endocannabinoid System Components: Overview and Tissue Distribution

"Marijuana/cannabinoid research has been transformed into mainstream science during the last half-century. Evidence based research and remarkable biotechnological advances demonstrate that phytocannabinoids and endocannabinoid (eCBs) acting on cannabinoid receptors (CBRs) regulate various aspects of human physiological, behavioral, immunological and metabolic functions. The distribution and function of the components of the endocannabinoid system (ECS) in the central nervous system (CNS) and immune processes have garnished significant research focus with major milestones. With these advances in biotechnology, rapid extension of the ECS research in the periphery has gained momentum. In this chapter, we review the components

and tissue distribution of this previously unknown but ubiquitous and complex ECS that is involved in almost all aspects of mammalian physiology and pathology."

-Rowan University School of Osteopathic Medicine, Stratford, NJ, USA.
-Department of Biology, William Paterson University, Wayne, NJ, USA
https://pubmed.ncbi.nlm.nih.gov/31332731

The endocannabinoid system and its therapeutic exploitation

"The term 'endocannabinoid' - originally coined in the mid-1990s after the discovery of membrane receptors for the psychoactive principle in Cannabis, Delta9-tetrahydrocannabinol and their endogenous ligands - now indicates a whole signalling system that comprises cannabinoid receptors, endogenous ligands and enzymes for ligand biosynthesis and inactivation. This system seems to be involved in an ever-increasing number of pathological conditions. With novel products already being aimed at the pharmaceutical market little more than a decade since the discovery of cannabinoid receptors, the endocannabinoid system seems to hold even more promise for the future development of therapeutic drugs. We explore the conditions under which the potential of targeting the endocannabinoid system might be realized in the years to come."

-Endocannabinoid Research Group, Institute of Biomolecular Chemistry, National Research Council, Pozzuoli, Napoli, Italy.
https://pubmed.ncbi.nlm.nih.gov/15340387/

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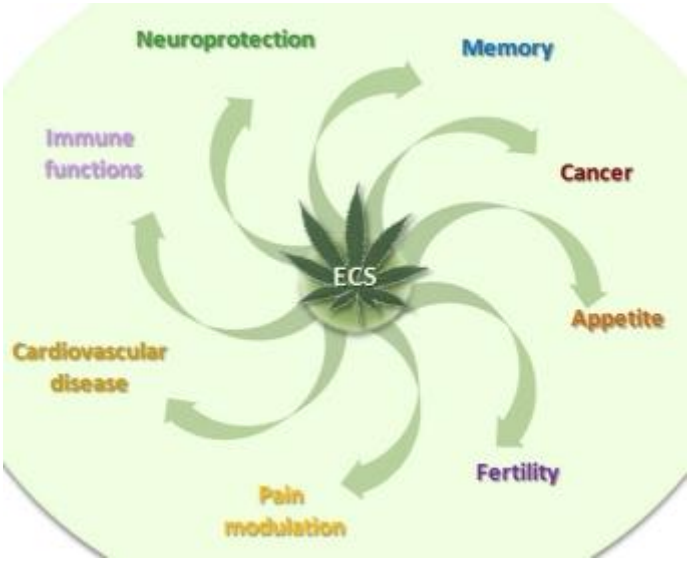
…"The presence of ECS in vertebrates, mammals, and humans implies a role in several physiological processes, including appetite, cancer, cardiovascular diseases, fertility, immune functions, memory, neuroprotection, and pain modulation *(Ligresti et al., 2009; Maccarrone et al., 2010) (Figure33)*."…



-Department of Biomedical Sciences, University of Teramo, Teramo, Italy
-European Center for Brain Research (CERC)/Santa Lucia Foundation, Rome, Italy
-Department of Experimental Medicine and Biochemical Sciences, University of Rome "Tor Vergata", Rome, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3303140

Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures--a short review

"In the last 25 years data has grown exponentially dealing with the discovery of the endocannabinoid system consisting of specific cannabinoid receptors, their endogenous ligands, and enzymatic systems of their biosynthesis and degradation. Progress is being made in the development of novel agonists and antagonists with receptor subtype selectivity which should help in providing a greater understanding of the physiological role of the endocannabinoid system and perhaps also in a broad number of pathologies. This could lead to advances with important therapeutic potential of drugs modulating activity of endocannabinoid system as hypnotics, analgesics, antiemetics, antiasthmatics, antihypertensives, immunomodulatory drugs, antiphlogistics, neuroprotective agents, antiepileptics, agents influencing glaucoma, spasticity and other "movement disorders", eating disorders, alcohol withdrawal, hepatic fibrosis, bone growth, and atherosclerosis. The aim of this review is to highlight distribution of the CB1 and CB2 receptor subtypes in the nervous system and functional involvement of their specific ligands."

-Department of Anatomy, Division of Neuroanatomy, Faculty of Medicine, Masaryk University,
https://pubmed.ncbi.nlm.nih.gov/18584858

Latest advances in cannabinoid receptor agonists

"Since the discovery of cannabinoid receptors and their endogenous ligands in early 1990s, the endocannabinoid system has been shown to play a vital role in several pathophysiological processes. It has been targeted for the treatment of several diseases including neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, Huntington's disease and MS), cancer, obesity, inflammatory bowel disease, neuropathic and inflammatory pain. The last decade has witnessed remarkable advances in the development of cannabinergic ligands displaying high selectivity and potency towards two subtypes of cannabinoid receptors, namely CB1 and CB2."…

-Northeastern University, Center for Drug Discovery, Boston, MA, USA.
https://pubmed.ncbi.nlm.nih.gov/19939187

The endocannabinoid system and its relevance for nutrition

"Endocannabinoids bind to cannabinoid, vanilloid, and peroxisome proliferator-activated receptors. The biological actions of these polyunsaturated lipids are controlled by key agents responsible for their synthesis, transport and degradation, which together form an endocannabinoid system (ECS). In the past few years, evidence has been accumulated for a role of the ECS in regulating food intake and energy balance, both centrally and peripherally. In addition, up-regulation of the ECS in the gastrointestinal tract has a potential impact on inflammatory bowel diseases. In this review, the main features of the ECS are summarized in order to put in better focus our current knowledge of the nutritional relevance of endocannabinoid signaling and of its role in obesity, cardiovascular pathologies, and gastrointestinal diseases. The central and peripheral pathways that underlie these effects are discussed, as well as the possible exploitation of ECS components as novel drug targets for therapeutic intervention in eating disorders."

-Department of Biomedical Sciences, University of Teramo, Teramo, Italy.
https://pubmed.ncbi.nlm.nih.gov/20645854

Exploration of Multiverse Activities of Endocannabinoids in Biological Systems

"Over the last 25 years, the human endocannabinoid system (ECS) has come into the limelight as an imperative neuro-modulatory system. It is mainly comprised of endogenous cannabinoid (endocannabinoid), cannabinoid receptors and the associated enzymes accountable for its synthesis and deterioration. The ECS plays a proven role in the management of several

neurological, cardiovascular, immunological, and other relevant chronic conditions. Endocannabinoid or endogenous cannabinoid are endogenous lipid molecules which connect with cannabinoid receptors and impose a fashionable impact on the behavior and physiological processes of the individual. Arachidonoyl ethanolamide or Anandamide and 2-arachidonoyl glycerol or 2-AG were the endocannabinoid molecules that were first characterized and discovered. The presence of lipid membranes in the precursor molecules is the characteristic feature of endocannabinoids. The endocannabinoids are released upon rapid enzymatic reactions into the extracellular space via activation through G-protein coupled receptors, which is contradictory to other neurotransmitter that are synthesized beforehand, and stock up into the synaptic vesicles. The current review highlights the functioning, synthesis, and degradation of endocannabinoid, and explains its functioning in biological systems."

-Chitkara College of Pharmacy, Chitkara University, Rajpura 140401, Punjab, India

-Pharmacy Practice Research Unit, Clinical Pharmacy Department of College of Pharmacy, Jazan University, Jazan 45142, Saudi Arabia

-Department of Pharmaceutical Chemistry and Pharmacognosy, College of Pharmacy, Jazan University, Jazan 45142, Saudi Arabia

-Department of Pharmaceutcal Chemistry, College of Pharmacy, Jazan University, Jazan 45142, Saudi Arabia

-Substance Abuse and Toxicology Research Center, Jazan University, Jazan 45142, Saudi Arabia

-Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, 410028 Oradea, Romania

-Doctoral School of Biomedical Sciences, University of Oradea, 410087 Oradea, Romania

https://www.mdpi.com/1422-0067/23/10/5734

See also National Institute of Health

Endocannabinoid Signaling in Reward & Addiction

"Brain endocannabinoid signaling influences the motivation for natural rewards (such as palatable food, sexual activity and social interaction) and modulates the rewarding effects of addictive drugs. Pathological forms of natural and drug-induced reward are associated with dysregulated endocannabinoid signaling that may derive from pre-existing genetic factors or from prolonged drug exposure. Impaired endocannabinoid signaling contributes to dysregulated synaptic plasticity, increased stress responsivity, negative emotional states, and craving that propel addiction. Understanding the contributions of endocannabinoid disruptions to behavioral and physiological traits provides insight into the endocannabinoid influence on addiction

vulnerability."

-Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, La Jolla, CA U.S.A

-Friedman Brain Institute, Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4652927/

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"Second, studies of endogenous cannabinoid (EC) regulation in animal models suggest that it plays a role in some aspects of memory, emotional recognition or processing, and reward, each an area of putative dysregulation in ADHD."

-Department of Human Genetics, University of California, Los Angeles, California

-Department of Epidemiology and Public Health, Imperial College London, London, United Kingdom

-Clinic of Child Psychiatry, University of Oulu, Oulu, Finland

-Center for Neurobehavioral Genetics, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, California

-Division of Child and Adolescent Psychiatry, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, California

-Wellcome Trust Sanger Institute, Cambridge, United Kingdom

-Institute for Molecular Medicine Finland (FIMM), University of Helsinki and National Public Health Institute, Helsiniki, Finland

-Broad Institute, Cambridge, Massachusetts

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2685476/

The CB1 receptor as an important mediator of hedonic reward processing.

"The endocannabinoid (ECB) system has emerged recently as a key mediator for reward processing. It is well known that cannabinoids affect appetitive learning processes and can induce reinforcing and rewarding effects."...

"Our data further indicate that the ECB system, and in particular CB1 receptor signaling, appears to be highly important for the mediation of hedonic aspects of reward processing."

-Reseach Group Developmental Neuropsychopharmacology, Institute of Psychopharmacology, Central Institute of Mental Health, Medical Faculty Mannheim,

-Heidelberg University, Mannheim, Germany.

-Institute of Molecular Psychiatry, University of Bonn, Bonn, Germany.

http://www.ncbi.nlm.nih.gov/pubmed/24718372

hedonic - relating to or considered in terms of pleasant (or unpleasant) sensations.

Regulation of brain reward by the endocannabinoid system: a critical review of behavioral studies in animals.

"The endocannabinoid system has been implicated in the regulation of a variety of physiological processes, including a crucial involvement in brain reward systems and the regulation of motivational processes. Behavioral studies have shown that cannabinoid reward may involve the same brain circuits and similar brain mechanisms with other drugs of abuse, such as nicotine, cocaine, alcohol and heroin, as well as natural rewards, such as food, water and sucrose, although the conditions under which cannabinoids exert their rewarding effects may be more limited."…

University of Crete, School of Social Sciences, Department of Psychology, Laboratory of Behavioral Neuroscience, Greece.

http://www.ncbi.nlm.nih.gov/pubmed/23829366

The Effects of Early Life Stress on Reward Processing

"Responsiveness to reward also involves the nucleus accumbens (in addition to other regions, such as the ventral pallidum), but opioids and endocannabinoids are the major neurochemical mediators of reward responsiveness (Mahler et al., 2007; Peciña and Berridge, 2005)."

-Mood Disorders Research Program and Laboratory for Clinical and Translational Neuroscience, Butler Hospital, Providence, RI, USA

-Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA

-Developmental Cognitive Neuroscience Lab (DCNL), Graduate Program in Psychology, Pontifical Catholic University of Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

-Center for Neurorestoration and Neurotechnology, Providence VA, Providence, RI, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889741/

Cannabinoid receptors in the bed nucleus of the stria terminalis control cortical excitation of midbrain dopamine cells in vivo.

"The endocannabinoid system is involved in multiple physiological functions including reward. Cannabinoids potently control the activity of midbrain dopamine cells, but the contribution of cortical projections in this phenomenon is unclear."

..."Our data identify a new neuronal substrate for the actions of cannabinoids in the reward pathway."

Pathophysiology of Synaptic Plasticity Group, INSERM, Neurocentre Magendie and Université de Bordeaux, France.

https://www.ncbi.nlm.nih.gov/pubmed/18923026

…"Endocannabinoids are endogenous lipid neurotransmitters that activate cannabinoid receptors and play a role in regulating motivated behaviors, such as feeding, anxiety, drug seeking, pain, and reproduction [4, 5]."….

-Department of Psychological and Brain Sciences, Indiana University, 1101 East 10th Street, Bloomington, IN, USA
-Department of Psychology, The University at Albany, SUNY, 1400 Washington Ave, Albany, NY, USA
-Department of Chemistry, University of Alaska-Fairbanks, 900 Yukon Drive, Fairbanks, AK, USA
https://www.hindawi.com/journals/ije/2013/436252/

Overeating, alcohol and sucrose consumption decrease in CB1 [cannabinoid type 1] receptor deleted mice.

"Administration of the cannabinoid CB1 receptor antagonist SR141716 (3-10 mg/kg i.p.) abolished neuropeptide Y-induced overeating and significantly reduced ethanol and sucrose intake in CB1 wild-type (+/+) mice. In CB1 receptor knockout (-/-) mice, neuropeptide Y totally lost its capacity to increase food consumption. Similarly, sucrose and ethanol intakes were significantly lower in CB1-/- vs. CB1+/+ mice. In CB1 deficient mice, SR141716 had no effect in these models."

http://www.ncbi.nlm.nih.gov/pubmed/12770700

Endocannabinoids

"Endocannabinoids [are] bioactive lipid mediators produced in virtually all cell types and organs of the body, which exert biological effects similar to those of marijuana. The most extensively studied endocannabinoids are AEA and 2-AG."

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ 07103, USA
-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck 23538, Germany
-School of Translational Medicine, University of Manchester, Manchester, M13 9PL, UK
-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

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"Endocannabinoids are defined as endogenous small molecules that activate the cannabinoid receptors CB1 and CB2, which are G-protein-coupled receptors that also recognize Δ9-tetrahydrocannabinol (THC), the psychoactive component of marijuana. [2, 3] The CB1 receptor is

the major cannabinoid receptor in the nervous system and is responsible for mediating most of the neurobehavioral effects of THC. [4, 5] The CB2 receptor is predominantly expressed in immune cells, [6] where it appears to play a role in mediating the immunosuppressive effects of cannabinoids. Two principal endocannabinoids have been identified in mammals, N-arachidonoyl ethanolamine (anandamide) [7] and 2-arachidonoylglycerol (2-AG) [8, 9] (Figure 1). Each endocannabinoid also belongs to a much larger class of lipids, termed N-acyl ethanolamines (NAEs) and monoacylglycerols (MAGs), respectively, where individual members differ in the length and degree of unsaturation of their acyl chains [Figure 1]. "

-Pfizer Global Research and Development, Groton, Connecticut, USA

-The Skaggs Institute for Chemical Biology and Department of Chemical Physiology, The Scripps Research Institute, La Jolla, California, USA

-The Scripps Research Institute

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3150828/

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"...To date, studies have shown their [endocannabinoids] effect on GI motility, inflammation and immunity, intestinal and gastric acid secretion, nociception and emesis pathways, and appetite control."

-Department of Gastroenterology, Temple University Hospital, Philadelphia, Pennsylvania.

-Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5665514/

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"Bioactive lipid mediators produced in virtually all cell types and organs of the body, which exert biological effects similar to those of marijuana. The most extensively studied endocannabinoids are AEA [anandamide] and 2-AG [2-Arachidonoylglycerol]."

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary

-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ, USA

-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck, Germany

-School of Translational Medicine, University of Manchester, Manchester, UK

-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

Cannabinoids

"Since the discovery of an endogenous cannabinoid system, research into the pharmacology and

therapeutic potential of cannabinoids has steadily increased. Two subtypes of G-protein coupled cannabinoid receptors, CB(1) and CB(1), have been cloned and several putative endogenous ligands (endocannabinoids) have been detected during the past 15 years. The main endocannabinoids are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), derivatives of arachidonic acid, that are produced "on demand" by cleavage of membrane lipid precursors. Besides phytocannabinoids of the cannabis plant, modulators of the cannabinoid system comprise synthetic agonists and antagonists at the CB receptors and inhibitors of endocannabinoid degradation. Cannabinoid receptors are distributed in the central nervous system and many peripheral tissues, including immune system, reproductive and gastrointestinal tracts, sympathetic ganglia, endocrine glands, arteries, lung and heart. There is evidence for some non-receptor dependent mechanisms of cannabinoids and for endocannabinoid effects mediated by vanilloid receptors. Properties of CB receptor agonists that are of therapeutic interest include analgesia, muscle relaxation, immunosuppression, anti-inflammation, antiallergic effects, improvement of mood, stimulation of appetite, antiemesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects. The current main focus of clinical research is their efficacy in chronic pain and neurological disorders. CB receptor antagonists are under investigation for medical use in obesity and nicotine addiction. Additional potential was proposed for the treatment of alcohol and heroine dependency, schizophrenia, conditions with lowered blood pressure, Parkinson's disease and memory impairment in Alzheimer's disease."

-Nova-Institut, Goldenbergstrasse 2, D-50354 Hürth, Germany.
https://pubmed.ncbi.nlm.nih.gov/16266285/

The endocannabinoid system: physiology and pharmacology

"The endogenous cannabinoid system is an ubiquitous lipid signalling system that appeared early in evolution and which has important regulatory functions throughout the body in all vertebrates. The main endocannabinoids (endogenous cannabis-like substances) are small molecules derived from arachidonic acid, anandamide (arachidonoylethanolamide) and 2-arachidonoylglycerol. They bind to a family of G-protein-coupled receptors, of which the cannabinoid CB(1) receptor is densely distributed in areas of the brain related to motor control, cognition, emotional responses, motivated behaviour and homeostasis. Outside the brain, the endocannabinoid system is one of the crucial modulators of the autonomic nervous system, the immune system and microcirculation. Endocannabinoids are released upon demand from lipid precursors in a receptor-dependent manner and serve as retrograde signalling messengers in GABAergic and glutamatergic synapses, as well as modulators of postsynaptic transmission, interacting with

other neurotransmitters, including dopamine. Endocannabinoids are transported into cells by a specific uptake system and degraded by two well-characterized enzymes, the fatty acid amide hydrolase and the monoacylglycerol lipase. Recent pharmacological advances have led to the synthesis of cannabinoid receptor agonists and antagonists, anandamide uptake blockers and potent, selective inhibitors of endocannabinoid degradation. These new tools have enabled the study of the physiological roles played by the endocannabinoids and have opened up new strategies in the treatment of pain, obesity, neurological diseases including multiple sclerosis, emotional disturbances such as anxiety and other psychiatric disorders including drug addiction. Recent advances have specifically linked the endogenous cannabinoid system to alcoholism, and cannabinoid receptor antagonism now emerges as a promising therapeutic alternative for alcohol dependence and relapse."

-Fundación IMABIS, Hospital Carlos Haya de Málaga, Avenida Carlos Haya 82, 29010 Málaga, Spain.
https://pubmed.ncbi.nlm.nih.gov/15550444/

Endocannabinoids & Neuroprotection

Endocannabinoids mediate neuroprotection after transient focal cerebral ischemia.

"The endocannabinoids anandamide (AEA) and palmitoylethanolamide (PEA) act as endogenous protective factors of the brain, using different pathways of neuroprotection against neuronal damage. Although several in vivo and in vitro studies confirmed the neuroprotective efficacy of endocannabinoids, no experimental settings compare and explore the neuroprotective potential of AEA and PEA in an acute stroke model. In this study, we investigated the neuroprotective potential by infarct measurement after high (30 mg/kg body weight) and low dosage administration (10 mg/kg body weight) of the endocannabinoid PEA in 49 male Wistar rats. In additions we studied infarct volumes of 22 male Wistar rats receiving the endocannabinoid AEA with a dosage of 10 mg/kg body weight or placebo. The neurological outcome was assessed 24 h after ischemia. Endocannabinoids were given intraperitoneally 30 min after initiation of transient middle cerebral artery occlusion (tMCAO). Infarct volume was calculated on the basis of 2.3.5-triphenyltetrazolium chloride staining. In the PEA high-dose group a significant total infarct reduction of 35% compared to the control group could be observed. AEA-treated rats presented a total infarct reducing effect of 26% compared to controls. Neurological scores, evaluated 24 h after tMCAO and physiological parameters, obtained 45 and 90 min after onset of ischemia showed no significant differences among the groups. As shown here, the endocannabinoids AEA

and PEA achieved a significant neuroprotective effect by reducing size of infarcted tissue after tMCAO. Both endocannabinoids may have the potential to treat acute stroke and exert neuroprotection through a variety of mechanisms."

-Department of Neurology, University of Heidelberg, Heidelberg, Germany.
https://www.ncbi.nlm.nih.gov/pubmed/18823959

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"Palmitoylethanolamide (PEA) has emerged as a potential nutraceutical, because this compound is naturally produced in many plant and animal food sources, as well as in cells and tissues of mammals, and endowed with important neuroprotective, anti-inflammatory and analgesic actions. Several efforts have been made to identify the molecular mechanism of action of PEA and explain its multiple effects both in the central and the peripheral nervous system. Here, we provide an overview of the pharmacology, efficacy and safety of PEA in neurodegenerative disorders, pain perception and inflammatory diseases. The current knowledge of new formulations of PEA with smaller particle size (i.e. micronized and ultra-micronized) when given alone or in combination with antioxidant flavonoids (i.e. luteolin) and stilbenes (i.e. polydatin) is also reviewed."

-Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Pozzuoli (NA), Italy
-Epitech Group S.p.A., Saccolongo (PD), Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5429331/

Cannabinoid receptors in brain: pharmacogenetics, neuropharmacology, neurotoxicology, and potential therapeutic applications

"Much progress has been achieved in cannabinoid research. A major breakthrough in marijuana-cannabinoid research has been the discovery of a previously unknown but elaborate endogenous endocannabinoid system (ECS), complete with endocannabinoids and enzymes for their biosynthesis and degradation with genes encoding two distinct cannabinoid (CB1 and CB2) receptors (CBRs) that are activated by endocannabinoids, cannabinoids, and marijuana use. Physical and genetic localization of the CBR genes CNR1 and CNR2 have been mapped to chromosome 6 and 1, respectively. A number of variations in CBR genes have been associated with human disorders including osteoporosis, attention deficit hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), drug dependency, obesity, and depression. Other family of lipid receptors including vanilloid (VR1) and lysophosphatidic acid (LPA) receptors appear to be related to the CBRs at the phylogenetic level. The ubiquitous abundance and differential

distribution of the ECS in the human body and brain along with the coupling to many signal transduction pathways may explain the effects in most biological system and the myriad behavioral effects associated with smoking marijuana. The neuropharmacological and neuroprotective features of phytocannabinoids and endocannabinoid associated neurogenesis have revealed roles for the use of cannabinoids in neurodegenerative pathologies with less neurotoxicity. The remarkable progress in understanding the biological actions of marijuana and cannabinoids have provided much richer results than previously appreciated cannabinoid genomics and raised a number of critical issues on the molecular mechanisms of cannabinoid induced behavioral and biochemical alterations. These advances will allow specific therapeutic targeting of the different components of the ECS in health and disease. This review focuses on these recent advances in cannabinoid genomics and the surprising new fundamental roles that the ECS plays in the retrograde signaling associated with cannabinoid inhibition of neurotransmitter release to the genetic basis of the effects of marijuana use and pharmacotherpeutic applications and limitations. Much evidence is provided for the complex CNR1 and CNR2 gene structures and their associated regulatory elements. Thus, understanding the ECS in the human body and brain will contribute to elucidating this natural regulatory mechanism in health and disease."

-Department of Biology, William Paterson University, Wayne, New Jersey 07470, USA.
https://pubmed.ncbi.nlm.nih.gov/19897083

Endocannabinoid Overactivity

"Cannabinoid receptors of type 1 and 2 (CB1 and CB2), endogenous ligands that activate them (endocannabinoids), and mechanisms for endocannabinoid biosynthesis and inactivation have been identified in the gastrointestinal system. Activation of CB1 receptors by endocannabinoids produces relaxation of the lower oesophageal sphincter and inhibition of gastric acid secretion, intestinal motility, and fluid stimulated secretion. However, stimulation of cannabinoid receptors impacts on gastrointestinal functions in several other ways. Recent data indicate that the endocannabinoid system in the small intestine and colon becomes over stimulated during inflammation in both animal models and human inflammatory disorders. The pathological significance of this "endocannabinoid overactivity" and its possible exploitation for therapeutic purposes are discussed here."…

-V Di Marzo, Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Napoli, Italy

-A A Izzo, Department of Experimental Pharmacology, University of Naples "Federico II", Naples, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1856409/

Endocrine System

"The endocrine system is the collection of glands that produce hormones that regulate metabolism, growth and development, tissue function, sexual function, reproduction, sleep, and mood, among other things."

-Live Science, Kim Ann Zimmermann
https://www.livescience.com/26496-endocrine-system.html

The role of the endocannabinoid system in the regulation of endocrine function and in the control of energy balance in humans

"The endocannabinoid system has been recently recognized as an important modulatory system in the function of brain, endocrine, and immune tissues. It appears to play a very important regulatory role in the secretion of hormones related to reproductive functions and response to stress. The important elements of this system are: endocannabinoid receptors (types CB1 and CB2), their endogenous ligands (N-arachidonoylethanolamide, 2-arachidonoyl glycerol), enzymes involved in their synthesis and degradation, as well as cannabinoid antagonists. In humans this system also controls energy homeostasis and mainly influences the function of the food intake centers of the central nervous system and gastrointestinal tract activity. The endocannabinoid system regulates not only the central and peripheral mechanisms of food intake, but also lipids synthesis and turnover in the liver and adipose tissue as well as glucose metabolism in muscle cells. Rimonabant, a new and selective central and peripheral cannabinoid-1 receptor (CB1) blocker, has been shown to reduce body weight and improve cardiovascular risk factor (metabolic syndrome) in obese patients by increasing HDL-cholesterol and adiponectin blood levels as well as decreasing LDL-cholesterol, leptin, and C-reactive protein (a proinflammatory marker) concentrations. It is therefore possible to speculate about a future clinical use of CB1 antagonists, as a means of improving gonadotrophin pulsatility and fertilization capacity as well as the prevention of cardiovasculary disease and type 2 diabetes mellitus. Drugs acting as agonists of CB1 receptors (Dronabinol, Dexanabinol) are currently proposed for evaluation as drugs to treat neurodegenerative disorders (Alzheimer's and Parkinson's diseases), epilepsy, anxiety, and stroke."

-Department of Endocrinology, Department of Endocrinology, Medical University of Lodz, Lodz, Poland.
https://pubmed.ncbi.nlm.nih.gov/17369778/

Note: This research abstract mentions rimonabant, it was withdrawn in 2008 due to serious psychiatric side effects and never approved in the USA.

Endogenous Opioid System

Putative ECS- Endogenous Opioid System (EOS) Interplay

"As mentioned above, the ECS may interact with several other signaling pathways, including the endogenous opioid system (EOS). Indeed, intraplantar administration of the CB2-selective agonist AM1241 (10 μM) stimulated β-endorphin release from keratinocytes via the activation of a CB2-Gi/o-Gβγ-ERK1/2 MAPK-Ca2+ signaling pathway [206]. The released β-endorphin was then found to activate local neuronal μ-opioid receptors thereby inhibiting nociception in rats, which was not the case for CB2−/− animals [207]. Similarly, capsaicin-induced pain was dose-dependently alleviated in mice by intraplantar injection of the highly CB2-selective agonist β-caryophyllene (18 μg) [208], most likely via stimulating β-endorphin release from the keratinocytes.

Intriguingly, further ECS-EOS interplay was evidenced in a few additional studies. Indeed, electroacupuncture (EA) was found to increase CB2 expression on keratinocytes and infiltrating inflammatory cells in inflamed skin tissues of rats [209]. EA and CB2 stimulation reduced inflammatory pain via activating μ-opioid receptors, and EA increased endogenous opioid expression in keratinocytes as well as in infiltrating immune cells at the inflammatory site through CB2 activation [210]. Furthermore, EA or AM1241 (1 mg/kg; s.c.) treatment significantly decreased the mRNA and protein levels of IL-1β, IL-6 and TNF-α in inflamed skin tissues in a CB2-dependent manner, since pretreatment with the CB2-selective antagonist/inverse agonist AM630 (150 μg/kg; s.c.) abrogated the effect of EA. Collectively, these data suggest that EA may reduce inflammatory pain and pro-inflammatory cytokine production by activating CB2 [211]."…

-Department of Physiology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-Department of Immunology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-HCEMM Nonprofit Ltd., Szeged, Hungary
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429381/

Endometriosis

"Endometriosis (en-doe-me-tree-O-sis) is an often painful disorder in which tissue similar to the tissue that normally lines the inside of your uterus — the endometrium — grows outside your uterus. Endometriosis most commonly involves your ovaries, fallopian tubes and the tissue lining

your pelvis. Rarely, endometrial tissue may spread beyond pelvic organs."…

- *Mayo Clinic*
https://www.mayoclinic.org/diseases-conditions/endometriosis/symptoms-causes/syc-20354656

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"Endometriosis is defined as the presence of endometrial tissue (glands and stroma) outside the uterine cavity [1] . It is a common disease among women of reproductive age and is clinically characterized by dysmenorrhea, infertility and dyspareunia [2] .

Rapid changes in the human diet, especially in the last 100 years, have been potent promoters of chronic diseases such as atherosclerosis, essential hypertension, obesity, diabetes and many types of cancer [3] . In the Western diet, the ratio of omega-6/omega-3 fatty acids ranges from 10:1 to 30:1, which is very different from the ratio of 1:1 to 2:1 in the diets of prehistoric populations [4] . The optimal dose or ratio of omega-6/omega-3 ranges from 1:1 to 1:4 depending on the disease considered [5] . The importance of the omega-6/omega-3 ratio was demonstrated in an apolipoprotein E (ApoE)-deficient mouse model that also expressed the fat-1 gene of Caenorhabditis elegans. The fat-1 transgenic mouse metabolizes omega-6 to omega-3 through an omega-3 desaturase enzyme, resulting in an approximate 1:1 omega-6/omega-3 ratio. After feeding with a high-fat diet for fourteen weeks, the ApoE-/- fat-1 transgenic mouse was found to have fewer atherosclerotic lesions than the ApoE-/- mouse [6] . Omega-6 fatty acids account for most polyunsaturated fatty acids in diets, especially the Western diet. When the diet is supplemented with omega-3 fatty acids, omega-6 fatty acids are partially replaced in virtually all cell membranes 7 . A study published in the 1980s suggesting the importance of consuming omega-3 polyunsaturated fatty acids was based on epidemiological observations of the low incidence of autoimmune and inflammatory disorders in a Greenland Eskimo population compared with that in groups living in Denmark [8] . With a Mediterranean diet providing a linoleic acid (LA):alpha-linolenic acid (ALA) ratio of 4:1, increased incorporation of ALA into cell membranes was observed. The 4:1 ratio of LA:ALA led to a 70% reduction in total mortality at the end of two years [9] . Omega-3 fatty acids affect interleukin metabolism by decreasing interleukin-1β (IL-1β) and interleukin-6 (IL-6) levels [5] . Interleukin-6 may stimulate the synthesis of all acute-phase proteins involved in the inflammatory response, such as C-reactive protein, serum amyloid A, fibrinogen, α1-chymotrypsin and haptaglobin 10 . Omega-3 fatty acids suppress the ability of monocytes to synthesize interleukin-1 (IL-1) and tumor necrosis factor (TNF) in healthy volunteers [7] . Omega-3 fatty acids inhibit the production of nuclear factor-kappa beta (NF-kB), which is a transcription factor for a large number of cytokines such as tumor necrosis factor alpha (TNF-α) and interleukins [11] .

Inflammation is one of the major mechanisms underlying visceral pain, and endometriosis is an inflammatory disease that triggers an inflammatory response [12] . Endometriosis occurs most frequently in the pelvic viscera and the peritoneum of the pelvic viscera; thus, endometriosis-associated pain is usually of a visceral origin. [13] "....

-Postgraduate Program in Medical and Surgical Sciences, Department of Surgery, Universidade Federal do Ceará (UFC), Fortaleza-Ce, Brazil. Conception of the study, technical procedures, acquisition of the data, manuscript writing.

-Department of Maternal and Child Health, UFC, Fortaleza-Ce, Brazil. Conception, design, intellectual and scientific content of the study; critical revision; final approval.

-Department of Medical Clinic, UFC, Fortaleza-Ce, Brazil. Statistical analysis.

-IVGraduate student, UFC, Fortaleza-Ce, Brazil. Acquisition of data.

-Correspondence: Francisco das Chagas Medeiros Faculdade de Medicina, Departamento de Saúde Materna e Infantil Departamento de Cirurgia, Universidade Federal do Ceará Rua Professor Costa Mendes

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6583929/

Endotoxin

An endotoxin is a toxin that is present inside a bacterial cell and is released when the cell disintegrates. It is sometimes responsible for the characteristic symptoms of a disease, e.g., in botulism. *(Oxford/Google)*

...“The ability of various blood cells to produce endocannabinoids is well established (Bisogno et al., 1997). Interest in the role endocannabinoids play in cardiovascular pathophysiology was initiated when Wagner et al. (1997) demonstrated, in a rat model of haemorrhagic shock, that activated macrophages release anandamide which may contribute towards the hypotension. Subsequently it was also found in endotoxic shock that the synthesis of 2-AG in platelets and anandamide in macrophages are increased and that these may contribute towards the associated hypotension (Varga et al., 1998). Further studies have confirmed that circulating cells produce endocannabinoids, for example, macrophages produce and release 2-AG (Di Marzo et al., 1999). Platelet-activating factor has also been shown to stimulate both platelets and a mouse macrophage cell line to produce 2-AG (Berdyshev et al., 2001). So, clearly blood cells represent an important circulating source of endocannabinoids which may participate in pathophysiological responses. Additionally, Maccarrone et al. (2001b) reported that lipopolysaccharide, a key component in endotoxic shock, causes a downregulation of FAAH expression in human lymphocytes, and the reduction in the metabolism of anandamide leads to increased levels. This mechanism could lead to further increases in circulating levels of anandamide in endotoxic shock.

Endotoxic shock is associated with disseminated intravascular coagulation (which involves widespread platelet aggregation). If the endocannabinoids released in circulatory shock are associated with causing uncontrolled platelet aggregation, then this might be the means of causing microemboli formation and contribute towards tissue-perfusion mismatches contributing to multi-organ failure."…

-School of Biomedical Sciences, University of Nottingham Medical School, Nottingham, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2190025/

Lipopolysaccharide downregulates fatty acid amide hydrolase expression and increases anandamide levels in human peripheral lymphocytes.

Lipopolysaccharide (LPS) increases the levels of the endogenous cannabinoid anandamide (N-arachidonoylethanolamine, AEA) in rat macrophages, but the mechanism responsible for this effect has not been elucidated. Here we demonstrate that LPS enhances the levels of AEA (fourfold over controls) also in human lymphocytes. We show that in these cells LPS inhibits the activity of the AEA-degrading enzyme fatty acid amide hydrolase (FAAH), by downregulating the gene expression at transcriptional level. Lymphocytes have also a specific AEA transporter and a functional CB1 cannabinoid receptor, which were not modulated by LPS. The effect of this endotoxin on FAAH was not mediated by AEA-induced activation of cannabinoid receptors. Conversely, the stimulatory action of LPS on AEA levels might be due to inhibition of FAAH, as suggested by the observation that an increase of AEA amounts was also induced by an irreversible FAAH inhibitor. These results suggest that lymphocytes take part in regulating the peripheral endocannabinoid system and endocannabinoid homeostasis.

-Department of Experimental Medicine and Biochemical Sciences, University of Rome "Tor Vergata,", Via di Tor Vergata 135, Rome
https://www.ncbi.nlm.nih.gov/pubmed/11556820

See also Neuroprotection

Energy Metabolism & Energy Balance

Novel CB1-ligands maintain homeostasis of the endocannabinoid system in ω3- and ω6-long-chain-PUFA deficiency

"Mammalian ω3- and ω6-PUFAs are synthesized from essential fatty acids (EFAs) or supplied by

the diet. **PUFAs are constitutive elements of membrane architecture and precursors of lipid signaling molecules. EFAs and long-chain (LC)-PUFAs are precursors in the synthesis of endocannabinoid ligands of Gi/o protein-coupled cannabinoid receptor (CB)1 and CB2 in the endocannabinoid system, which critically regulate energy homeostasis as the metabolic signaling system in hypothalamic neuronal circuits and behavioral parameters.**"...

-Center of Molecular Medicine (CMMC), Laboratory of Molecular Neurosciences, Institute of Biochemistry, University of Cologne, 50931 Cologne, Germany.

-Cluster of Excellence, Cellular Stress Response in Aging Related Diseases (CECAD) University of Cologne, 50931 Cologne, Germany.

-Institute of Biochemistry Deutsche Sporthochschule (DSHS) Cologne, 50933 Cologne, Germany.

-Institute of Vegetative Physiology, Center of Physiology and Pathophysiology, University of Cologne, 50931 Cologne, Germany.

-Center of Molecular Medicine (CMMC), Laboratory of Molecular Neurosciences, Institute of Biochemistry, University of Cologne, 50931 Cologne, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6672042/

Critical role of the endocannabinoid system in the regulation of food intake and energy metabolism, with phylogenetic, developmental, and pathophysiological implications

"The endocannabinoid system (ECS) consists of two receptors (CB(1) and CB(2)), several endogenous ligands (primarily anandamide and 2-AG), and over a dozen ligand-metabolizing enzymes. The ECS has deep phylogenetic roots and regulates many aspects of embryological development and homeostasis, including neuroprotection and neural plasticity, immunity and inflammation, apoptosis and carcinogenesis, pain and emotional memory, and the focus of this review: hunger, feeding, and metabolism. The ECS controls energy balance and lipid metabolism centrally (in the hypothalamus and mesolimbic pathways) and peripherally (in adipocytes and pancreatic islet cells), acting through numerous anorexigenic and orexigenic pathways (e.g., ghrelin, leptin, orexin, adiponectin, endogenous opioids, and corticotropin-releasing hormone). Obesity leads to excessive endocannabinoid production by adipocytes, which drives CB(1) in a feed-forward dysfunction. Phylogenetic research suggests the genes for endocannabinoid enzymes, especially DAGLalpha and NAPE-PLD, may harbor mildly deleterious alleles that express disease-related phenotypes. Several CB(1) inverse agonists have been developed for the treatment of obesity, including rimonabant, taranabant, and surinabant. These drugs are efficacious at reducing food intake as well as abdominal adiposity and cardiometabolic risk factors. However, given the myriad beneficial roles of the ECS, it should be no surprise that systemic CB(1) blockade induces various adverse effects. Alternatives to systemic blockade

include CB(1) partial agonists, pleiotropic drugs, peripherally restricted antagonists, allosteric antagonists, and endocannabinoid ligand modulation. The ECS offers several discrete targets for the management of obesity and its associated cardiometabolic sequelae."

-Departamento de Fisiología (Fisiología Animal II), Facultad de Biología, Universidad Complutense de Madrid, 28040 Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/18782018/

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…"CB(1) receptors, and tissue concentrations of endocannabinoids sufficient to activate them, are present in all brain and peripheral organs involved in the control of energy balance, including the hypothalamus, nucleus accumbens, pancreas, adipose tissue, skeletal muscle and liver. At the central level, the endocannabinoid system seems to play a dual role in the regulation of food intake by hedonic and homeostatic energy regulation. At the peripheral level, the endocannabinoid system seems to behave as a system that reduces energy expenditure and directs energy balance towards energy storage into fat. The emerging role of the endocannabinoid system in energy balance at both central and peripheral levels will be discussed in this review."

-U862 Centre de Recherche INSERM François Magendie, Université de Bordeaux, Bordeaux, France.

https://pubmed.ncbi.nlm.nih.gov/18426508

Effect of dietary fat on endocannabinoids and related mediators: consequences on energy homeostasis, inflammation and mood

"Among the several known fatty acid-derived chemical signals, the endogenous ligands of cannabinoid receptors type-1 and -2, two G-protein-coupled receptors involved in several aspects of mammalian physiology and pathology, are perhaps those the levels of which have proven to be most sensitive to the fatty acid composition of the diet. The two most studied such ligands, known as endocannabinoids, are N-arachidonoyl-ethanolamine and 2-archidonoylglycerol, and are found in tissues together with other N-acyl-ethanolamines and 2-acylglycerols, not all of which activate the cannabinoid receptors, although several of them do exhibit important pharmacological effects. In this review article, we describe literature data indicating that the tissue concentrations of the endocannabinoids and related signalling molecules, and hence the activity of the respective receptors, can be modulated by modifying the fatty acid composition of the diet, and particularly its content in long chain PUFAs or in long chain PUFA precursors. We also discuss the potential impact of these diet-induced changes of endocannabinoid tone on three of the major pathological conditions in which cannabinoid

receptors have been involved, that is metabolic dysfunctions, inflammation and affective disorders."

-Dipartimento di Biologia Sperimentale, Università di Cagliari, Cagliari, Italy.
https://pubmed.ncbi.nlm.nih.gov/20013888

The endocannabinoid system as a link between homoeostatic and hedonic pathways involved in energy balance regulation

"The endocannabinoid system (ECS) and, in particular, cannabinoid CB(1) receptors, their endogenous agonists (the endocannabinoids anandamide and 2-arachidonoylglycerol) and enzymes for the biosynthesis and degradation of the latter mediators are emerging as key players in the control of all aspects of food intake and energy balance. The ECS is involved in stimulating both the homoeostatic (that is, the sensing of deficient energy balance and gastrointestinal load) and the hedonic (that is, the sensing of the salience and the incentive/motivational value of nutrients) aspects of food intake. The orexigenic effects of endocannabinoids are exerted in the brain by CB(1)-mediated stimulatory and inhibitory effects on hypothalamic orexigenic and anorectic neuropeptides, respectively; by facilitatory actions on dopamine release in the nucleus accumbens shell; and by regulating the activity of sensory and vagal fibres in brainstem-duodenum neural connections. In turn, the levels of anandamide and 2-arachidonoylglycerol and/or CB(1) receptors in the brain are under the control of leptin, ghrelin and glucocorticoids in the hypothalamus, under that of dopamine in the limbic forebrain and under that of cholecystokinin and ghrelin in the brainstem. These bi-directional communications between the ECS and other key players in energy balance ensure local mediators such as the endocannabinoids to act in a way coordinated in both 'space' and 'time' to enhance food intake, particularly after a few hours of food deprivation. Alterations of such communications are, however, also among the underlying causes of overactivity of the ECS in hyperphagia and obesity, a phenomenon that provided the rationale for the development of anti-obesity drugs from CB(1) receptor antagonists."

-Endocannabinoid Research Group, Institute of Biomolecular Chemistry, National Research Council, Pozzuoli (NA), Italy.
https://pubmed.ncbi.nlm.nih.gov/19528974/

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…"The ECS has been shown to have a key role in the regulation of energy balance, and modulation of this system may affect multiple cardiometabolic risk factors. Clinical studies involving pharmacologic blockade of CB1 receptors in overweight patients with and without type

2 diabetes have demonstrated effective weight loss and improvements in several risk factors for cardiovascular disease."

-Division of Diabetes, Endocrinology and Metabolism, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, USA.

https://pubmed.ncbi.nlm.nih.gov/18194939/

Note: This research abstract mentions rimonabant, it was withdrawn in 2008 due to serious psychiatric side effects and never approved in the USA.

Enlarged Spleen

Nutrition, inflammation and liver-spleen axis

"Chronic low-grade systemic inflammation represents a mechanism common to many diseases linked to atherosclerosis-related pathways. There is a growing body of evidence indicating that the combination of food quantity and quality along with genetic susceptibility are able to induce the aberrant activation of innate immune signalling, which initially contributes to chronic low-grade inflammation. Liver represents the central player to inflammatory response. Dietary/metabolic factors contribute to the pathogenesis of Non-alcoholic Fatty Liver Disease (NAFLD), the main causes of liver disease in the Western world. Enlargement of the spleen, central organ in regulating the inflammation-related immune response, is commonly seen in patients with of NAFLD, depicting the so called "liver-spleen axis." The aim of this review was to provide an at-a-glance overview of the possible bi-directional mechanisms linking nutrition and inflammation, particularly pinpointing the inflammatory effects stemmed by nutrition on "liver-spleen axis." In particular, the role of unhealthy diet, healthy dietary patterns, such as the Mediterranean diet style, dietary vitamins and micronutrients, such as vitamin D or Magnesium, and Glucagon-Like Peptide-1, a well-known incretin released in response to meal intake, will be discussed. The highly variability of the inflammatory response highlights the role of expert nutritionists in refining methodologies apt to assess nutritional epidemiology and to apply appropriate dietary intervention to counteract diet-induced inflammation mechanisms."

-I.O.S. & COLEMAN Srl, Medicina Futura Medical Center , Acerra, Naples , Italy.

-IRCCS, SDN , Naples , Italy.

-Dipartimento di Medicina Clinica e Chirurgia , Federico II University Medical School of Naples ,Naples , Italy.

-Department of Pharmacy , University of Naples "Federico II" , Naples , Italy.

-Department of Sports Science and Wellness , Unit of Endocrinology, "Parthenope" University of Naples , Italy.

-Dipartimento di Medicina Clinica e Chirurgia , Unit of Endocrinology, Federico II University Medical School of Naples ,

Via Sergio Pansini 5, Naples , Italy.
https://pubmed.ncbi.nlm.nih.gov/28799803

See also Non-Alcoholic Fatty Liver Disease (NAFLD)

Epilepsy

Neural Stem Cells and Cannabinoids in the Spotlight as Potential Therapy for Epilepsy

"Epilepsy is one of the most common brain diseases worldwide, having a huge burden in society. The main hallmark of epilepsy is the occurrence of spontaneous recurrent seizures, having a tremendous impact on the lives of the patients and of their relatives. Currently, the therapeutic strategies are mostly based on the use of antiepileptic drugs, and because several types of epilepsies are of unknown origin, a high percentage of patients are resistant to the available pharmacotherapy, continuing to experience seizures overtime. Therefore, the search for new drugs and therapeutic targets is highly important. One key aspect to be targeted is the aberrant adult hippocampal neurogenesis (AHN) derived from Neural Stem Cells (NSCs). Indeed, targeting seizure-induced AHN may reduce recurrent seizures and shed some light on the mechanisms of disease. The endocannabinoid system is a known modulator of AHN, and due to the known endogenous antiepileptic properties, it is an interesting candidate for the generation of new antiepileptic drugs. However, further studies and clinical trials are required to investigate the putative mechanisms by which cannabinoids can be used to treat epilepsy. In this manuscript, we will review how cannabinoid-induced modulation of NSCs may promote neural plasticity and whether these drugs can be used as putative antiepileptic treatment."

-Institute of Pharmacology and Neurosciences, College of Medicine, University of Lisbon, Portugal.
-Institute of Molecular Medicine, College of Medicine, University of Lisbon, Portugal.
https://pubmed.ncbi.nlm.nih.gov/33022963

The Interplay between the Endocannabinoid System, Epilepsy and Cannabinoids

"Epilepsy is a neurological disorder that affects approximately 50 million people worldwide. There is currently no definitive epilepsy cure. However, in recent years, medicinal cannabis has been successfully trialed as an effective treatment for managing epileptic symptoms, but whose

mechanisms of action are largely unknown. Lately, there has been a focus on neuroinflammation as an important factor in the pathology of many epileptic disorders. In this literature review, we consider the links that have been identified between epilepsy, neuroinflammation, the endocannabinoid system (ECS), and how cannabinoids may be potent alternatives to more conventional pharmacological therapies. We review the research that demonstrates how the ECS can contribute to neuroinflammation, and could therefore be modulated by cannabinoids to potentially reduce the incidence and severity of seizures. In particular, the cannabinoid cannabidiol has been reported to have anti-convulsant and anti-inflammatory properties, and it shows promise for epilepsy treatment. There are a multitude of signaling pathways that involve endocannabinoids, eicosanoids, and associated receptors by which cannabinoids could potentially exert their therapeutic effects. Further research is needed to better characterize these pathways, and consequently improve the application and regulation of medicinal cannabis.

“Neurological disorders, such as epilepsy, tic disorders, dementia, multiple sclerosis, and Parkinson’s disease have constituted over 6% of the global disease burden since 2006, but gaps in our understanding of fundamental aspects of neurological disorders remain despite their broad health implications [1]. Recent research advances, including novel therapies, are helping to better elucidate the causes of neurological disorders, and to improve treatment of patients. In particular, the endocannabinoid system (ECS) is central to neurological function, and the modulation of this system shows therapeutic promise.

This review summarizes the current state of knowledge on the role of the ECS in the important neurological disorder of epilepsy and its interactions with cannabinoids in the context of epilepsy treatment. In particular, we consider the links between neuroinflammation, the ECS and cannabinoids.

Neuroinflammation has been detected in brains that have experienced epilepsy, which suggests a role in disease pathology. Specifically, neuroinflammation has been shown to occur both after an epileptic event and before the onset of epilepsy, which indicates that neuroinflammation might have a causal role in seizures.”…

-Institute of Health and Biomedical Innovation (IHBI), Faculty of Health, Queensland University of Technology (QUT), Centre for Children's Health Research (CCHR), South Brisbane, Australia.

-Children's Health Queensland (CHQ) and University of Queensland (UQ), Centre for Children's Health Research, South Brisbane, Australia.

-School of Medical Science, Griffith University, Southport, Australia.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6929011/

Cannabinoids: is there a potential treatment role in epilepsy?

…”The anticonvulsant properties of the non-psychotropic cannabinoid, CBD, have been known

for half a century, but only recently have they re-surfaced for their therapeutic potential towards the control of pediatric refractory seizures. Although a number of physiological effects of CBD in the brain have been identified, the mechanism(s) underlying its anticonvulsant properties are not yet understood.

Experimental and clinical findings reviewed above clearly indicate the anticonvulsant potential of targeting the ECS. Preliminary clinical findings demonstrate a therapeutic potential of CBD for the treatment of drug-resistant seizures disorders, and is a promising development. Continued research efforts are ongoing to increase our understanding of the brain ECS in hopes of developing novel therapeutic strategies for the treatment of epilepsy and other neurological conditions."

-Assistant Professor, Virginia Commonwealth University School of Medicine, Department of Neurology, Richmond, VA, USA

-George Bliley Professor, Virginia Commonwealth University School of Medicine, Departments of Neurology, Biochemistry, and Pharmacology and Toxicology, Richmond, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4845642

Cerebrospinal fluid levels of the endocannabinoid anandamide are reduced in patients with untreated newly diagnosed temporal lobe epilepsy

"Purpose: The endocannabinoid system is involved in excitatory/inhibitory balance mechanisms within the central nervous system (CNS). Growing evidence shows that its perturbation leads to development of epileptic seizures in experimental models, thus indicating that endocannabinoids play an intrinsic protective role in suppressing pathologic neuronal excitability. Experimental data also demonstrate that the endocannabinoid anandamide (AEA) can antagonize epileptic discharges in hippocampal tissue. The objective of our study was to measure endocannabinoids levels in the cerebrospinal fluid (CSF) of drug-naive patients affected by temporal lobe epilepsy (TLE)."…

"Results: A significant reduction of AEA was found in the CSF of patients with compared with healthy controls (epileptic patients = 2.55 +/- 1.78 pmol/ml; healthy controls = 11.65 +/- 7.53 pmol/ml; n = 9 for both groups, $p < 0.01$). 2-AG levels, however, were not affected (epileptic patients = 209.5 +/- 146.56; healthy controls = 159.6 +/- 110.2) (n = 6 for both groups, $p = 0.48$).

Discussion: Our findings seem to be consistent with experimental evidence demonstrating a significant prevention of epileptic seizures induced by endocannabinoids in models of epilepsy. Furthermore, they support the hypothesis that AEA may be involved in its pathogenesis, suggesting a hypothetical primary impairment of the endocannabinoid system in untreated TLE. The actual role of this in vivo dysregulation still remains unclear."

-Dept. of Neuroscience, Università degli Studi di Roma Tor Vergata, Roma, Italy.
https://pubmed.ncbi.nlm.nih.gov/19817812

Alterations of endocannabinoids in cerebrospinal fluid of dogs with epileptic seizure disorder

"Epilepsy is one of the most common chronic neurological disorders in dogs characterized by recurrent seizures. The endocannabinoid (EC) system plays a central role in suppressing pathologic neuronal excitability and in controlling the spread of activity in an epileptic network. Endocannabinoids are released on demand and their dysregulation has been described in several pathological conditions. Recurrent seizures may lead to an adverse reorganization of the EC system and impairment of its protective effect. In the current study, we tested the hypothesis that cerebrospinal fluid (CSF) concentrations of the endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2AG) are altered in epileptic dogs. Concentrations of AEA and total AG (sum of 2AG and 1AG) were measured in 40 dogs with idiopathic epilepsy and in 16 unaffected, healthy control dogs using liquid chromatography combined with tandem mass spectrometry."…

Conclusion

"In conclusion, we present the first endocannabinoid measurements in canine CSF and confirm the hypothesis that the EC system is altered in canine idiopathic epilepsy."

-Department of Small Animal Medicine and Surgery, University of Veterinary Medicine, Hannover, Germany
-Institute for Clinical Pharmacology, Hannover Medicine School, Hannover, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883475

Endocannabinoid signaling as a synaptic circuit breaker in neurological disease

"Cannabis sativa is one of the oldest herbal plants in the history of medicine. It was used in various therapeutic applications from pain to epilepsy, but its psychotropic effect has reduced its usage in recent medical practice. However, renewed interest has been fueled by major discoveries revealing that cannabis-derived compounds act through a signaling pathway in the human body. Here we review recent advances showing that endocannabinoid signaling is a key regulator of synaptic communication throughout the central nervous system. Its underlying molecular architecture is highly conserved in synapses from the spinal cord to the neocortex, and as a negative feed-back signal, it provides protection against excess presynaptic activity. The endocannabinoid signaling machinery operates on demand in a synapse-specific manner; therefore, its modulation offers new therapeutic opportunities for the selective control of

deleterious neuronal activity in several neurological disorders."

-Institute of Experimental Medicine, Hungarian Academy of Sciences, Szigony utca 43, H-1083 Budapest, Hungary
https://pubmed.ncbi.nlm.nih.gov/18776886

The Interplay between the Endocannabinoid System, Epilepsy and Cannabinoids

"Epilepsy is a neurological disorder that affects approximately 50 million people worldwide. There is currently no definitive epilepsy cure. However, in recent years, medicinal cannabis has been successfully trialed as an effective treatment for managing epileptic symptoms, but whose mechanisms of action are largely unknown. Lately, there has been a focus on neuroinflammation as an important factor in the pathology of many epileptic disorders. In this literature review, we consider the links that have been identified between epilepsy, neuroinflammation, the endocannabinoid system (ECS), and how cannabinoids may be potent alternatives to more conventional pharmacological therapies. We review the research that demonstrates how the ECS can contribute to neuroinflammation, and could therefore be modulated by cannabinoids to potentially reduce the incidence and severity of seizures. In particular, the cannabinoid cannabidiol has been reported to have anti-convulsant and anti-inflammatory properties, and it shows promise for epilepsy treatment. There are a multitude of signaling pathways that involve endocannabinoids, eicosanoids, and associated receptors by which cannabinoids could potentially exert their therapeutic effects. Further research is needed to better characterize these pathways, and consequently improve the application and regulation of medicinal cannabis."

The Role of the Endocannabinoid System in Neuroinflammation and Epilepsy

"Epilepsy has been associated with ECS dysfunction and, in particular, neuroinflammation. There are already comprehensive reviews [6,7] detailing neuroinflammation and epilepsy, therefore this review will only briefly introduce this complex topic here. Neuroinflammation is a physiological response to insult and/or injury that is mainly mediated by glial cells in the brain. Microglia are a type of glial cells that serve as the resident immune cells of the central nervous system (CNS) and primarily function in protecting the neuronal population. The microglia are activated by pathogens, products from injured/inflamed neurons, and blood-brain barrier disruptions, alongside a wide variety of chemical threat signals, including chemokines and cytokines (e.g., Interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α)) [8,9,10]. While neuroinflammation is a normal defensive mechanism, it seems that there is an overreaction and inability to effectively downregulate the response in diseased brains, when compared to healthy brains [11]. Many of the

ligands and receptors of the ECS are involved in inflammatory pathways. Therefore, the ECS is likely to be central in the development and occurrence of neuropathology, where the complex signaling pathways can be affected at multiple points.

There are already recent review articles detailing the ECS [12,13], so this broad topic will only be summarized here. The ECS is one of the major axes of the CNS. Its principal role is to modulate synaptic activity (excitatory and inhibitory) through the release of endogenous cannabinoids (endocannabinoids); this complex system is comprised of endocannabinoids, cannabinoid receptors, and the enzymes that are responsible for the synthesis and degradation of endocannabinoids [14]. The ECS is heavily involved in the regulation of several aspects of brain development/health, namely neural progenitor proliferation, lineage commitment, neuronal migration, axonal guidance, and synaptic plasticity [15]. "....

-Institute of Health and Biomedical Innovation (IHBI), Faculty of Health, Queensland University of Technology (QUT), Centre for Children's Health Research (CCHR), South Brisbane,Australia;

-Children's Health Queensland (CHQ) and University of Queensland (UQ), Centre for Children's Health Research, 62 Graham Street, South Brisbane, Australia;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6929011

Esophageal Cancer

The Tumor Microenvironment in Esophageal Cancer

"Transforming growth factor-β (TGF-β) signaling regulates tumor initiation, progression and metastasis [151]. Classically, TGF-β family ligands bind the extracellular domain of the TGF-β receptor, which triggers downstream activation of canonical Smad protein signaling, leading to transcription of genes important for tissue homeostasis, neoplastic growth and progression [151]. Interestingly, TGF-β signaling appears to have a dual role in regulating tumorigenesis: in early stages it is a growth suppressor, but later it promotes EMT [epithelial-to-mesenchymal transition] and metastasis [151,152].

This dual role has been described in both EAC and ESCC. Early in esophageal carcinogenesis, TGF-β signaling appears to have an inhibitory effect on tumor growth, with both EAC and ESCC cell lines showing decreased TGF-β responsiveness via downregulation of Smad4 or TGF-β-resistant c-Myc expression [153]. Consistent with this, Smad4 expression was progressively decreased in the metaplasia-dysplasia-adenocarcinoma sequence of EAC with recovery of the antiproliferative response upon Smad4 restoration [154]. Interestingly, ESCC-specific studies have had mixed findings. Whereas TGF-β downregulation by DACH1 methylation or decreased Smad4 expression were associated with increased depth of invasion, later tumor stage and poor differentiation

[155,156], TGF-β downregulation by proteasomal degradation actually suppressed growth and invasion in vivo [157]. Still, ESCC patient studies have supported a tumor-suppressive role for TGF-β, with decreased signaling correlated with more aggressive tumor characteristics and a worse prognosis [158]."

-Division of Gastroenterology, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
-Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania
-Department of Medical Oncology, Dana Farber Cancer Institute
-Department of Genetics, University of Pennsylvania, Philadelphia, Pennsylvania
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5003768/

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…"These results indicated that cannabinoid CB2 receptors modulate fibrogenesis and the TGF-β/Smad profibrotic signaling pathway during skin wound repair in the mouse."

-Department of Forensic Pathology, School of Forensic Medicine, China Medical University, Shenyang, Liaoning , P.R. China
-Department of Forensic Medicine, Xuzhou Medical College, Xuzhou, Jiangsu, P.R. China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4805070/

Essential Oils

A Systematic Review of Essential Oils and the Endocannabinoid System: A Connection Worthy of Further Exploration

"Aromatic compounds have a long history of use as medicines in most recorded cultures. An increasing interest in these therapeutic volatile molecules in both scientific and lay communities has led to the advancement of essential oils as phytomedicines. Recent discoveries suggest essential oils augment the endocannabinoid system in a positive manner to mitigate various pathologies. However, the exact mechanisms whereby essential oils influence endocannabinoid system activity are not fully known, these studies provide a glimpse into their involvement and warrant further evaluation. Additional study of the interaction between essential oils and the endocannabinoid system may lead to promising phytomedicines for the treatment of diseases and conditions involving dysregulation or activation of the endocannabinoid system."…

"A large body of evidence describes the effects of odors on the human brain and emotions. Essential oil molecules are uniquely qualified to influence mood, alertness, stress, anxiety, and task performance because of their direct connection to areas of the brain involved in emotions and cognition, especially the limbic system [3]. Studies evaluating the effects of essential oils on

human physiology and specific disease states are also growing, but much of this to date has been performed in vitro or animal research. Hundreds of clinical trials have also investigated essential oils, with the majority occurring in the last decade. Nevertheless, multiple promising properties have been confirmed—anxiolytic, antidepressant, anti-inflammatory, analgesic, hormonogenic, antidiabetic, antitumoral, immunomodulatory, and more—that await confirmation in randomized, controlled, and blinded human trials [3].”…

“Essential oils are complex mixtures of volatile organic compounds, which generally contain dozens to hundreds of low molecular weight compounds. In general, monoterpenes and sesquiterpenes are the predominant compounds of essential oils. Terpenes are a potential source of lipid modulators of the endogenous lipid systems, including the ECS, with the ability to stimulate cannabinergic signaling [28, 100, 101]. Some compounds can dominate the composition of the essential oil (such as methyl salicylate, which makes up more than 95% of genuine wintergreen oil), while others may be present in only fractions (such as incensole acetate in frankincense). Sometimes the main compound is responsible for the biological effects of the oil, but this is not always the case, and frequently greater activity is observed with the whole oil rather than isolated major compounds [2]. Among plant products, essential oils deserve particular attention for clinical use because of their use in numerous healing systems throughout the history.”

-dōTERRA International, LLC, Pleasant Grove, UT, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7246407/

Essential Fatty Acids

“Essential fatty acids (EFAs), linoleic acid (LA), and alpha-linolenic acid (ALA) are essential for humans, and are freely available in the diet. Hence, EFA deficiency is extremely rare in humans. To derive the full benefits of EFAs, they need to be metabolized to their respective long-chain metabolites, i.e., dihomo-gamma-linolenic acid (DGLA), and arachidonic acid (AA) from LA; and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA. Some of these long-chain metabolites not only form precursors to respective prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), but also give rise to lipoxins (LXs) and resolvins that have potent anti-inflammatory actions. Furthermore, EFAs and their metabolites may function as endogenous angiotensin-converting enzyme and 3-hdroxy-3-methylglutaryl coenzyme A reductase inhibitors, nitric oxide (NO) enhancers, anti-hypertensives, and anti-atherosclerotic molecules. Recent studies revealed that EFAs react with NO to yield respective nitroalkene derivatives that exert cell-signaling actions via ligation and activation of peroxisome proliferator-

activated receptors. The metabolism of EFAs is altered in several diseases such as obesity, hypertension, diabetes mellitus, coronary heart disease, schizophrenia, Alzheimer's disease, atherosclerosis, and cancer. Thus, EFAs and their derivatives have varied biological actions and seem to be involved in several physiological and pathological processes."

-Undurti N Das 1
-UND Life Sciences, Shaker Heights, OH 44120, USA.
https://pubmed.ncbi.nlm.nih.gov/16892270/

Ethylene Oxide (EtO)

A common "organic" compound often used in spices,
however some spices specifically say NON-ETO.

"It is emitted from fossil fuels such as petroleum, natural gas, and coal, and from tobacco products. Ethylene oxide is used to make antifreeze, adhesives, detergents, polyester, fumigants and pesticides, and sterilization agents for medical equipment."

-U.S National Library of Medicine
https://toxtown.nlm.nih.gov/chemicals-and-contaminants/ethylene-oxide

Carcinogenicity of ethylene oxide: key findings and scientific issues.

"In support of the Integrated Risk Information System (IRIS), the U.S. Environmental Protection Agency (EPA) completed an evaluation of the inhalation carcinogenicity of ethylene oxide (EtO) in December 2016. This article reviews key findings and scientific issues regarding the carcinogenicity of EtO in EPA's Carcinogenicity Assessment. EPA's assessment critically reviewed and characterized epidemiologic, laboratory animal, and mechanistic studies pertaining to the human carcinogenicity of EtO, and addressed some key scientific issues such as the analysis of mechanistic data as part of the cancer hazard evaluation and to inform the quantitative risk assessment. The weight of evidence from the epidemiologic, laboratory animal, and mechanistic studies supports a conclusion that EtO is carcinogenic in humans, with the strongest human evidence linking EtO exposure to lymphoid and breast cancers. Analyses of the mechanistic data establish a key role for genotoxicity and mutagenicity in EtO-induced carcinogenicity and reveal little evidence supporting other mode-of-action hypotheses. In conclusion, EtO was found to be

carcinogenic to humans by inhalation, posing a potential human health hazard for lymphoid and breast cancers."

-National Center for Environmental Assessment , U.S. Environmental Protection Agency , Washington , DC , USA.
https://www.ncbi.nlm.nih.gov/pubmed/29210319

■■■

…"However, among those workers with very high EtO exposures, (combination of exposure levels and years worked); there was evidence of an elevated risk for blood cancers among men and breast cancers among women."

Persons exposed to very high levels of EtO may be at an increased risk of developing blood cancers among men and breast cancers among women.

Why Did NIOSH Do the EtO Studies?

Since the early 1980s, we have been doing research on the chemical ethylene oxide (EtO). Our purpose has been to determine if EtO is related to cancer or other diseases.Animal studies have shown an increase in leukemia and brain cancer. Also, some earlier and much smaller studies of humans who work around EtO found more leukemia, stomach cancer, and cancer of the pancreas than expected.

However, some other studies did not find a cancer increase among workers. Since it was unclear from these studies whether exposure to EtO caused cancer or other diseases, NIOSH did its own studies to look further into this issue."…

-NIOSH / CDC
https://www.cdc.gov/niosh/pgms/worknotify/ethyleneoxide.html

Exercise & Training

Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the 'runner's high'

"Humans report a wide range of neurobiological rewards following moderate and intense aerobic activity, popularly referred to as the 'runner's high', which may function to encourage habitual aerobic exercise. Endocannabinoids (eCBs) are endogenous neurotransmitters that appear to play a major role in generating these rewards by activating cannabinoid receptors in brain reward regions during and after exercise. Other species also regularly engage in endurance exercise (cursorial mammals), and as humans share many morphological traits with these taxa, it

is possible that exercise-induced eCB signaling motivates habitual high-intensity locomotor behaviors in cursorial mammals. If true, then neurobiological rewards may explain variation in habitual locomotor activity and performance across mammals. We measured circulating eCBs in humans, dogs (a cursorial mammal) and ferrets (a non-cursorial mammal) before and after treadmill exercise to test the hypothesis that neurobiological rewards are linked to high-intensity exercise in cursorial mammals. We show that humans and dogs share significantly increased exercise-induced eCB signaling following high-intensity endurance running. eCB signaling does not significantly increase following low-intensity walking in these taxa, and eCB signaling does not significantly increase in the non-cursorial ferrets following exercise at any intensity. This study provides the first evidence that inter-specific variation in neurotransmitter signaling may explain differences in locomotor behavior among mammals. Thus, a neurobiological reward for endurance exercise may explain why humans and other cursorial mammals habitually engage in aerobic exercise despite the higher associated energy costs and injury risks, and why non-cursorial mammals avoid such locomotor behaviors."

School of Anthropology, University of Arizona
https://www.ncbi.nlm.nih.gov/pubmed/22442371

Intense exercise increases circulating endocannabinoid and BDNF levels in humans--possible implications for reward and depression.

"These findings provide evidence in humans that acute exercise represents a physiological stressor able to increase peripheral levels of AEA [anandamide] and that BDNF might be a mechanism by which AEA influences the neuroplastic and antidepressant effects of exercise."

University Lille Nord, France
http://www.ncbi.nlm.nih.gov/pubmed/22029953

A runner's high depends on cannabinoid receptors in mice

"Exercise is rewarding, and long-distance runners have described a runner's high as a sudden pleasant feeling of euphoria, anxiolysis, sedation, and analgesia. A popular belief has been that endogenous endorphins mediate these beneficial effects. However, running exercise increases blood levels of both β-endorphin (an opioid) and anandamide (an endocannabinoid). Using a combination of pharmacologic, molecular genetic, and behavioral studies in mice, we demonstrate that cannabinoid receptors mediate acute anxiolysis and analgesia after running. We show that anxiolysis depends on intact cannabinoid receptor 1 (CB1) receptors on forebrain GABAergic neurons and pain reduction on activation of peripheral CB1 and CB2 receptors. We

thus demonstrate that the endocannabinoid system is crucial for two main aspects of a runner's high. Sedation, in contrast, was not influenced by cannabinoid or opioid receptor blockage, and euphoria cannot be studied in mouse models."

-Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, University Medicine Mannheim, University of Heidelberg, Mannheim, Germany; Institute for Sex Research and Forensic Psychiatry, Center of Psychosocial Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;

-Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, University Medicine Mannheim, University of Heidelberg, Mannheim, Germany;

-Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany;

-Department of Clinical Neuroendocrinology, Max Planck Institute of Psychiatry, 80804 Munich, Germany;

-Medizinisches Labor Bremen, Bremen, Germany.

https://pubmed.ncbi.nlm.nih.gov/26438875/

Mechanisms of exercise-induced hypoalgesia.

"Blood was drawn before and after exercise. Results indicated circulating concentrations of two endocannabinoids, N-arachidonylethanolamine (AEA [anandamide]) and 2-arachidonoylglycerol (2-AG) as well as related lipids oleoylethanolamide (OEA), palmitoylethanolamide (PEA), N-docsahexaenoylethanolamine (DHEA), and 2- oleoylglycerol (2-OG) increased significantly ($p < 0.05$) following exercise."

-Department of Kinesiology, University of Wisconsin-Madison

-Department of Rehabilitation Medicine, University of Wisconsin-Madison

-Department of Pharmacology and Toxicology, Medical College of Wisconsin

http://www.ncbi.nlm.nih.gov/pubmed/25261342

Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System

"Raichlen et al., [240] measured circulating eCBs in humans and dogs (cursorial mammals) and ferrets (a non-cursorial mammal) before and after treadmill exercise to test the hypothesis that neurobiological rewards are linked to high-intensity exercise in cursorial mammals. The authors showed that humans and dogs share significantly increased exercise-induced eCB signaling following high-intensity endurance running, whereas eCB signaling did not significantly increase following low-intensity walking, nor did it increase in the non-cursorial ferrets following exercise at any intensity. The same research group showed that serum AEA levels in male and female

runners significantly increased after 30 minutes of moderately intense treadmill running (70–80% age-adjusted maximum heart rate), and not after very high or very low intensity exercises [240], [241].”

- GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom,
- Department of Family Medicine, University of Vermont, Burlington, Vermont, USA,
- Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei, Pozzuoli, Napoli, Italy,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951193/

Omega-3 Polyunsaturated Fatty Acids: Benefits and Endpoints in Sport

“The influence of nutrition has the potential to substantially affect physical function and body metabolism. Particular attention has been focused on omega-3 polyunsaturated fatty acids (n-3 PUFAs), which can be found both in terrestrial features and in the marine world. They are responsible for numerous cellular functions, such as signaling, cell membrane fluidity, and structural maintenance. They also regulate the nervous system, blood pressure, hematic clotting, glucose tolerance, and inflammatory processes, which may be useful in all inflammatory conditions. Animal models and cell-based models show that n-3 PUFAs can influence skeletal muscle metabolism. Furthermore, recent human studies demonstrate that they can influence not only the exercise and the metabolic response of skeletal muscle, but also the functional response for a period of exercise training. In addition, their potential anti-inflammatory and antioxidant activity may provide health benefits and performance improvement especially in those who practice physical activity, due to their increased reactive oxygen production. This review highlights the importance of n-3 PUFAs in our diet, which focuses on their potential healthy effects in sport.”

-Human and Clinical Nutrition Unit, Department of Medical, Oral and Biotechnological Sciences, University G. D’Annunzio, 66100 Chieti, Italy;
-Cardiology Unit, Cardiology Department, San Camillo De Lellis Hospital, Manfredonia, Foggia, Italy
-Department of Internal and Specialistic Medicine DIBIMIS, University of Palermo, Palermo, Italy;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6357022/

Exercise-induced endocannabinoid signaling is modulated by intensity

“Endocannabinoids (eCB) are endogenous ligands for cannabinoid receptors that are densely expressed in brain networks responsible for reward. Recent work shows that exercise activates the eCB system in humans and other mammals, suggesting eCBs are partly responsible for the reported improvements in mood and affect following aerobic exercise in humans. However, exercise-induced psychological changes reported by runners are known to be dependent on

exercise intensity, suggesting that any underlying molecular mechanism should also change with varying levels of exercise intensity. Here, we examine circulating levels of eCBs following aerobic exercise (treadmill running) in recreationally fit human runners at four different intensities. We show that eCB signaling is indeed intensity dependent, with significant changes in circulating eCBs observed following moderate intensities only (very high and very low intensity exercises do not significantly alter circulating eCB levels). Our results are consistent with intensity-dependent psychological state changes with exercise and therefore support the hypothesis that eCB activity is related to neurobiological effects of exercise. Thus, future studies examining the role of exercise-induced eCB signaling on neurobiology or physiology must take exercise intensity into account."

-School of Anthropology, University of Arizona, Tucson, AZ 85721, USA.
https://pubmed.ncbi.nlm.nih.gov/22990628/

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…"EPA/DHA supplementation increases blood levels of these fatty acids and results in decreased resting levels of inflammatory biomarkers in exercise-trained men, but does not appear necessary for exercise-induced attenuation in either inflammation or oxidative stress. This may be due to the finding that trained men exhibit a minimal increase in both inflammation and oxidative stress in response to moderate duration (60 minute) aerobic exercise."…

-Cardiorespiratory/Metabolic Laboratory, Department of Health and Sport Sciences, The University of Memphis, Memphis, USA.
https://pubmed.ncbi.nlm.nih.gov/19691834/

Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) in Muscle Damage and Function

"Nutritional supplementation not only helps in improving and maintaining performance in sports and exercise, but also contributes in reducing exercise fatigue and in recovery from exhaustion. Fish oil contains large amounts of omega-3 fatty acids, eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3). It is widely known that omega-3 fatty acids are effective for improving cardiac function, depression, cognitive function, and blood as well as lowering blood pressure. In the relationship between omega-3 fatty acids and exercise performance, previous studies have been predicted improved endurance performance, antioxidant and anti-inflammatory responses, and effectivity against delayed-onset muscle soreness. However, the optimal dose, duration, and timing remain unclear. This review focuses on the effects of omega-3 fatty acid on muscle damage and function as evaluated by human and animal studies and

summarizes its effects on muscle and nerve damage, and muscle mass and strength."

-Faculty of Bioscience and Applied Chemistry, Hosei University, Kajino, Koganei, Tokyo Japan
-Faculty of Modern life, Teikyo Heisei University, Nakano, Tokyo, Japan;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5986432

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See Supplements for related research quotes.

The Effect of Omega-3 Fatty Acid Supplementation on the Inflammatory Response to eccentric strength exercise

…"inflammation is known to be involved in the pathogenesis of numerous diseases, including heart disease, cancer, and diabetes, it is likely prudent for individuals to use inflammation-attenuating interventions, such as omega-3 supplementation, to keep inflammatory responses to physical activity at a minimum."…

-Doisy College of Health Sciences, Department of Nutrition and Dietetics, Saint Louis University, St. Louis, MO, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3737804/

Exhale

Exhaled markers of inflammation

"Exhaled markers of inflammation allow completely noninvasive monitoring of inflammation and oxidative stress in the respiratory tract in inflammatory lung diseases, including asthma, chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis and interstitial lung diseases. Such noninvasive techniques are simple to perform, may be repeated frequently and can be applied in children, including neonates and patients with severe disease in whom more invasive procedures are not possible. Several volatile chemicals can be measured in the breath (nitric oxide, carbon monoxide, hydrocarbons), and many nonvolatile molecules (mediators, oxidation and nitration products, proteins) may be measured in exhaled breath condensate."

-National Heart and Lung Institute, Imperial College, London, UK
https://pubmed.ncbi.nlm.nih.gov/11964692/

Exosomes

Also called extracellular vesicles (EVs)

Active endocannabinoids are secreted on extracellular membrane vesicles

"Endocannabinoids primarily influence neuronal synaptic communication within the nervous system. To exert their function, endocannabinoids need to travel across the intercellular space. However, how hydrophobic endocannabinoids cross cell membranes and move extracellularly remains an unresolved problem. Here, we show that endocannabinoids are secreted through extracellular membrane vesicles produced by microglial cells. We demonstrate that microglial extracellular vesicles carry on their surface N-arachidonoylethanolamine [anandamide] (AEA), which is able to stimulate type-1 cannabinoid receptors (CB1), and inhibit presynaptic transmission, in target GABAergic neurons. This is the first demonstration of a functional role of extracellular vesicular transport of endocannabinoids."…

"Endocannabinoids (eCBs) are lipid messengers which potently modulate synaptic function [1]. Their impact on synaptic transmission is widespread and diverse: Short-term forms of plasticity induced by eCBs have been described in numerous brain areas, while eCB-mediated modulation of long-term plasticity has implicated these bioactive lipids in learning and memory [2, 3]. Since eCB-binding receptors are localized more prominently on inhibitory than excitatory terminals, eCB signaling is widely thought to be involved in regulating over-excitability and in promoting synaptic homeostasis. In addition to modulating the activity of mature synapses, eCBs have been implicated in synapse formation and neurogenesis [4]."…

"Some components of the eCB system, including CB1 receptors, have been previously described in MVs shed from microglia [17].

-Department of Medical Biotechnology and Translational Medicine, University of Milano, Milano, Italy
-Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Teramo, Italy
-European Center for Brain Research/IRCCS Santa Lucia Foundation, Rome, Italy
-CNR Institute of Neuroscience, Milano, Italy
-Department of Clinical Sciences and Community Health, University of Milano, Milano, Italy
-IRCCS Humanitas, Rozzano, Italy
-Center of Integrated Research, Campus Bio-Medico, University of Rome, Rome, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4328748

The crosstalk: exosomes and lipid metabolism

"Exosomes have been considered as novel and potent vehicles of intercellular communication, instead of "cell dust". Exosomes are consistent with anucleate cells, and organelles with lipid bilayer consisting of the proteins and abundant lipid, enhancing their "rigidity" and "flexibility". Neighboring cells or distant cells are capable of exchanging genetic or metabolic information via exosomes binding to recipient cell and releasing bioactive molecules, such as lipids, proteins, and nucleic acids. Of note, exosomes exert the remarkable effects on lipid metabolism, including the synthesis, transportation and degradation of the lipid. The disorder of lipid metabolism mediated by exosomes leads to the occurrence and progression of diseases, such as atherosclerosis, cancer, non-alcoholic fatty liver disease (NAFLD), obesity and Alzheimer's diseases and so on. More importantly, lipid metabolism can also affect the production and secretion of exosomes, as well as interactions with the recipient cells. Therefore, exosomes may be applied as effective targets for diagnosis and treatment of diseases."

-School of Pharmacy, Hanpu Science and Education District, Hunan University of Chinese Medicine, 300 Xueshi Road, Changsha, 410208 Hunan China

-Division of Stem Cell Regulation and Application, Hunan University of Chinese Medicine, Changsha, Hunan China

-The First Affiliated Hospital, Hunan University of Chinese Medicine, Changsha, Hunan China

-Department of Neurosurgery in Changsha, 921 hospital, joint service support force of People's Liberation Army, Changsha, China

-College of Chinese Medicine, Hunan University of Chinese Medicine, Changsha, Hunan China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7398059

Ceramide and Exosomes: A Novel Target in Cancer Biology and Therapy

"Exosomes are secreted extracellular vesicles (EVs) that carry micro RNAs and other factors to reprogram cancer cells and tissues affected by cancer. Exosomes are exchanged between cancer cells and other tissues, often to prepare a premetastatic niche, escape immune surveillance, or spread multidrug resistance. Only a few studies investigated the function of lipids in exosomes although their lipid composition is different from that of the secreting cells. Ceramide is one of the lipids critical for exosome formation, and it is also enriched in these EVs. New research suggests that lipids in the exosomal membrane may organize and transmit "mobile rafts" that turn exosomes into extracellular signalosomes spreading activation of cell signaling pathways in oncogenesis and metastasis. Ceramide may modulate the function of mobile rafts and their effect on these cell signaling pathways. The critical role of lipids and, in particular, ceramide for formation, secretion, and function of exosomes may lead to a radically new understanding of cancer biology and therapy."

-Department of Physiology, University of Kentucky, Lexington, KY, United States.

https://pubmed.ncbi.nlm.nih.gov/30060807

Circulating exosomes deliver free fatty acids from the bloodstream to cardiac cells: Possible role of CD36

"Regulation of circulating free fatty acid (FFA) levels and delivery is crucial to maintain tissue homeostasis. Exosomes are nanomembranous vesicles that are released from diverse cell types and mediate intercellular communication by delivering bioactive molecules."…

"Finally, we found that circulating exosomes could delivery FFA analogue BODIPY into cardiac cells ex vivo and in vivo in a mice model. Overall, our results suggest a novel mechanism in which circulating exosomes can delivery FFAs from the bloodstream to cardiac tissue. Further studies will be necessary to understand this mechanism and, in particular, its potential involvement in metabolic pathologies such as obesity, diabetes and atherosclerosis."

-GECORP, Buenos Aires, Argentina.
-Regenerative Medicine and Heart Transplantation Unit, Instituto de Investigación Sanitaria La Fe, Valencia, Spain.
-Joint Research Unit for Cardiovascular Repair IISLAFE-CIPF, Valencia, Spain.
-Joint Research Unit of Cytomics CIPF-UVEG, Valencia, Spain.
-Department of Biochemistry, University of Valencia, Valencia, Spain.
-Bioceros BV, Utrecht, The Netherlands.
-Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark.
-Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark.
https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/31141569

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…"Exosomes are secreted vesicles of approximately 100 nm in diameter that mediate the transport of proteins, RNAs, or lipid cargos. In the central nervous system, exosomes serve as a form of intercellular communication and participate in neurodevelopment, synaptic function, and neuronal maintenance (Budnik et al., 2016). In neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, exosomes affect disease progression by facilitating the clearance of protein aggregates or the spread of toxic signals (Budnik et al., 2016)."…

-Graduate Institute of Physiology, College of Medicine, National Taiwan University, Taipei, Taiwan
https://www.biorxiv.org/content/10.1101/2020.11.10.376046v1.full

Exosome-associated tau is secreted in tauopathy models and is selectively phosphorylated in cerebrospinal fluid in early Alzheimer disease

"Recent demonstrations that the secretion, uptake, and interneuronal transfer of tau can be modulated by disease-associated tau modifications suggest that secretion may be an important element in tau-induced neurodegeneration. Here, we show that much of the tau secreted by M1C cells occurs via exosomal release, a widely characterized mechanism that mediates unconventional secretion of other aggregation-prone proteins (α-synuclein, prion protein, and β-amyloid) in neurodegenerative disease. Exosome-associated tau is also present in human CSF samples and is phosphorylated at Thr-181 (AT270), an established phosphotau biomarker for Alzheimer disease (AD), in both M1C cells and in CSF samples from patients with mild (Braak stage 3) AD. A preliminary analysis of proteins co-purified with tau in secreted exosomes identified several that are known to be involved in disease-associated tau misprocessing. Our results suggest that exosome-mediated secretion of phosphorylated tau may play a significant role in the abnormal processing of tau and in the genesis of elevated CSF tau in early AD."

-Department of Biological Sciences, University of Massachusetts, Lowell, Massachusetts
-MassBay Community College Science Department STEM Division, Wellesley Hills, Massachusetts 02481,
-GRECC Unit, Veterans Affairs Medical Center, Bedford, Massachusetts
-Departments of Neurology and Pathology, Boston University School of Medicine, Boston, Massachusetts
-Chemical Instrumentation Center, Department of Chemistry, Boston University, Boston, Massachusetts
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3281682

Exosome Determinants of Physiological Aging and Age-Related Neurodegenerative Diseases

"Aging is consistently reported as the most important independent risk factor for neurodegenerative diseases. As life expectancy has significantly increased during the last decades, neurodegenerative diseases became one of the most critical public health problem in our society. The most investigated neurodegenerative diseases during aging are Alzheimer disease (AD), Frontotemporal Dementia (FTD) and Parkinson disease (PD). The search for biomarkers has been focused so far on cerebrospinal fluid (CSF) and blood. Recently, exosomes emerged as novel biological source with increasing interest for age-related neurodegenerative disease biomarkers. Exosomes are tiny Extracellular vesicles (EVs; 30–100 nm in size) released by all cell types which originate from the endosomal compartment. They constitute important vesicles for the release and transfer of multiple (signaling, toxic, and regulatory) molecules among cells. Initially considered with merely waste disposal function, instead exosomes have been recently recognized as fundamental mediators of intercellular communication. They can

move from the site of release by diffusion and be retrieved in several body fluids, where they may dynamically reflect pathological changes of cells present in inaccessible sites such as the brain. Multiple evidence has implicated exosomes in age-associated neurodegenerative processes, which lead to cognitive impairment in later life. Critically, consolidated evidence indicates that pathological protein aggregates, including Aβ, tau, and α-synuclein are released from brain cells in association with exosomes. Importantly, exosomes act as vehicles between cells not only of proteins but also of nucleic acids [DNA, mRNA transcripts, miRNA, and non-coding RNAs (ncRNAs)] thus potentially influencing gene expression in target cells. In this framework, exosomes could contribute to elucidate the molecular mechanisms underneath neurodegenerative diseases and could represent a promising source of biomarkers. Despite the involvement of exosomes in age-associated neurodegeneration, the study of exosomes and their genetic cargo in physiological aging and in neurodegenerative diseases is still in its infancy. Here, we review, the current knowledge on protein and ncRNAs cargo of exosomes in normal aging and in age-related neurodegenerative diseases."…

"It is undeniable that last two decades have been characterized by an exponential increase in the number of publications regarding exosomes and their role in the pathogenesis of diseases as well as in the field of clinical biomarker research. Indeed due to their intrinsic ability to transfer biomolecules to other cells and to cross the BBB in both directions, they are becoming an attractive source of potential new biomarkers and/or reservoir of validated ones. The times when exosomes were considered full of junk are long gone. Indeed, new roles and functions for exosomes emerged to the point where these small EVs have been proposed with a double-edged sword role, "Trojan horses" of neurodegeneration or neuroprotective from neurodegeneration. This means that their involvement in neurodegenerative diseases is not totally understood. Some questions remain opened and the most interesting seem to be: (1) are exosomes carrier of disease propagating pathogenic molecules also in vivo; (2) can targeting the release of exosomes, or the release of their cargo have an inhibitor effect on the progression of diseases; and (3) can specific protein, or ncRNA signatures isolated from patients be used as biomarker of disease. Further investigations will clarify these aspects as well as the basic research on exosomes improving the comprehension on the role of exosomes in the etiology and progression of these pathologies."

-Department of Pathophysiology and Transplantation, Dino Ferrari Center, Faculty of Medicine and Surgery, University of Milan, Milan, Italy

-Department of Clinical Sciences and Community Health, Faculty of Medicine and Surgery, University of Milan, Milan, Italy

-Geriatrics Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

-Neurodegenerative Diseases Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

-Department of Biomedical, Surgical and Dental Sciences, Dino Ferrari Center, Faculty of Medicine and Surgery,

University of Milan, Milan, Italy
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC6722391

See also Alzheimer's Disease

Eye Care, Disorders & Diseases

The role of endocannabinoid system in physiological and pathological processes in the eye

"Plant of Cannabis sativa/ marihuana except for its psychotropic effects possesses a range of pharmacological properties, that has been utilized for medical purposes over a period of millenia. Investigations concerning biochemical mechanism of action of the main and most active pharmacological compound of Cannabis sativa, cannabinoid 9-THC, contributed to the discovery of cannabinoid receptors both in the central nervous system (CNS) and peripheral tissues, that mediated actions of this substance. The discovery made possible identification of a new, endogenous signaling system reffered to as the endocannabinoid system. Besides cannabinoid receptors CB1 and CB2, the system includes it's endogenic ligands (endocannabinoids) and compounds that participate in their biosynthesis and inactivation. Structure and functioning of the endocannabinoid system is conservative in all vertebrates. It's activation with plant, synthetic and endogenous cannabinoids has an influence on multiple physiological and pathological processes within the eye."

-Clinics of Ophthalmology and Rehabilitation, Visual, Medical University of Lodz.
https://pubmed.ncbi.nlm.nih.gov/19195174

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"PURPOSE. Diet-induced deficiencies in Omega-3 (ω-3) fatty acids are well known to alter photoreceptor function. In this study, the broader functional changes in a diversity of retinal neurons were considered.

RESULTS. Omega-3 deficiency caused a 48.6% decrease in total retinal docosahexaenoic acid (DHA). This change induced significant amplitude decreases only in the rod PII (−8.2%) and positive (p)STR components (−27.4%), with widespread delays in all signals (PIII 5.7%, PII 13.6%, pSTR 7.6%, and negative [n]STR 8.3%). Omega-3 deficiency exerted its greatest effects on signals originating in the inner retina (pSTR).

CONCLUSIONS. Increasing dietary ω-3 has beneficial effects across the retina, with the greatest improvement occurring in ganglion cell function."

- Christine T. O. Nguyen / Department of Optometry and Vision Sciences, University of Melbourne, Parkville, Victoria, Australia.
Algis J. Vingrys / Department of Optometry and Vision Sciences, University of Melbourne, Parkville, Victoria, Australia.
Bang V. Bui / Department of Optometry and Vision Sciences, University of Melbourne, Parkville, Victoria, Australia.
https://iovs.arvojournals.org/article.aspx?articleid=2125829

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Face Masks

There has been a lot of back and forth regarding the use of face masks during the so called "pandemic" of 2020+. This section will cover a few research quotes on this topic and how it ties in to inflammation and health issues.

"If you are healthy, you only need to wear a mask if you are taking care of a person with suspected SARS-CoV-2 infection." (APRIL 2020) - *World Health Organization (WHO)*

https://archive.is/n7DDK

FADS Gene

"The protein encoded by the FADS1 gene is a member of the fatty acid desaturase (FADS) gene family and desaturates omega-3 and omega-6 polyunsaturated fatty acids at the delta-5 position, catalyzing the final step in the formation of eicosapentaenoic acid (EPA) and Arachidonic acid.[6]"

-Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853
https://en.wikipedia.org/wiki/FADS1
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2681401

FADS genotypes and desaturase activity estimated by the ratio of arachidonic acid [omega-6] to linoleic acid are associated with inflammation and coronary artery disease

Background: The delta-5 and delta-6 desaturases, encoded by FADS1 and FADS2 genes, are key enzymes in polyunsaturated fatty acid (PUFA) metabolism that catalyze the conversion of linoleic acid (LA) into arachidonic acid (AA) and that of alpha-linolenic acid (ALA) into eicosapentaenoic acid (EPA). Single-nucleotide polymorphisms (SNPs) in FADS1 and FADS2 have been associated with different concentrations of AA and LA, and those associations have possible functional consequences for desaturase activity.

Objective: We aimed to evaluate the possible association among FADS genotypes, desaturase activity, inflammation, and coronary artery disease (CAD).

Design: Thirteen FADS SNPs and the ratio of AA to LA (AA/LA) on red blood cell (RBC) membranes, a marker of desaturase activity, were evaluated in 876 subjects with (n = 610) or without (n = 266) angiographically documented CAD.

Results: Both AA/LA and the ratio of EPA to ALA (EPA/ALA) were higher in patients with CAD than in those without CAD, but, in a multiple logistic regression model, only a higher AA/LA resulted an independent risk factor for CAD (odds ratio: 2.55; 95% CI: 1.61, 4.05 for higher compared with lower ratio tertile; P for trend < 0.001). Furthermore, concentrations of high-sensitivity C-reactive protein increased progressively across tertiles of AA/LA. Graded increases in high-sensitivity C-reactive protein concentrations and CAD risk were related to the carriership of FADS haplotypes, including the alleles associated with a higher ratio.

Conclusion: In populations following a Western diet, subjects carrying FADS haplotypes that are associated with higher desaturase activity may be prone to a proinflammatory response favoring atherosclerotic vascular damage.

-Department of Clinical and Experimental Medicine and the Section of Biology and Genetics, University of Verona, Verona, Italy.

https://pubmed.ncbi.nlm.nih.gov/18842780

Erythrocyte polyunsaturated fatty acid composition is associated with depression and FADS genotype in Caucasians

Background: Polyunsaturated fatty acids (PUFAs) play an important role in the pathophysiology of major depressive disorder (MDD), related, in part, to their role in inflammatory systems. The enzymes δ-5 and δ-6 desaturase are the rate-limiting steps in the metabolism of PUFAs and are encoded in the genes fatty acid desaturase (FADS) 1 and 2, respectively. Single nucleotide

polymorphisms (SNPs) and haplotypes within the FADS gene cluster have been shown to influence PUFA composition.

Aim: The objective of this study was to determine whether key omega-3 (n-3) and omega-6 (n-6) fatty acids may be associated with depression, and to explore the role of FADS genotype in PUFA variation.

Conclusion: Precursor LC-PUFAs, LA and ALA, appear to be associated with MDD and potentially modulated by genetic variation in the FADS gene cluster. These results provide support for the consideration of PUFA composition, diet and FADS genetic variation in the pathophysiology of MDD.

-The Melbourne Clinic, Department of Psychiatry, The University of Melbourne , Melbourne , Australia.
-Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne , Parkville , Australia.
-Department of General Practice , The University of Melbourne , Parkville , Australia.
-Florey Institute of Neuroscience and Mental Health, The University of Melbourne , Parkville , Australia.
-Centre for Human Psychopharmacology, Swinburne University of Technology , Hawthorn , Australia.
-NICM, Western Sydney University , Campbelltown , Australia.
https://pubmed.ncbi.nlm.nih.gov/28552045

Failure-to-Thrive, Nonorganic (NOFTT)

The endocannabinoid-CB receptor system: Importance for development and in pediatric disease.

“We propose that a dysfunctional Endocannabinoid-CB1 Receptor system in infants with growth failure resulting from an inability to ingest food, may resolve the enigma of "non-organic failure-to-thrive" (NOFTT). Developmental observations suggest further that CB1 receptors develop only gradually during the postnatal period, which correlates with an insensitivity to the psychoactive effects of cannabinoid treatment in the young organism. Therefore, it is suggested that children may respond positively to medicinal applications of cannabinoids without undesirable central effects. Excellent clinical results have previously been reported in pediatric oncology and in case studies of children with severe neurological disease or brain trauma. We suggest cannabinoid treatment for children or young adults with cystic fibrosis in order to achieve an improvement of their health condition including improved food intake and reduced inflammatory exacerbations.”

Department of Behavioral Sciences, College of Judea and Samaria, Ariel 44837, Israel
https://www.ncbi.nlm.nih.gov/pubmed/15159678

Fasting

…."Endocannabinoid signaling mechanisms in the gut have been proposed to participate in the control of food intake and energy balance via indirect actions with the vagus nerve,[3,4] which bidirectionally communicates neurotransmission between the gut and brain.[37] The first suggestion of a peripheral mechanism for endocannabinoid control of feeding was made by Gomez et al.[40] and substantiated over the years by several other groups.[41–46] Fasting was found to increase production of the endocannabinoid, anandamide, in the rat proximal small intestine.[40] Systemic administration of WIN or anandamide increased feeding, while rimonabant inhibited feeding, and these effects were absent following chemical ablation of sensory afferents with capsaicin. Together, the results imply a peripheral mechanism for endocannabinoid signaling in feeding that is mediated through the vagus nerve."…

-Division of Biomedical Sciences, School of Medicine, University of California, Riverside, Riverside, California.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4940133/

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…"It is well established that lifespan as well as the progress of different diseases can be positively influenced by dietary changes.[1] This is particularly due to the fact that a number of diseases are associated with obesity and overweight which show increasing incidences worldwide. Accordingly, fasting or caloric restriction (CR) and weight loss have been related to improvement of, for example, hypertension or diabetes type 2, respectively.[2,3] In addition, a number of studies indicate that CR is associated with antinociceptive effects. Mice fed 30%–60% of their daily average food quantity showed reduced responses in models of acute thermal and formalin-induced inflammatory nociception.[4,5] Alternate day fasting revealed antinociceptive effects towards acute thermal noxious stimulation and acetic acid-induced visceral nociception.[6] Furthermore, clinical studies on fasting have shown beneficial pain-relieving effects for patients with rheumatoid arthritis or fibromyalgia[7–9] However, the detailed molecular mechanisms involved in CR-induced antinociception are still not completely elucidated, although a number of potential signaling pathways have already been uncovered. These mechanisms include changes in the endogenous opioid system after CR or fasting[6,10,11] and decreases of glutamate receptors,[12] inflammatory mediators, or reactive oxygen species.[13]

Activation of AMP-activated kinase (AMPK) has also been reported after CR of 20%–40% for four weeks, 40% for eight weeks or progressive CR from 10%–30% over periods of three to seven weeks, respectively.[9,14–16] The latter CR regimen was associated with a reduced acute nociceptive

response in the Hot Plate test. Furthermore, there is evidence that endocannabinoids, effectors of an endogenous neuromodulatory system, are regulated in the nervous system during food restriction. After drastic CR to 20% of normal daily intake in rats or fasting in mice, levels of two endogenous cannabinoids, anandamide (AEA), and 2-arachidonoyl glycerol (2-AG), significantly increased in specific brain regions.[17] In addition, it has been shown that expression of the corresponding receptors, predominantly cannabinoid receptor type 1 (CB1 receptor), is also influenced by dietary conditions.[18] Since activation of AMPK and the endocannabinoid system are involved in reduced nociception,[19,20] it might be suggested that they represent a part of the physiological pathways that are activated upon CR and might, thus, contribute to antinociceptive effects."…

-Pharmazentrum frankfurt/ZAFES, Institut für Klinische Pharmakologie, Klinikum der Goethe-Universität Frankfurt, Frankfurt am Main, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5426584

Fat Cell Life Cycle

"The definition of a healthy fat cell is one that can easily expand to sequester incoming fats, in particular, for long-term storage, and also governs the controlled release of stored fat for ATP production in the peripheral tissues. The ability to sequester circulating fat into the fat cell depends upon the integrity of insulin signaling that brings adequate levels of glucose into the fat cell that can be converted to glycerol. This necessary step is required to convert incoming free fatty acids into triglycerides for long-term storage.

The problem begins to arise when AA levels become too great in a particular fat cell. As an initial defensive mechanism, the generation of new fat cells is induced by metabolites of AA [42, 43]. Although this is associated with greater adiposity [44], the creation of new healthy fat cells maintains the capacity of the adipose tissue to prevent potential lipotoxicity. However, as the AA levels continue to increase in any particular fat cell, the cell's response to insulin signaling becomes compromised due to internal silent inflammation that interrupts the flow of glucose into the fat cell to provide the necessary glycerol for fatty acid storage [45]. It appears this is a consequence of the generation of pro-inflammatory eicosanoids (leukotrienes) that are derived from AA [46, 47]. As a result, the fat cell has a more difficult time sequestering newly formed AA as well as other fatty acids circulating in the blood. At the same time, insulin inhibition of the hormone-sensitive lipase in that particular fat cell becomes compromised because of the same disruption in the insulin-signaling cascade. As a result, more free fatty acids are being released into circulation [48, 49]. These are the hallmarks of classical insulin resistance. It appears that insulin

resistance due to increased AA levels may arise in the fat cell prior to developing in the muscle cells [50, 51]. As a result, greater amounts of AA remain in circulation to be taken up by other cells potentially leading to acceleration of insulin resistance in the muscle cells, which in turn causes increased hyperinsulinemia. To further compound the situation, a compromised fat cell is releasing greater amounts of previously sequestered AA in the fat cells into the circulation [52].

As the levels of AA further increase in any one particular fat cell beyond a critical threshold barrier, cell death can take place [53]. The necrosis of that particular fat cell causes a migration of macrophages into the adipose tissue [54, 55]. This increase in macrophage accumulation in the adipose tissue is clearly seen in both animal models of obesity as well as in humans [56]. These newly recruited macrophages cause the secretion of additional inflammatory mediators, such as IL-1, IL-6 and TNFα, which increase inflammation within the adipose tissue [57–69]. These newly released inflammatory cytokines can interact with their receptors at the surface of nearby fat cells to signal a further activation of NF-κB, the key gene transcription factor that drives the inflammatory responses of the innate immune system. Support for this hypothesis of AA-driven inflammation in the fat cells comes from the observations that the amount of macrophage accumulation can be significantly reduced upon supplementation with high-dose fish oil rich in EPA to reduce the inflammation in the adipose tissue [70–72].

As inflammation in the adipose tissue increases, inflammatory cytokines, such as IL-6 derived from the macrophages attracted to the inflamed fat cells, can exit into the circulatory system to cause an increase in CRP formation in the liver. Hence the correlation between obesity and CRP levels [73]. Likewise TNFα generated by the same macrophages causes further insulin resistance in the surrounding fat cells, thus decreasing their ability to sequester newly formed AA as well as causing the release of even more stored AA into the circulatory system. In many ways, the staging area for insulin resistance in other organs (muscles, liver, and eventually the pancreas) can be considered to start in the adipose tissue. As insulin resistance spreads to other organs, the end result is lipotoxicity in the muscle cells (both smooth muscle and cardiac muscle), liver, and the beta cells in the pancreas.

As long as the adipose tissue is composed of healthy fat cells, any increased production of dietary-induced AA can be safely handled by their continued expansion that can rapidly remove any excess AA from the blood and store it safely in the fat cells. In the absence of a large percentage of healthy fat cells in the adipose tissue, the combination of the growing lack of ability to sequester AA from the blood coupled with the accelerated release of stored AA from the fat mass into the circulation is similar to the metastatic spread of a tumor; only now it is silent inflammation that is spreading. Depositions of lipid droplets that cause lipotoxicity characterize this metastasis of silent inflammation. If these accumulated lipid droplets are also

enriched in AA, then the development of inflammatory diseases, such as type 2 diabetes, will be accelerated.

Understanding the role of healthy fat cells may explain why approximately one-third of obese individuals are actually quite healthy [37]. These individuals appear to have higher levels of the adipose-derived hormone adiponectin [74]. This is confirmed by studies of the overexpression of adiponectin in diabetic animals [75]. It should be noted that adiponectin is an adipose-derived hormone that can be increased by high levels of fish oil rich in EPA possibly acting through the PPARγ transcription factor [76–78].

One of the first indications that lipotoxicity is taking place is the appearance of metabolic syndrome. Metabolic syndrome can be considered to be prediabetes. It is characterized by a combination of clinical markers, such as a high TG/HDL ratio, increasing abdominal fat, and hyperinsulinemia. Recent data indicate that there is a strong correlation between metabolic syndrome and levels of AA in the adipose tissue [50].

Left untreated, metabolic syndrome will usually result in the development of type 2 diabetes within 8–10 years. During this time period, the insulin resistance of the individual is continually increasing. This will cause even more AA formation, especially if consumption of omega-6 fatty acids remains high. Since the fat cells are now compromised in their ability to sequester this increased AA production, the AA levels remain in the blood to be picked up by other organs.

The final development of type 2 diabetes only occurs when the lipotoxicity has metastasized to the pancreas, causing a decreased output of insulin [79]. With insulin secretion decreased, there is a rapid rise of blood sugar levels. The development of type 2 diabetes indicates that the metastasis of silent inflammation from the adipose tissue to the pancreas is now complete.

Ironically, even extreme lipotoxicity can be reversed by the creation of new healthy fat cells. This has been demonstrated in transgenic obese, diabetic mice that over-express adiponectin, an adipocyte-derived hormone that reduces insulin resistance [75]. It is hypothesized that this increased production of adiponectin activates PPARγ, which causes the proliferation of adipose stem cells to produce new healthy adipocytes. These transgenetic obese mice become even more obese, but there is a normalization of blood glucose and lipid levels [75]. This is similar to the elevated levels of adiponectin found in metabolically healthy obese individuals [74]. One mechanism of protection against lipotoxicity might be that the new healthy fat cells in the adipose tissue can now sequester circulating fatty acids (including AA) more effectively to allow the resolution of the inflammatory lipid droplets in the muscle, liver and beta cells of the panaceas. Essentially this resolution process represents a reverse flow of the lipotoxic lipid droplets in other organs back to the adipose tissue and reverses insulin resistance in the muscle

and liver cells as well as decreasing the inflammation in the beta cells of the pancreas.

Support of this hypothesis regarding the impact of AA on fat cell metabolism comes from studies on AA levels in fat cells on various chronic disease conditions. In particular, increased AA levels in the fat cells are significantly associated with increased body fat, development of metabolic syndrome, and incidence of nonfatal heart attacks [44, 50, 80].”

-Inflammation Research Foundation, Marblehead, USA
-Diabetes Research Institute, University of Miami, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952901/

Fatigue

…“Research shows that omega-3 fatty acids reduce inflammation and may help lower risk of chronic diseases such as heart disease, cancer, and arthritis. Omega-3 fatty acids are highly concentrated in the brain and appear to be important for cognitive (brain memory and performance) and behavioral function. In fact, infants who do not get enough omega-3 fatty acids from their mothers during pregnancy are at risk for developing vision and nerve problems. Symptoms of omega-3 fatty acid deficiency include fatigue, poor memory, dry skin, heart problems, mood swings or depression, and poor circulation.”…

-Icahn School of Medicine at Mount Sinai
https://www.mountsinai.org/health-library/supplement/omega-3-fatty-acids

See also Autoimmune Diabetes , Chronic Fatigue Syndrome (CFS) , Lion’s Mane (Hericium erinaceus) , Major Depression

Fatty Acid Amide Hydrolase (FAAH)

…“Anandamide is released in selected regions of the brain and is deactivated through a two-step process consisting of transport into cells followed by intracellular hydrolysis. Pharmacological blockade of the enzyme fatty acid amide hydrolase (FAAH), which is responsible for intracellular anandamide degradation, produces anxiolytic-like effects in rats without causing the wide spectrum of behavioral responses typical of direct-acting cannabinoid agonists. These findings suggest that anandamide contributes to the regulation of emotion and anxiety, and that FAAH might be the target for a novel class of anxiolytic drugs.”

-Department of Psychiatry, University of California, Irvine, CA, USA.
https://www.ncbi.nlm.nih.gov/pubmed/14604824

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”eCBs [endocannabinoids] after their actions are rapidly eliminated by cellular uptake and enzymatic hydrolysis. To this regard, AEA [anandamide] is mainly inactivated by fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996; Dinh et al., 2002), whereas 2-AG [2-arachidonoylglycerol] is predominantly catalyzed by monoacylglycerol lipase (Dinh et al., 2002).”…

-Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy
-Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy
-Laboratory of Virology, The Regina Elena National Cancer Institute, IRCCS, Rome, Italy
-Edited by: Marialessandra Contino, University of Bari Aldo Moro, Italy
-Reviewed by: Luigi Bubacco, University of Padua, Italy; Kevin Donald Broad, UCL Institute for Women's Health, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5288380/

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…“Fatty acid amide hydrolase (FAAH) is an intracellular membrane-bound enzyme that degrades and inactivates members of the fatty acid amide (FAA) family of endogenous signaling lipids, including anandamide (1, Figure 1) and oleamide (2).1,2 Anandamide3 binds and activates the CB1 and CB2 cannabinoid receptors,4 the molecular targets of plant-derived (−)-Δ9-terahydrocannabinol ((−)-Δ9-THC), while oleamide induces physiological sleep5 and modulates serotonergic systems6 and GABAergic transmission.7 “…

-Center for Drug Discovery and Departments of Chemistry and Chemical Biology and Pharmaceutical Sciences, Northeastern University, Boston, MA, USA
-Department of Chemistry and Chemical Biology and Barnett Institute of Chemical and Biological Analysis, Northeastern University, Boston, MA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678964/

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…“The principal enzyme for the degradation of anandamide is fatty acid amide hydrolase (FAAH). FAAH is found in neurons throughout the brain, where its postsynaptic distribution is consistent with the idea that the function of anandamide may be primarily to mediate anterograde or intracellular signaling (Gulyas et al., 2004; Tsou et al., 1998). A surprising finding is that levels of anandamide are not only regulated by FAAH, but are reduced in DAGL-α−/− mice, pointing to a convergence in

endocannabinoid signaling pathways where 2-AG production regulates the levels of anandamide (Gao et al., 2010). Exactly how this is occurs is not known. Convergence of endocannabinoid signaling was also revealed using dual FAAH and MAGL inhibitors and MAGL inhibitors in FAAH−/− mice (Long et al., 2009; Wise et al., 2012). These studies suggest there is significant cross-talk between these ligand systems and the cannabinoid receptors."…

-Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, Alberta, Canada
-Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, California, USA
-Department of Psychology, University of Guelph, Ontario, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883513/

See also Monoacylglycerol Lipase (MAGL or MGL) , Lung Cancer

Fatty Acid Desaturases

Delta-5 (Δ5), Delta-6 (Δ6), Delta-9 (Δ9) - Desaturases

Structure, function, and dietary regulation of delta6, delta5, and delta9 desaturases.

"Fatty acid desaturases introduce a double bond in a specific position of long-chain fatty acids, and are conserved across kingdoms. Degree of unsaturation of fatty acids affects physical properties of membrane phospholipids and stored triglycerides. In addition, metabolites of polyunsaturated fatty acids are used as signaling molecules in many organisms. Three desaturases, Delta9, Delta6, and Delta5, are present in humans. Delta-9 catalyzes synthesis of monounsaturated fatty acids. Oleic acid, a main product of Delta9 desaturase, is the major fatty acid in mammalian adipose triglycerides, and is also used for phospholipid and cholesteryl ester synthesis. Delta-6 and Delta5 desaturases are required for the synthesis of highly unsaturated fatty acids (HUFAs), which are mainly esterified into phospholipids and contribute to maintaining membrane fluidity. While HUFAs may be required for cold tolerance in plants and fish, the primary role of HUFAs in mammals is cell signaling. Arachidonic acid is required as substrates for eicosanoid synthesis, while docosahexaenoic acid is required in visual and neuronal functions. Desaturases in mammals are regulated at the transcriptional level. Reflecting overlapping functions, three desaturases share a common mechanism of a feedback regulation to maintain products in membrane phospholipids. At the same time, regulation of Delta9 desaturase differs

from Delta6 and Delta5 desaturases because its products are incorporated into more diverse lipid groups. Combinations of multiple transcription factors achieve this sophisticated differential regulation."

-Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA.
https://www.ncbi.nlm.nih.gov/pubmed/15189125

A vertebrate fatty acid desaturase with Δ5 and Δ6 activities

"Δ5 and Δ6 fatty acid desaturases are critical enzymes in the pathways for the biosynthesis of the polyunsaturated fatty acids arachidonic, eicosapentaenoic, and docosahexaenoic acids. They are encoded by distinct genes in mammals and Caenorhabditis elegans."

…"Vertebrates lack the Δ12 and Δ15 fatty acid desaturases responsible for converting oleic acid (18:1n-9) into linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3) and thus are unable to biosynthesize polyunsaturated fatty acids (PUFA) de novo [1, 2]. PUFAs therefore are essential dietary nutrients for vertebrates [1, 2]. The physiologically active PUFAs are arachidonic acid (20:4n-6), eicosapentaenoic acid (20:5n-3), and docosahexaenoic acid (22:6n-3) and are required for optimal health and normal development of vertebrates [3–6]. The pathway from 18:2n-6 to arachidonic acid and from 18:3n-3 to eicosapentaenoic acid involves desaturations at the Δ6 and Δ5 positions in the carbon backbone, and an intermediate 2-carbon chain elongation step [7]."

-Institute of Aquaculture, University of Stirling, Stirling, Scotland
https://www.pnas.org/content/98/25/14304

Fatty Acid Desaturases, Polyunsaturated Fatty Acid Regulation, and Biotechnological Advances

"Polyunsaturated fatty acids (PUFAs) are considered to be critical nutrients to regulate human health and development, and numerous fatty acid desaturases play key roles in synthesizing PUFAs. Given the lack of delta-12 and -15 desaturases and the low levels of conversion to PUFAs, humans must consume some omega-3 and omega-6 fatty acids in their diet. Many studies on fatty acid desaturases as well as PUFAs have shown that fatty acid desaturase genes are closely related to different human physiological conditions. Since the first front-end desaturases from cyanobacteria were cloned, numerous desaturase genes have been identified and animals and plants have been genetically engineered to produce PUFAs such as eicosapentaenoic acid and docosahexaenoic acid. Recently, a biotechnological approach has been used to develop clinical treatments for human physiological conditions, including cancers and neurogenetic disorders. Thus, understanding the functions and regulation of PUFAs associated with human health and

development by using biotechnology may facilitate the engineering of more advanced PUFA production and provide new insights into the complexity of fatty acid metabolism."…

"Polyunsaturated fatty acids (PUFAs) consist of more than two double bonds and are a group of critical nutrients that modulate brain development and cognition as well as many diseases such as cardiovascular disease, cancers, and diabetes [1,2]. Twenty-carbon PUFAs are precursors of eicosanoids that regulate inflammatory and immune responses through pro- and anti-inflammatory activities; docosahexaenoic acid (DHA, 22:6n-3) is a precursor of anti-inflammatory docosanoids [3,4]. In humans, PUFAs are synthesized by fatty acid desaturases (FADSs), which are encoded by three genes on the human chromosome 11 [5] and are regulated by PUFA consumption after ingestion of linoleic acid (LA, 18:2n-6) and α-linolenic acid (ALA, 18:3n-3), which are dietary essential fatty acids in humans. However, only a small proportion of fatty acids is converted to PUFAs consisting of more than 20 carbons [6]."….

-Department of Horticultural Science, Kyungpook National University, Korea;
-Department of Food Engineering, Dankook University, Cheonan, Chungnam 31116, Korea;
-Citrus Research Station, National Institute of Horticultural & Herbal Science, RDA, Seogwipo 63607, Korea;
-Department of Marine Food Science and Technology, Gangneung-Wonju National University, Gangneung, Gangwon 25457, Korea
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728637/

What Is Delta-6 Desaturase and What Is Its Significance?

"Delta-6 desaturase is the main enzyme that both omega-6 and omega-3 fatty acids use in the cascade of events that leads to the production of prostaglandins and leukotrienes (see Fig. 88-3). Certain situations influence this enzyme to catalyze reactions along the omega-6 pathway, resulting in larger numbers of inflammatory mediators.[17] This shift can be caused by excessive alcohol consumption, diabetes, stress, and a high ratio of omega-6 to omega-3 fatty acids. This finding may help explain why these conditions are associated with a high risk for inflammatory complications."

-Dr. David Rakel MD,
-Dr J. Adam Rindfleisch MD
-Integrative Medicine (Second Edition), 2007
https://www.sciencedirect.com/topics/medicine-and-dentistry/linoleoyl-coenzyme-a-desaturase

Loss of delta-6-desaturase activity as a key factor in aging

"Aging is characterized by a wide variety of defects, particularly in the cardiovascular and immune systems. Cyclic AMP levels fall, especially in lymphocytes. Delta-6-desaturase (D6D)

levels have been found to fall rapidly in the testes and more slowly in the liver in aging rats. D6D is an enzyme which converts cis-linoleic acid to gamma-linolenic acid (GLA). **Other factors which inhibit D6D activity are diabetes, alcohol and radiation, all of which may be associated with accelerated aging**. In meat eaters or omnivores which can acquire arachidonic acid from food, the main consequences of D6D loss will be deficiencies of GLA, dihomogamma-linolenic acid (DGLA) and prostaglandin (PG) E1. PGE1 activates T lymphocytes, inhibits smooth muscle proliferation and thrombosis, is important in gonadal function and raises cyclic AMP levels in many tissues. It is a good candidate for a key factor lost in aging. Moderate food restriction, the only manoeuvre which consistently slows aging in homoiotherms, raises D6D activity by 300%. Other factors important in regulating D6D and the conversion of GLA to PGE1 are zinc, pyridoxine, ascorbic acid, the pineal hormone, melatonin, and possibly vitamin B3. GLA administration to humans has been found to lower blood pressure and cholesterol, and to cause clinical improvement in patients with Sjogren's syndrome, scleroderma and alcoholism. These diseases are associated with some features of accelerated aging. The proposition that D6D loss is not only a marker of aging but a cause of some of its major manifestations is amenable to experimental test even in humans. The blocked enzyme can be by-passed by giving GLA directly."

-Medical Hypotheses
-D. F. Horrobin
https://pubmed.ncbi.nlm.nih.gov/6270521/

A defect in the activity of Delta6 and Delta5 desaturases may be a factor in the initiation and progression of atherosclerosis

"Atherosclerosis is a dynamic process. Dyslipidemia, diabetes mellitus, hypertension, obesity, and shear stress of blood flow, the risk factors for the development of atherosclerosis, are characterized by abnormalities in the metabolism of essential fatty acids (EFAs). Gene expression profiling studies revealed that at the sites of atheroslcerosis-prone regions, endothelial cells showed upregulation of pro-inflammatory genes as well as antioxidant genes, and endothelial cells themselves showed changes in cell shape and proliferation. Uncoupled respiration (UCP-1) precedes atherosclerosis at lesion-prone sites but not at the sites that are resistant to atherosclerosis. UCP-1 expression in aortic smooth muscle cells causes hypertension, enhanced superoxide anion production and decreased the availability of NO, suggesting that inefficient metabolism in blood vessels causes atherosclerosis without affecting cholesterol levels. Thus, mitochondrial dysfunction triggers atherosclerosis. Atherosclerosis-free aortae have abundant concentrations of the EFA-linoleate, whereas fatty streaks (an early stage of atherosclerosis) are deficient in EFAs. EFA deficiency promotes respiratory uncoupling and atherosclerosis. I propose

that a defect in the activity of Delta6 and Delta5 desaturases decreases the formation of gamma-linolenic acid (GLA), dihomo-DGLA (DGLA), arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) from dietary linoleic acid (LA) and alpha-linolenic acid (ALA). This, in turn, leads to inadequate formation of prostaglandin E1 (PGE1), prostacyclin (PGI2), PGI3, lipoxins (LXs), resolvins, neuroprotectin D1 (NPD1), NO, and nitrolipids that have anti-inflammatory and platelet anti-aggregatory actions, inhibit leukocyte activation and augment wound healing and resolve inflammation and thus, lead to the initiation and progression atheroslcerosis. In view of this, it is suggested that Delta6 and Delta5 desaturases could serve as biological target(s) for the discovery and development of pharmaceuticals to treat atherosclerosis."

-Undurti N Das
https://pubmed.ncbi.nlm.nih.gov/17466497

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…"Linoleic acid conversion to ARA [arachidonic acid (AA) / omega-6] is, however, low. Linoleic acid is readily oxidized by delta 6-desaturase to γ-linolenic acid (18:3-n6), but several factors such as aging, nutrition, smoking impair the activity of the enzyme."…

-Zoology Department, Faculty of Science, Cairo University, Giza 12613, Egypt
-Department of Chemistry, School of Science and Engineering, American University in Cairo, New Cairo 11835, Cairo, Egypt
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6052655

Fear

The endocannabinoid system in guarding against fear, anxiety and stress

"The endocannabinoid (eCB) system has emerged as a central integrator linking the perception of external and internal stimuli to distinct neurophysiological and behavioural outcomes (such as fear reaction, anxiety and stress-coping), thus allowing an organism to adapt to its changing environment. eCB signalling seems to determine the value of fear-evoking stimuli and to tune appropriate behavioural responses, which are essential for the organism's long-term viability, homeostasis and stress resilience; and dysregulation of eCB signalling can lead to psychiatric disorders. An understanding of the underlying neural cell populations and cellular processes enables the development of therapeutic strategies to mitigate behavioural maladaptation."

-Institute of Physiological Chemistry, University Medical Center Mainz, Duesbergweg 6, Mainz, Germany
-Institut national de la santé et de la recherche médicale (INSERM)

-U862 NeuroCentre Magendie, Group Endocannabinoids and Neuroadaptation, Bordeaux, France

-University of Bordeaux, 146 rue Léo Saignat, Bordeaux, France

-Laboratori de Neurofarmacologia, Facultat de Ciències de la Salut i de la Vida, Universitat Pompeu Fabra, Dr. Aiguader 88, Barcelona, Spain

-Department of Pharmacology and Toxicology, Neuroscience Research Center, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5871913/

Cannabinoid CB1 receptor deficiency increases contextual fear memory under highly aversive conditions and long-term potentiation in vivo.

"The cannabinoid receptor type 1 (CB1) is abundantly expressed in the central nervous system where it negatively controls the release of several neurotransmitters. CB1 activity plays a crucial role in learning and memory and in synaptic plasticity."

...."In conclusion, CB1 deficiency leads to enhanced contextual fear memory and altered synaptic plasticity in the hippocampus, supporting the key role of endocannabinoid signalling in learning and memory, in particular following highly aversive encounters."

Max Planck Institute of Psychiatry, Kraepelinstrasse 2, Munich, Germany.

https://www.ncbi.nlm.nih.gov/pubmed/22579951

Female Reproductive System

Updates in Reproduction Coming from the Endocannabinoid System

..."Moreover, wild-type mice treated with methanandamide, a CB1 agonist, also exhibit a similar phenomenon, collectively suggesting that a tonic endocannabinoid signaling is essential for normal embryo transport from the oviduct into the uterus prior to blastocyst implantation. The endogenous levels of AEA, one of the primary endocannabinoid, are maintained by its synthesis and degradation activity. In this respect, FAAH −/− mice exhibit an elevated level of AEA in the oviduct during early pregnancy, accompanied with a derailed oviductal embryo transport [133]. **Thus, an aberrant cannabinoid signaling impairs the oviductal transport of embryos, preventing on-time implantation** [132, 133]. **This finding is clinically relevant to human ectopic pregnancy, since high AEA levels and aberrant expression of FAAH and CB1 in fallopian tubes have been observed in women with ectopic pregnancy** [130, 134, 135]. Synchronized embryo development to blastocyst and uterine differentiation to receptive state are important for successful implantation. In the

mouse, at pregnant day 1 to day 4 (day 1 = vaginal plug), the ovarian hormones estrogen and progesterone control the uterine undergoing from prereceptive to receptive stage. **In this respect, lower levels of AEA in the receptive uterus and at the implantation site have been observed in contrast to its high levels in the nonreceptive uterus** [13, 131]. Moreover, the CB1 expression in activated blastocyst is significantly lower than that in dormant blastocysts [12, 131]. These observations suggest a biphasic role of endocannabinoid signaling in synchronizing trophoblast differentiation and uterine preparation to the receptive state for implantation. Also in female rats, ovarian hormones operate in conjunction with the blastocyst intrinsic programme, in order to regulate the synthesis of AEA in a specific manner during the crucial reproductive events that may compromise pregnancy outcome [136]. However, the interaction between lysophosphatidic acid, prostaglandins, and ECS during the window of implantation in the rat uterus has also been reported [137]."...

-Dipartimento di Scienze Motorie e del Benessere, Università di Napoli Parthenope, via Medina 40, Napoli, Italy
-Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Teramo, Italy
-European Center for Brain Research (CERC), Santa Lucia Foundation, Rome, Italy
-Department of Psychological and Brain Sciences, The Kinsey Institute for Research in Sex, Gender, and Reproduction, Indiana University, Bloomington, IN, USA
-State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3914453/

The role of the endocannabinoid system in female reproductive tissues

"There has been increasing interest in the role of endocannabinoids as critical modulators of the female reproductive processes. Endocannabinoids are natural ligands of cannabinoid, vanilloid, and peroxisome proliferator-activated receptors. Together with their receptors, enzymes and downstream signaling targets, they form the endocannabinoid system (ECS). While the ECS is known to modulate pain and neurodevelopment, it is also known to impact the female reproductive system where it affects folliculogenesis, oocyte maturation, and ovarian endocrine secretion. In addition, the ECS affects oviductal embryo transport, implantation, uterine decidualization and placentation. There is a complex interplay between the ECS and the hypothalamic-pituitary-ovarian axis, and an intricate crosstalk between the ECS and steroid hormone production and secretion. Exogenous cannabinoids, derived from plants such as Cannabis sativa, are also ligands for cannabinoid receptors. These have been shown to have clinical outcomes related to ECS dysregulation, including multiple sclerosis, Alzheimer's disease, and amyotrophic lateral sclerosis, along with adverse effects on female reproduction. The aim of this review is to describe and discuss data from human, animal, and in vitro studies that support

the important role of the endocannabinoid system in female reproductive tissues and processes. In particular, we will discuss some of the mechanisms by which endocannabinoid signaling can affect ovarian function in both physiological and pathophysiological states."

…"The data available to date suggests that the ECS is intimately involved in the central and local control of female reproductive events. Perturbations by exogenous cannabinoids in cannabis may disrupt the homeostatic mechanisms of the ECS in female reproductive processes [37] and lead to infertility through dysregulation of ovarian function. The current evidence delineates the presence of ligands, receptors and metabolic enzymes for the synthesis and degradation of endocannabinoids in the female reproductive tract and presents a complex clinical picture. Given the high prevalence of cannabis use in youth [72], combined with the increasing number of municipalities that are legalizing this plant and its extracts for medical and recreational use, it is critical that we more clearly elucidate its impact on the female reproductive process."

Department of Pediatrics, and the Graduate Program in Medical Sciences, McMaster University, 1280 Main Street West, Hamilton, Canada

https://www.biomedcentral.com/epdf/10.1186/s13048-018-0478-9

Fever

(Pyrexia, pyrogenic)

Also covers thermoregulation

Fever associated with inflammation

"Its stimulation leads to increased synthesis of prostanoids including prostaglandin (PG)E2, which acts in the pre-optic nucleus of the hypothalamus slowing the firing rate of the warm sensitive neurons and resulting in an increase in body temperature. The bioactive lipid derivative, ceramide, which has a proapoptotic as well as a cell signalling role, may act as a second messenger independent of PGE2, and may be of particular importance in the early stages of fever generation [7]. Lipopolysaccharides (LPS) from gram-negative bacteria may stimulate peripheral production of PGE2 from hepatic Kupffer cells [8, 9]. LPS-stimulated fever may also be neurally mediated [10]. Neural pathways may account for the rapid onset of fever, with cytokine production responsible for the maintenance, rather than the initiation, of fever [11]. Fever generation is also thought to occur by signalling via the Toll-like receptor cascade, which may be independent of the cytokine cascade [12] (Fig. 1)."…

"In critically ill patients, inflammation is commonly observed to aid repair after traumatic or

infective insults. The four cardinal features of pain, heat, redness, and swelling were originally described by Celsus around 2000 years ago and, at about the same time, Hippocrates noted that the fever was of benefit. Fever is a ubiquitous component of inflammation across the animal kingdom, and enhances the host response. A large number of both the cell-derived and plasma-derived inflammatory mediators are pyrogenic; fever associated with inflammation is probably mediated in a similar way to sepsis as described above. Chronic inflammation is deleterious; the recently described compensatory anti-inflammatory response syndrome (CARS) restores homeostasis, and it is likely that the magnitude and relative timings of the inflammatory and anti-inflammatory responses are both important in determining the host outcome."

-Department of Intensive Care Medicine, Royal Surrey County Hospital, Egerton Road, Guildford, Surrey GU2 7XX UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944485

Neural Mechanisms of Inflammation-Induced Fever

"Fever is a common symptom of infectious and inflammatory disease. It is well-established that prostaglandin E2 is the final mediator of fever, which by binding to its EP3 receptor subtype in the preoptic hypothalamus initiates thermogenesis. Here, we review the different hypotheses on how the presence of peripherally released pyrogenic substances can be signaled to the brain to elicit fever. We conclude that there is unequivocal evidence for a humoral signaling pathway by which proinflammatory cytokines, through their binding to receptors on brain endothelial cells, evoke fever by eliciting prostaglandin E2 synthesis in these cells. The evidence for a role for other signaling routes for fever, such as signaling via circumventricular organs and peripheral nerves, as well as transfer into the brain of peripherally synthesized prostaglandin E2 are yet far from conclusive. We also review the efferent limb of the pyrogenic pathways. We conclude that it is well established that prostaglandin E2 binding in the preoptic hypothalamus produces fever by disinhibition of presympathetic neurons in the brain stem, but there is yet little understanding of the mechanisms by which factors such as nutritional status and ambient temperature shape the response to the peripheral immune challenge."…

Introduction

"A little more than 20 years ago, Clifford Saper and Christopher Breder summarized in an authoritative review in The New England Journal of Medicine what was known at that time about "The Neurological Basis of Fever" (Saper and Breder 1994). While the critical role of peripherally released cytokines for the febrile response was recognized, it was not clear how these substances could signal to the brain since they could not pass the blood-brain barrier. And although it also was known that prostaglandins were involved in the elaboration of fever, it was not clear where and by which cells the fever-inducing prostaglandins were produced. Furthermore, although it was

known that the elevated body temperature was generated by increased energy production and diminished energy loss (by peripheral vasoconstriction), little was known about central neural circuits involved. In this review, we will address our current knowledge of these issues and also point out outstanding questions that deserve further investigation.

Fever is a hallmark of infectious and inflammatory diseases. It is generated by the concerted action of various autonomic responses, such as peripheral vasoconstriction and decreased sweating, reducing heat loss, and shivering, and possibly also non-shivering, thermogenesis. Fever is considered beneficial because an elevated body temperature enhances the activity of the immune cells while at the same time it impairs the replication of many microorganisms (Evans and others 2015; Kluger 1991), although controlled clinical studies of the benefit of fever are lacking (Harden and others 2015). The elevation of the body temperature on immune challenge is a stereotypic response seen in all vertebrates, including poikilotherms, which have been shown to prefer a warmer environment when they have an infection (Boltana and others 2013).

It was demonstrated already at the end of the 19th century that fever required the involvement of the brain (see Atkins 1982). The American pathologist/bacteriologist William H. Welch showed that animals with cervical spinal cord transection did not respond with fever when given an intravenous (i.v.) injection of a pyrogen. It was also understood at that time that the inflammatory process resulted in the release of substances that produced the fever. However, it remained for long unclear how these substances, later named endogenous pyrogens and subsequently identified as cytokines (Dinarello 2015), could influence the brain, since the brain was protected by the blood-brain barrier, described early in the 20th century (Goldman 1913). Nevertheless, injection of endogenous pyrogens into the carotid artery was demonstrated to result in a rapid and strong febrile response, suggesting a direct action on the thermoregulatory center in the brain (King and Wood 1958), and this idea was further supported by the finding that when injected directly into the brain, endogenous pyrogens elicited fever when administered into the anterior hypothalamus/preoptic region, but not when injected into other brain areas (Cooper and others 1967). Based on subsequent observations that prostaglandins of the E-series, when injected into the cerebral ventricles, elicited fever (Milton and Wendlandt 1970), it was further suggested that the endogenous pyrogens acted by releasing prostaglandins (Feldberg and Saxena 1971), an idea that was reinforced by the demonstration that antipyretic drugs like aspirin exerted their mode of action by prostaglandin inhibition (Vane 1971).”

- *Department of Clinical and Experimental Medicine, Faculty of Medicine and Health, Linköping University, Linköping, Sweden.*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6047205/

Endocannabinoid catabolic enzymes play differential roles in thermal homeostasis in response to environmental or immune challenge

"Cannabinoid receptor agonists, such as Δ9-THC, the primary active constituent of Cannabis sativa, have anti-pyrogenic effects in a variety of assays. Recently, attention has turned to the endogenous cannabinoid system and how endocannabinoids, including 2-arachidonoyglycerol (2-AG) and anandamide, regulate multiple homeostatic processes, including thermoregulation. Inhibiting endocannabinoid catabolic enzymes, monoacylglycerol lipase (MAGL) or fatty acid amide hydrolase (FAAH), elevates levels of 2-AG or anandamide in vivo, respectively. The purpose of this experiment was to test the hypothesis that endocannabinoid catabolic enzymes function to maintain thermal homeostasis in response to hypothermic challenge."…

"These data indicate that unlike direct acting cannabinoid receptor agonists, which elicit profound hypothermic responses on their own, neither MAGL nor FAAH inhibitors affect normal body temperature. However, these endocannabinoid catabolic enzymes play distinct roles in thermoregulation following hypothermic challenges."…

- Department of Psychology, West Virginia University, Morgantown WV, USA
- The Skaggs Institute for Chemical Biology and Dept. of Chemical Physiology, The Scripps Research Institute, USA
- Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4477849

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"Anandamide (arachidonylethanolamide), an arachidonic acid derivative isolated from the porcine brain, displays binding characteristics indicative of an endogenous ligand for the cannabinoid receptor. The functional activity of anandamide was tested in vivo using behavioral and physiological paradigms in laboratory rodents. At IP doses from 2 to 20 mg/kg in mice, anandamide significantly decreased spontaneous motor activity in a Digiscan open field. Rectal body temperature significantly decreased at doses of 10 and 20 mg/kg in rats. "…

"These results demonstrate that anandamide has biological and behavioral effects in awake rodents, some of which are similar to the reported actions of THC."

-Section on Behavioral Neuropharmacology, National Institute of Mental Health, Bethesda, MD, USA
http://www.ncbi.nlm.nih.gov/pubmed/7906042

Fibrocystic Breast Disease

Metabolic Response to Omega-3 Fatty Acids and Vitamin E Co-Supplementation in Patients with Fibrocystic Breast Disease: A Randomized, Double-Blind, Placebo-Controlled Trial

"Background: There is scarce data on the effects of omega-3 fatty acids and vitamin E co-supplementation on metabolic status in patients with fibrocystic breast disease (FBD). The current study was carried out to determine the effects of omega-3 fatty acids and vitamin E co-supplementation on metabolic status in patients with FBD."…

"Conclusion: Overall, omega-3 fatty acids and vitamin E co-supplementation for 12 weeks had beneficial effects on inflammatory markers and metabolic profiles in patients with FBD."

-Clinical Biochemistry and Genetics Department, School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran.

-Department of Clinical Biochemistry, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

-Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran.

-Surgery Department, Kashan University of Medical Sciences, Kashan, I.R. Iran.

-Department of Gynecology and Obstetrics, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran.

https://pubmed.ncbi.nlm.nih.gov/28846009/

■■■

…"Our results support a protective effects of n–3 fatty acid intake and the n–7 saturation index against benign fibrocystic breast changes and the progression of proliferative changes to breast cancer."…

-From the Center for Research on Occupational and Environmental Toxicology, Oregon Health and Science University, Portland, OR (JS);

-Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (IBK, JWL, RMR, M-GL, and DBT);

-the Department of Epidemiology, Zhong Shan Hospital Cancer Center, Shanghai, China (DLG);

-the Institute of Medical Biology, University of Tromsø, Tromsø, Norway (HS).

-Supported by grant R01-CA 75332 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2647713/

Fibromyalgia

"Cannabinoid receptors have been localized in the central and peripheral nervous system as well as on cells of the immune system, but recent studies on animal tissue gave evidence for the presence of cannabinoid receptors in different types of tissues. Their presence was supposed also in myofascial tissue, suggesting that the endocannabinoid system may help resolve myofascial trigger points and relieve symptoms of fibromyalgia."

…"Indeed the endocannabinoid receptors of fascial fibroblasts can contribute to modulate the fascial fibrosis and inflammation."

-Department of Molecular Medicine, University of Padua, Italy
-Department of Surgery, Oncology and Gastroenterology, Orthopedic Clinic, University of Padua, Italy
-Section of Anatomy, Department of Molecular Medicine, University of Padua, Padova, Italy.
https://pubmed.ncbi.nlm.nih.gov/27349320/

See also Irritable Bowel Syndrome (IBS) , Pain & Inflammation

Fluoride

Fluoride competes with iodine, because they are structurally similar. The higher the intake of fluoride the more likely it is to cause iodine deficiency.

…"Fluorine is an abundant element and is toxic to organisms from bacteria to humans, but the mechanisms by which eukaryotes resist fluoride toxicity are unknown."…

-Molecular, Cellular and Developmental Biology, Chemistry, and
Molecular Biophysics and Biochemistry and Howard Hughes Medical Institute, Yale University, New Haven
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3839697

Fluoride as a factor initiating and potentiating inflammation in THP1 differentiated monocytes/macrophages

"It is well known that exposure to fluorides lead to an increased ROS production and enhances the inflammatory reactions. Therefore we decided to examine whether cyclooxygenases (particular COX-2) activity and expression may be changed by fluoride in THP1 macrophages and in this way may change the prostanoids biosynthesis. In the present work we demonstrate that fluoride increased concentration of PGE2 and TXA2 in THP1 macrophages. Following exposure to

1-10 µM NaF, COX-2 protein and COX-2 transcript increased markedly. COX-2 protein up-regulation probably is mediated by ROS, produced during fluoride-induced inflammatory reactions. Additional fluoride activates the transcription factor, nuclear factor (NF)-kappaB, which is involved in the up-regulation of COX-2 gene expression. This study indicated that even in small concentrations fluoride changes the amounts and activity of COX-1 and COX-2 enzymes taking part in the initiating and development of inflammatory process."

-Department of Biochemistry and Human Nutrition, Pomeranian Medical University, Poland.
-Department of Biochemistry, Pomeranian Medical University, Poland.
-Department of Histology and Embryology, Pomeranian Medical University, Poland.
https://pubmed.ncbi.nlm.nih.gov/26119525/

Fluoride exposure in utero linked to lower IQ in kids, study says

"Increased levels of prenatal fluoride exposure may be associated with lower cognitive function in children, a new study says.

The study, published Tuesday in the journal Environmental Health Perspectives, evaluated nearly 300 sets of mothers and children in Mexico and tested the children twice for cognitive development over the course of 12 years. Fluoride is not added to public water supplies in Mexico, but people are exposed through naturally occurring fluoride in water and fluoridated salt and supplements.

The study found a drop in scores on intelligence tests for every 0.5 milligram-per-liter increase in fluoride exposure beyond 0.8 milligrams per liter found in urine. However, although the researchers found a potential connection to a child's exposure to fluoride in utero, they found no significant influence from fluoride exposure on brain development once a child was born.Fluoride is not added to public water supplies in Mexico, but people are exposed through naturally occurring fluoride in water and fluoridated salt and supplements."…

https://www.cnn.com/2017/09/19/health/fluoride-iq-neurotoxin-study/index.html *(September 21, 2017)*

Fluoride Exposure Induces Inhibition of Sodium/Iodide Symporter (NIS) Contributing to Impaired Iodine Absorption and Iodine Deficiency: Molecular Mechanisms of Inhibition and Implications for Public Health

…"While it is acknowledged that iodine deficiency increases the risk of fluoride (F) induced toxicity on thyroid function [9], it has also been reported that dietary iodine absorption and incorporation is reduced by F [10,11,12,13,14,15,16]. Indeed, in 2002, the Scientific Committee on Food,

the main committee providing the European Commission with scientific advice on food safety, reported that dietary iodine absorption and incorporation is reduced by F in food and water [11]. Yang et al. observed that thyroid iodine uptake was markedly reduced in children when urinary F levels were approximately 2.0 mg/L. In this study, higher F exposure was also associated with dental fluorosis, higher serum TSH and lower IQ than age matched controls from a low F area [15]. Susheela et al. reported that elevated F uptake may cause iodine deficiency in fluorotic individuals, even when they reside in non-iodine deficient areas [12]. More recently, Sarkar and Pal suggested that F intoxication may contribute to iodine deficiency by inhibition of absorption of the iodine in humans as well as contributing to decreased retention of iodine through the interaction of F. [13]. A recent cross-sectional study conducted in Canada, which utilized weighted population-based data from Cycle 3 (2012–2013) of the Canadian Health Measure Survey (CHMS), found that UIC's were lower in fluoridated than non-fluoridated communities. Moreover, iodine deficient individuals were found to have higher urinary F concentrations compared with the non-iodine deficient group [14]. This finding is supported by epidemiological data from China [17], which found that higher urinary F excretion was associated with significantly lower UIC in children. Further studies conducted in China, also found that excessive F exposure inhibited thyroid iodine uptake in children [10]. Similar effects were observed in a Russian study examining the effects of occupation exposure to F among subjects with signs of chronic fluorosis [18]. Consistent with these findings, a recent all Ireland study which measured iodine status in adolescent girls throughout the island of Ireland; which includes the Republic of Ireland (RoI) and Northern Ireland (NI), found that median UIC's were significantly lower in adolescent girls in all participating locations in the RoI compared to NI. In addition, the percentage of adolescent girls with moderate to severe iodine deficiency (<50 µg/L) were 2–4-fold higher in the RoI compared to NI [19]. In examining this data, it is of fundamental importance to understand that approximately 84% of all households in the RoI have fluoridated water supplies [20], while drinking water is non-fluoridated in NI. Thus, the population in the RoI have higher exposure to F than NI. Therefore, this data validates the findings of the aforementioned studies suggesting that F exposure directly affects the bioavailability of iodine in humans."…

-EnviroManagement Services,, Ireland;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6466022

Damaged Reproduction: The Most Important Consequence of Iodine Deficiency

"The term "iodine deficiency disorders" serves to emphasize the many other consequences of iodine deficiency [3]. Of these, damage to reproductive function and to the developing fetus and

infant is the most severe and is the focus of this commentary. Aspects of this topic have been reviewed in detail elsewhere [4–6], and Smallridge et al. [7] discuss the related issue of hypothyroidism in pregnancy in this issue of the journal."

-The Journal of Clinical Endocrinology & Metabolism, Volume 86, Issue 6, 1 June 2001,
https://academic.oup.com/jcem/article/86/6/2360/2848412

Food

Endocannabinoid signal in the gut controls dietary fat intake.

…"The endocannabinoid system has gained recent attention for its central and peripheral roles in regulating food intake, energy balance, and reward."
…"Collectively, the results suggest that the endocannabinoid system in the gut exerts a powerful regulatory control over fat intake and might be a target for antiobesity drugs."

Department of Pharmacology, University of California, Irvine, School of Medicine
http://www.ncbi.nlm.nih.gov/pubmed/21730161

Understanding metabolic homeostasis and imbalance: what is the role of the endocannabinoid system?

"Endogenous endocannabinoids (ECs) (anandamide and 2-arachidonoyl glycerol) are part of the leptin-regulated neural circuitry involved in appetite regulation."…

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health
http://www.ncbi.nlm.nih.gov/pubmed/17720356

A number of studies like the one above, suggest blocking Cannabinoid Receptor 1 (CB1) activity, however Endocannabinoid Overactivity has been linked to inflammation. Blocking CB1 receptors has been shown to cause many issues as seen with the now recalled medication known as rimonabant. Resolving the inflammation with proper diet, by avoiding inflammatory foods, and correcting Omega Ratio should be considered.

Chocolate: food or drug?

…"Chocolate contains several biologically active constituents (methylxanthines, biogenic amines, and cannabinoid like fatty acids), all of which potentially cause abnormal behaviors and psychological sensations that parallel those of other addictive substances. Most likely, a

combination of chocolate's sensory characteristics, nutrient composition, and psychoactive ingredients, compounded with monthly hormonal fluctuations and mood swings among women, will ultimately form the model of chocolate cravings. Dietetics professionals must be aware that chocolate cravings are real. The psychopharmacologic and chemosensory effects of chocolate must be considered when formulating recommendations for overall healthful eating and for treatment of nutritionally related health issues."

Arizona Prevention Center, University of Arizona, College of Medicine
http://www.ncbi.nlm.nih.gov/pubmed/10524390

Dietary conditions and highly palatable food access alter rat cannabinoid receptor expression and binding density.

"Endogenous cannabinoid signaling, mediated predominantly by CB1 [cannabinoid type 1] receptor activation, is involved in food intake control and body weight regulation."...

-Department of Animal Sciences, Rutgers, The State University of New Jersey, New Brunswick, USA
http://www.ncbi.nlm.nih.gov/pubmed/22005165

Truffles contain endocannabinoid metabolic enzymes and anandamide.

..."Overall, our unprecedented results suggest that anandamide and ECS metabolic enzymes have evolved earlier than endocannabinoid-binding receptors, and that anandamide might be an ancient attractant to truffle eaters, that are well-equipped with endocannabinoid-binding receptors."

-Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy.
-Faculty of Veterinary Medicine, University of Teramo, Teramo, Italy; StemTeCh Group, Chieti, Italy
-Faculty of Veterinary Medicine, University of Teramo, Teramo, Italy.
-Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Teramo, Italy; European Center for Brain Research/IRCCS Santa Lucia Foundation, Rome, Italy.
-Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Teramo, Italy.
-European Center for Brain Research/IRCCS Santa Lucia Foundation, Rome, Italy; Center of Integrated Research, Campus Bio-Medico University of Rome, Rome, Italy.
http://www.ncbi.nlm.nih.gov/pubmed/25433633.

The endocannabinoid system and appetite: relevance for food reward.

"Mounting evidence substantiates the central role of the endocannabinoid system (ECS) in the modulation of both homeostatic and hedonic elements of appetite and food intake. Conversely,

feeding status and dietary patterns directly influence activity of the ECS. Following a general introduction on the functioning of the ECS, the present review specifically addresses its role in the modulation of hedonic eating. Humans possess strong motivational systems triggered by rewarding aspects of food. Food reward is comprised of two components: one appetitive (orienting towards food); the other consummatory (hedonic evaluation), also referred to as 'wanting' and 'liking', respectively. Endocannabinoid tone seems to influence both the motivation to feed and the hedonic value of foods, probably by modifying palatability. Human physiology underlying hedonic eating is still not fully understood. A better understanding of the role of the ECS in the rewarding value of specific foods or diets could offer new possibilities to optimise the balance between energy and nutrient intake for different target groups. These groups include the obese and overweight, and potentially individuals suffering from malnutrition. Examples for the latter group are patients with disease-related anorexia, as well as the growing population of frail elderly suffering from persistent loss of food enjoyment and appetite resulting in malnutrition and involuntary weight loss. It has become clear that the psychobiology of food hedonics is extremely complex and the clinical failure of CB1 inverse agonists including rimonabant (Accomplia®) has shown that 'quick wins' in this field are unlikely."

Division of Human Nutrition, Wageningen University, The Netherlands
http://www.ncbi.nlm.nih.gov/pubmed/24933167

Is fat taste ready for primetime?

"Mounting evidence suggests that gustation is important for the orosensory detection of dietary fats, and might contribute to preferences that humans, rodents, and possibly other mammals exhibit for fat-rich foods. In contrast to sweet, sour, salty, bitter, and umami, fat is not widely recognized as a primary taste quality. Recent investigations, however, provide a wealth of information that is helping to elucidate the specific molecular, cellular, and neural mechanisms required for fat detection in mammals. The latest evidence supporting a fat taste will be explored in this review, with a particular focus on recent studies that suggest a surprising role for gut-brain endocannabinoid signaling in controlling intake and preference for fats based on their proposed taste properties."

Department of Anatomy and Neurobiology, University of California, Irvine, School of Medicine, USA
http://www.ncbi.nlm.nih.gov/pubmed/24631296

The role of the endocannabinoid system in eating disorders: neurochemical and behavioural preclinical evidence.

"The endocannabinoid system has long been known as a modulator of several physiological functions, among which the homeostatic and hedonic aspects of eating. CB1 receptors are widely expressed in brain regions that control food intake, reward and energy balance. Animal and human studies indicate that CB1 receptor agonists possess orexigenic effects enhancing appetite and increasing the rewarding value of food. Conversely, CB1 antagonists have been shown to inhibit the intake of food. Eating disorders include a range of chronic and disabling related pathological illnesses that are characterized by aberrant patterns of feeding behaviour and weight regulation, and by abnormal attitudes and perceptions toward body shape image. The psychological and biological factors underlying eating disorders are complex and not yet completely understood. However in the last decades, converging evidence have led to hypothesise a link between defects in the endocannabinoid system and eating disorders, including obesity. Here we review the neurochemical and behavioural preclinical evidence supporting the role of the endocannabinoid system in eating disorders to offer the reader an update regarding the state of the art. Despite the recent withdrawal from the market of rimonabant for treating obesity and overweight individuals with metabolic complications due to its psychiatric side effects, preclinical findings support the rationale for the clinical development of drug which modulate the endocannabinoid system in the treatment of eating disorders."

Department of Biomedical Sciences, Division of Neuroscience and Clinical Pharmacology, University of Cagliari, Italy
http://www.ncbi.nlm.nih.gov/pubmed/23829365

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…"Identification of an endocannabinoid hotspot for sensory pleasure gives insight into brain mechanisms of natural reward, and may be relevant to understanding the neural effects of cannabinoid drugs of abuse and therapeutic agents."

Department of Psychology, The University of Michigan
https://www.ncbi.nlm.nih.gov/pubmed/17406653

Fragile X Syndrome

"Fragile X syndrome (FXS) is an X-linked dominant disorder caused by a mutation in the fragile X mental retardation 1 gene. Cannabidiol (CBD) is an exogenous phytocannabinoid with therapeutic potential for individuals with anxiety, poor sleep, and cognitive deficits, as well as

populations with endocannabinoid deficiencies, such as those who suffer from FXS. The objective of this study was to provide a brief narrative review of recent literature on endocannabinoids and FXS and to present a case series describing three patients with FXS who were treated with oral CBD-enriched (CBD+) solutions. We review recent animal and human studies of endocannabinoids in FXS and present the cases of one child and two adults with FXS who were treated with various oral botanical CBD+ solutions delivering doses of 32.0 to 63.9 mg daily. Multiple experimental and clinical models of FXS combine to highlight the therapeutic potential of CBD for management of FXS. All three patients described in the case series exhibited functional benefit following the use of oral CBD+ solutions, including noticeable reductions in social avoidance and anxiety, as well as improvements in sleep, feeding, motor coordination, language skills, anxiety, and sensory processing. Two of the described patients exhibited a reemergence of a number of FXS symptoms following cessation of CBD+ treatment (e.g., anxiety), which then improved again after reintroduction of CBD+ treatment. Findings highlight the importance of exploring the therapeutic potential of CBD within the context of rigorous clinical trials."….

"CBD, the primary, noneuphoric exogenous phytocannabinoid in cannabis, may attenuate the loss of endogenous cannabinoid (i.e., endocannabinoid) signaling observed in preclinical models of FXS, allowing a component of the FMRP deficiency inherent in FXS to be bypassed. Specifically, many abnormalities seen in FXS appear to be rooted in dysregulation of the endocannabinoid pathways in the central nervous system, with a reduction of endogenous stimulation of endocannabinoid receptors.[19–21] CBD has the capacity to interact with an FXS-compromised endocannabinoid system. Indeed, deletion of FMRP within a mouse model of FXS led to reduced production of 2-AG, decreasing activation of CB1 receptors in the central nervous system.[20] CBD has been shown to increase 2-AG availability,[22] potentially attenuating or reversing one of the biological mechanisms of abnormal cellular function in FXS.[20] Importantly, CB1 protein expression appears unaffected in FMR1 knockout (KO) mice, suggesting that the downstream elements of endocannabinoid signaling can be engaged, even in the absence of FMRP.[19]

In addition to the role of 2-AG, recent work has begun to highlight the potential importance of AEA in addressing social impairment as well as deficits in learning and memory among those with FXS. In an FMR1 KO mouse model of FXS, Qin et al. demonstrated that increased levels of AEA were associated with greater cognitive performance.[23] Similarly, Wei et al. utilized mouse models of FXS to show that AEA-mediated signaling at CB1 receptors, driven by oxytocin, controls social reward24 and that increasing AEA activity resulted in reductions in social impairment.[25] Much like its impact on 2-AG, CBD has been shown to increase levels of AEA by binding to fatty acid-binding proteins, which transport AEA to the catabolic enzyme fatty acid amide hydrolase, an

enzyme that breaks down AEA.[26–28] Binding to fatty acid-binding proteins is thought to increase AEA availability and CB1 activation."

-Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado.
-Zynerba Pharmaceuticals, Devon, Pennsylvania.
-Department of Pediatrics, MIND Institute, University of California Davis Medical Center, Sacramento, California.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6446166/

Fructose

Dietary fructose in nonalcoholic fatty liver disease

"Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in adults and children. A number of genetic and environmental factors are known to predispose individuals to NAFLD. Certain dietary sugars, particularly fructose, are suspected to contribute to the development of NAFLD and its progression. The increasing quantity of fructose in the diet comes from sugar additives (most commonly sucrose and high fructose corn syrup) in beverages and processed foods. Substantial links have been demonstrated between increased fructose consumption and obesity, dyslipidemia, and insulin resistance. Growing evidence suggests that fructose contributes to the development and severity of NAFLD. In human studies, fructose is associated with increasing hepatic fat, inflammation, and possibly fibrosis. Whether fructose alone can cause NAFLD or if it serves only as a contributor when consumed excessively in the setting of insulin resistance, positive energy balance, and sedentary lifestyle is unknown. Sufficient evidence exists to support clinical recommendations that fructose intake be limited through decreasing foods and drinks high in added (fructose-containing) sugars."

-Pediatrics, Emory University School of Medicine, Atlanta, GA, USA.
https://pubmed.ncbi.nlm.nih.gov/23390127/

Fructose: Toxic effect on cardiorenal risk factors and redox state

"Prolonged exposure to fructose induces oxidative stress, systolic blood pressure, and increase in triacylglycerol. When stopped fructose consumption, Ex group presented improvement in these variables, suggesting the toxicity effect of fructose when consumed in high amounts and prolonged exposure."…

"Fructose, commonly known as fruit sugar, is also a major component of sweeteners such as table sugar, honey, and high-fructose corn syrup (HFCS). The consumption of this type of sugar has significantly increased in the last years, partly because of the introduction of HFCS in the

food industry.[1] Increased fructose consumption can lead to increase in blood lipids,[2] development of insulin resistance,[3] increase in inflammatory biomarkers and oxidative stress, risk on development of obesity, and comorbidities such as hypertension and diabetes mellitus type II,[4] all risk factors for kidney and cardiac dysfunction. Experimental studies suggest the toxic effect of fructose in these two organs.[5–8] Kidney dysfunction is characterized by albuminuria, elevated serum creatinine, renal hypertrophy, and progressive renal disease. Heart disease is characterized by impaired left ventricular relaxation and diastolic dysfunction.[9]"

-State University (Unesp), Medical School, Botucatu
-State University (Unesp), Institute of Biosciences, Botucatu
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5354174

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…"The fruits that we consume now are hybrids, which means that over the years, they created these fruits to be sweeter and sweeter and sweeter. honey crisp apple, for example, is 19 grams of sugar. I mean, take a look at a crab Apple doesn't have 19 grams of sugar. So we're consuming more sugary fruits. Okay, that's one thing. Number two fruits should be seasonal."…"If you're consuming all year round, that's not really natural. Some people also don't differentiate between whole fruit and fruit juice.

They say the same, but they're not. The juice is not only without the fiber, but without the nutrients because they pasteurize it, they heat it and that kills a lot of the enzymes allow the heat sensitive vitamins. So now we have basically pure sugar, okay, versus this which has vitamins and minerals, phytonutrients and fiber. So it is true that these fruits have these nutrients, okay, which are protective against DNA damage against the complications of diseases like diabetes, for example. However, fruit has a larger amount of a certain sugar called fructose."…"Fructose does not go to all the cells in the body, like glucose does. It only goes to the liver 100% of it goes to the liver. What does that mean? It means that it's not going to spike your blood sugar as much, okay? And if you consume food and check your blood sugars, and you go, Wow, it didn't affect my blood sugars, it must be good. What you're missing is that all that fruit house is going to the liver and the liver has to deal with it. If you do too much, it could lead to insulin resistance, which will raise insulin. So if the liver has to deal with too much fructose, it has to put it somewhere so it converts it to fat, and cholesterol and triglycerides. So my advice is because of the percent of the population that has a problem with blood sugars and pre-diabetes, I recommend that you stick with a small amount of berries and not do fruit. I mean, if you think about what is diabetes, diabetes is high blood sugar. So why would we want to add fruit to that it's going to add more sugar to a condition that is already too high in sugar."…

-Dr. Eric Berg DC
https://www.youtube.com/watch?v=ef-uEe_fcdU

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…"Most plant foods including fruit contain natural sugars, yet these Whole Foods also contain fiber and other nutrients that slow the digestion process. This slow digestion is beneficial because it allows the sugars to be slowly absorbed into the bloodstream, providing a more sustained level of energy and hunger satisfaction, then added sugar. Added sugars go by many names including table sugar, corn syrup, brown sugar, and so on. But regardless of its name, at one time, it was a plant for instance, table sugar typically comes from sugar cane or sugar beets. However, it no longer looks anything like a plant because it has been highly refined, which strips away the fiber and nutrients needed to slow the digestion. As a result, table sugar or one of its close cousins still contains the same basic sugar units as a piece of fruit, but gets digested and absorbed much quicker. This quick absorption causes a spike in blood sugar, that gives you a brief energy surge. However, once that quick energy is used up your blood sugar drops, dropping your energy and leaving you feeling hungry. If we compare natural sugar to added sugar we also see a difference in how they affect insulin levels, which ultimately affects how you gain weight. insulins job is to move sugar out of the bloodstream and into the cells where it can be used for energy, your body tries to keep your blood sugar level within a narrow range. When it goes too high, insulin works overtime, to bring that level back down. If your cells don't need the immediate energy, your body is forced to put the sugar into storage. Your liver and muscles can store some in the form of glycogen. However, these storage closets are small, so any extra gets converted and stored in the fat cells which are the long term easily expandable storage units of our bodies. Because a piece of fruit contains elements that slow the rise of your blood sugar, your body has time to use or burn the sugar limiting the amount that must be stored. However, when you drink a 12 ounce can of soda, you are dumping 11 teaspoons of sugar into your body with no fiber or nutrients to slow down the absorption you get a blood sugar surge and an insulin spike that encourages fat storage. So we see that fruit has weight loss advantages when compared to added sugar. However, the news is not all good when it comes to the natural sugar found in fruit. One of the sugars in fruit is fructose, and like glucose, which goes straight into your bloodstream and raises your blood sugar and insulin, fructose takes a less direct path, it must first visit your liver and be converted into glucose, so it doesn't have the same quick blood sugar and insulin impact as glucose. However, if you are eating too much and taking in more fructose than your body can handle, your liver gets overloaded and converts the fructose to fat, some of which stays in the liver contributing to a common health problem known as fatty liver or non alcoholic fatty liver disease. Another issue with fruit is that not all fruits are created equal.

Some are naturally lower in sugar than others. If your goal is to lose weight, you want to pick foods that are low sugar and avoid high sugar varieties. Low sugar fruits include berries, particularly strawberries, blackberries and raspberries, lemons and limes are also low sugar fruits, as are honeydew melon, cantaloupe, grapefruit and peaches. Oranges are in the mid range. But as long as you are limiting your intake and you eat the whole fruit rather than drinking the juice, you may find that they work into your diet. High sugar fruits that should be limited or avoided include bananas, grapes, mangoes, apples, pears, and any type of dried fruits including dates, raisins, and prunes. The bottom line is that fruit has fiber and nutrients that slow the absorption of the naturally occurring sugars that it contains. However, you can overdo it on fruit. If you overeat, you can overload your liver with fructose increasing fat production by your liver. How much fruit you can consume will depend on factors such as your metabolism, activity level and age, but I think you'll be happiest with your weight loss results if you stick with the low sugar fruit options I shared earlier. You know there is no doubt that there is a lot to learn when you are trying to create a healthy way of eating to lose weight. It pays to have a solid foundation in place."…

-Dr. Becky Gillaspy DC
https://www.youtube.com/watch?v=tlNUiyMw4iY

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Gallstone Disease

Biliary Polyunsaturated Fatty Acids and Telocytes in Gallstone Disease

"It has been reported that intake of ω-3 [omega-3] polyunsaturated fatty acids (PUFAs) reduces the risk of coronary heart disease. It also influences bile composition, decreasing biliary cholesterol saturation in the bile of patients with gallstones. In addition to bile composition disturbances, gallbladder hypomotility must be a cofactor in the pathogenesis of cholelithiasis, as it leads to the prolonged nucleation phase. Our current knowledge about gallbladder motility has been enhanced by the study of a population of newly described interstitial (stromal) cells—telocytes (TCs). The purpose of this study was to determine whether TC loss, reported by our team recently, might be related to bile lithogenicity, expressed as cholesterol saturation index or the difference in biliary PUFA profiles in patients who suffer from cholecystolithiasis and those

not affected by this disease. We determined biliary lipid composition including the fatty acid composition of the phospholipid species in bile. Thus, we investigated whether differences in biliary fatty acid profiles (ω-3 PUFA and ω-6 [omega-6] PUFA) in gallbladder bile may influence its lithogenicity and the quantity of TCs within the gallbladder wall. We conclude that the altered PUFA concentrations in the gallbladder bile, with elevation of ω-6 PUFA, constitute important factors influencing TC density in the gallbladder wall, being one of the possible pathophysiological components for the gallstone disease development. This study established that altered bile composition in patients with cholelithiasis may influence TC quantity within the gallbladder muscle, and we concluded that reduction in TC number may be a consequence of the supersaturated bile toxicity, while some other bile components (ω-3 PUFA, glycocholic, and taurocholic acids) may exert protective effects on TC and thus possibly influence the mechanisms regulating gallbladder and extrahepatic bile duct motility. Thus, ω-3 PUFA may represent a possible option to prevent formation of cholesterol gallstones."

-First Department of General, Oncological and Gastrointestinal Surgery, Jagiellonian University Medical College, Krakow, Poland

-Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland

-Department of Clinical Biochemistry, Jagiellonian University Medical College, Krakow, Poland

-Department of Experimental and Clinical Surgery, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland

-Department of Histology, Jagiellonian University Medical College, Krakow, Poland

-Department of Pathophysiology, Jagiellonian University Medical College, Krakow, Poland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5657685/

Garlic

Cannabinoid Ligands Targeting TRP Channels

"Many endogenous and exogeneous compounds activate receptors found in the TRP superfamily. Natural, pungent compounds like capsaicin and allicin, from chili peppers and **garlic** respectively, can activate and gate specific TRP channels. In addition to these pungent compounds, the six TRP channels that make up the ionotropic cannabinoid receptors can also be modulated by endogenous, phytogenic, and synthetic cannabinoids."

-Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, NC, United States

-Edited by: Eric Murillo-Rodriguez, Anahuac Mayab University, Mexico

-Reviewed by: Chiayu Chiu, Universidad de Valparaíso, Chile; Jeong Hee Hong, Gachon University, South Korea

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340993/

Investigation of Antioxidant and Antimicrobial Properties of Garlic Peel Extract (Allium sativum) and Its Use as Natural Food Additive in Cooked Beef

"Garlic is widely used around the world for its pungent flavor as a seasoning or condiment. Garlic cloves are used for consumption (raw or cooked) or for medicinal purposes. Garlic contains three times greater levels of organosulphur compounds than onion [1]. Due to the health problems associated with synthethic antioxidants, application of garlic as an alternative antioxidant [2,3,4] and antimicrobial [5,6] agents in food system is reported. Garlic cloves are used as a remedy for infections (especially chest problems), digestive disorders, and fungal infections such as thrush [7,8].

In another study, the effect of garlic in improving cardiovascular health by lowering blood pressure and cholesterol levels, and inhibition of several steps in the inflammation process was reported [9]. Furthermore, several clinical reports and meta-analyses have revealed the cholesterol-lowering effects of raw garlic and some garlic supplements, such as garlic essential oil [10,11]. In addition, garlic supplementation significantly reduced aortic plaque deposits of cholesterol-fed rabbits [12]. Recent studies have demonstrated the effectiveness of aged garlic extract (AGE) to reduce the plasma concentration of homocysteine in rats with hyperhomocysteinemia induced by severe folic acid deficiency [13,14].

Garlic, onion and other fruits are used to prevent gastric cancers and countries where garlic is consumed in higher amounts, in traditional cuisine, have been found to have a lower prevalence of cancer [15]. In addition to the anticarcinogenic activity of garlic components studies, a number of researchers have recently focused on its antimutagenic activity, observing that certain sulphur compounds have an effect on DNA repair mechanisms [16]. It has been demonstrated that aged garlic extract exerted an anti-allergic [17] and antitumor effect [18].

Several products of garlic are available in the international market, which include; garlic essential oil, garlic oil macerate, garlic powder as garlicin and aged garlic extract [19], however, there has been no report on the garlic peel. Garlic peel has been treated as waste and may constitute nuisance, therefore, this study was carried out to investigate the antioxidant and antimicrobial properties of garlic peel and its application as preservative in cooked beef."

-Department of Food Science and Technology, Federal University of Technology Akure, Nigeria.
-Department of Food Technology, Federal Polythecnic Ado-Ekiti, Nigeria.
http://www.journalrepository.org/media/journals/JSRR_22/2014/Jan/Ifesan352013JSRR5726_1.pdf

See also Allicin

Gastrointestinal Diseases

Targeting the endocannabinoid system for gastrointestinal diseases: future therapeutic strategies.

"Cannabinoids extracted from the marijuana plant (Cannabis sativa) and synthetic cannabinoids have numerous effects on gastrointestinal (GI) functions. Recent experimental data support an important role for cannabinoids in GI diseases. Genetic studies in humans have proven that defects in endocannabinoid metabolism underlie functional GI disorders. **Mammalian cells have machinery, the so-called endocannabinoid system (ECS), to produce and metabolize their own cannabinoids in order to control homeostasis of the gut in a rapidly adapting manner.** Pharmacological manipulation of the ECS by cannabinoids, or by drugs that raise the levels of endogenous cannabinoids, have shown beneficial effects on GI pathophysiology. This review gives an introduction into the functions of the ECS in the GI tract, highlights the role of the ECS in GI diseases and addresses its potential pharmacological exploitation."

-Division of Gastroenterology, Department of Medicine, University of Calgary
http://www.ncbi.nlm.nih.gov/pubmed/22111567

Endocannabinoids in the Gut

"Cannabis has been used medicinally for centuries to treat a variety of disorders, including those associated with the gastrointestinal tract. The discovery of our bodies' own "cannabis-like molecules" and associated receptors and metabolic machinery—collectively called the endocannabinoid system—enabled investigations into the physiological relevance for the system and provided the field with evidence of a critical function for this endogenous signaling pathway in health and disease. Recent investigations yield insight into a significant participation for the endocannabinoid system in the normal physiology of gastrointestinal function and its possible dysfunction in gastrointestinal pathology. Many gaps, however, remain in our understanding of the precise neural and molecular mechanisms across tissue departments that are under the regulatory control of the endocannabinoid system. This review highlights research that reveals an important—and at times surprising—role for the endocannabinoid system in the control of a variety of gastrointestinal functions, including motility, gut–brain-mediated fat intake and hunger signaling, inflammation and gut permeability, and dynamic interactions with gut microbiota."…

"The endocannabinoid system is ubiquitously expressed throughout the rodent and human body and serves a multitude of physiological roles, including the regulation of gastrointestinal function.[1,2] Activating cannabinoid receptors within the gut inhibits peristalsis and gastric acid

secretion and enhances food intake.[1,3,4]

Evidence also suggests that dysregulation of the endocannabinoid system might play a role in intestinal disorders, including inflammatory bowel disease, irritable bowel syndrome, as well as obesity.[1,5]"...

-Division of Biomedical Sciences, School of Medicine, University of California, Riverside, Riverside, California.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4940133/

Endocannabinoids in the gastrointestinal tract

"The endocannabinoid system mainly consists of endogenously produced cannabinoids (endocannabinoids) and two G protein-coupled receptors (GPCRs), cannabinoid receptors 1 and 2 (CB1 and CB2). This system also includes enzymes responsible for the synthesis and degradation of endocannabinoids and molecules required for the uptake and transport of endocannabinoids. In addition, endocannabinoid-related lipid mediators and other putative endocannabinoid receptors, such as transient receptor potential channels and other GPCRs, have been identified. **Accumulating evidence indicates that the endocannabinoid system is a key modulator of gastrointestinal physiology, influencing satiety, emesis, immune function, mucosal integrity, motility, secretion, and visceral sensation.** In light of therapeutic benefits of herbal and synthetic cannabinoids, the vast potential of the endocannabinoid system for the treatment of gastrointestinal diseases has been demonstrated. This review focuses on the role of the endocannabinoid system in gut homeostasis and in the pathogenesis of intestinal disorders associated with intestinal motility, inflammation, and cancer. Finally, links between gut microorganisms and the endocannabinoid system are briefly discussed."

-College of Pharmacy, Pusan National University, Busan, Korea; and.

-Section of Inflammatory Bowel Disease & Inflammatory Bowel Disease Center, Division of Digestive Diseases, David Geffen School of Medicine, UCLA, Los Angeles, California.

-College of Pharmacy, Pusan National University, Busan, Korea;

https://pubmed.ncbi.nlm.nih.gov/27538961/

Endocannabinoid system acts as a regulator of immune homeostasis in the gut

"Exogenous cannabinoids such as marijuana exert their influence through cannabinoid receptors. Endogenous cannabinoids such as anandamide (AEA) function through the same receptors, and their physiological roles are a subject of intense study. Here, we show that AEA plays a pivotal role in maintaining immunological health in the gut. The immune system in the gut actively

tolerates the foreign antigens present in the gut through mechanisms that are only partially understood. We show that AEA contributes to this critical process by promoting the presence of CX3CR1hi macrophages, which are immunosuppressive. These results uncover a major conversation between the immune and nervous systems. In addition, with the increasing prevalence of ingestion of exogenous marijuana, our study has significant implications for public health."

-Department of Immunology and Carole and Ray Neag Comprehensive Cancer Center, University of Connecticut School of Medicine, Farmington, CT;
-Division of Diabetes and Endocrinology, Connecticut Children's Medical Center, Farmington, CT
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5441729/

Allergy and the gastrointestinal system

"The gastrointestinal system plays a central role in immune system homeostasis. It is the main route of contact with the external environment and is overloaded every day with external stimuli, sometimes dangerous as pathogens (bacteria, protozoa, fungi, viruses) or toxic substances, in other cases very useful as food or commensal flora. The crucial position of the gastrointestinal system is testified by the huge amount of immune cells that reside within it. Indeed, gut-associated lymphoid tissue (GALT) is the prominent part of mucosal-associated lymphoid tissue (MALT) and represents almost 70% of the entire immune system; moreover, about 80% of plasma cells [mainly immunoglobulin A (IgA)-bearing cells] reside in GALT. GALT interacts strictly with gastrointestinal functions in a dynamic manner; for instance, by increasing intestinal permeability in replay to particular stimulations, or orientating the immune response towards luminal content, allowing either tolerance or elimination/degradation of luminal antigens, or sometimes provoking damage to the intestinal mucosa, such as in coeliac disease or food allergy. The immune mechanisms implicated in these actions are very complex and belong to both innate and adaptive immunity; innate immunity supplies an immediate non-specific response that is indispensable before specific adaptive immunity, which needs 7–10 days to be efficacious, takes place. The results of their interactions depend upon different contexts in which contact with external agents occurs and may change according to different genetic settings of the hosts."

-Clinical Pharmacology and Pharmacovigilance, Niguarda Ca' Granda Hospital, Milan, Italy
-Institute of Pediatrics, Department of Medical and Surgical Specialties and Public Health, Perugia, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515351/

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…"Endocannabinoids are endogenously produced ligands that exert effects on CBRs. The major

ligands, anandamide (AEA) and 2-arachidonylglycerol (2-AG), play a role in maintaining GI homeostasis and have been found at increased levels in GI disease states, including celiac disease, diverticulosis, and colorectal cancer.[28–30] Exogenous cannabinoids, both plant-derived phytocannabinoids (cannabis sativa) and synthetic cannabinoids, also directly activate CBRs. They have been shown to play a role in both GI pathophysiology (e.g., cannabinoid hyperemesis syndrome) and therapies (e.g., antiemetics and appetite stimulant).[31]"…

-Department of Gastroenterology, Temple University Hospital, Philadelphia, Pennsylvania.
-Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5665514/

Alternative targets within the endocannabinoid system for future treatment of gastrointestinal diseases

"Many beneficial effects of herbal and synthetic cannabinoids on gut motility and inflammation have been demonstrated, suggesting a vast potential for these compounds in the treatment of gastrointestinal disorders. These effects are based on the so-called 'endocannabinoid system' (ECS), a cooperating network of molecules that regulate the metabolism of the body's own and of exogenously administered cannabinoids. The ECS in the gastrointestinal tract quickly responds to homeostatic disturbances by de novo synthesis of its components to maintain homeostasis, thereby offering many potential targets for pharmacological intervention. Of major therapeutic interest are nonpsychoactive cannabinoids or compounds that do not directly target cannabinoid receptors but still possess cannabinoid-like properties. Drugs that inhibit endocannabinoid degradation and raise the level of endocannabinoids are becoming increasingly promising alternative therapeutic tools to manipulate the ECS."

…"Extracts from Cannabis sativa have been used in traditional medicine to treat inflammation and diarrhea. AEA and 2-AG represent the best-studied endoCBs and act via classical (CB1 and CB2) and, probably, via novel CB receptors such as GPR55, GPR119 or GPR18. EndoCBs and CB receptors are integrated in the ECS, which displays a high degree of plasticity in GI diseases with the aim of protecting GI homeostasis. The fact that cells produce their own CBs offers a unique opportunity for future drug targeting – either to manipulate endoCB receptors, or to inhibit the degradation of endoCBs to increase their levels in the extracellular space. Available studies suggest that CB1 agonists may be useful in emesis, IBD, colon cancer and functional disorders associated with hypermotility and diarrhea, while CB2 agonists may be future drugs used for the treatment of IBD. Additionally, there are strong arguments supporting the use of CBs for the treament of IBS."…

-Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Austria;

-Division of Gastroenterology, Department of Medicine, University of Calgary, Calgary, Alberta;
-Department of Medicine, Ludwig Maximilians University, Munich, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3174079/

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…"Stress affects the function of the GI tract. Stress has been shown to alter gastric secretion, intestinal motility, epithelial cell permeability, and blood flow to the mucosal layers [86]. Acute and chronic stress are also both associated with visceral hypersensitivity to painful stimuli as a result of reduced pain thresholds [89]. CB1R are present in cholinergic neurons in the myenteric and submucosal plexi of the enteric nervous system [20, 88]. CB1R−/− mice exposed to 4 days of 2-h immobilization and acoustic stress exposure exhibit increased permeability of the colonic barrier; enhanced inflammation; lower IgA secretion and higher bacterial translocation into the mesenteric lymph nodes than wild-type mice [161]. These results indicate that CB1R oppose rather than mediate the effects of stress on GI function."…

-Department of Pharmacology and Toxicology, and Neuroscience Research Center, Medical College of Wisconsin, Milwaukee, Wisconsin, USA
-Department of Medicine, and Neuroscience Research Center, Medical College of Wisconsin, Milwaukee, Wisconsin, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5871916

Cannabinoids and the gut: new developments and emerging concepts

"Cannabis has been used to treat gastrointestinal (GI) conditions that range from enteric infections and inflammatory conditions to disorders of motility, emesis and abdominal pain. The mechanistic basis of these treatments emerged after the discovery of Delta(9)-tetrahydrocannabinol as the major constituent of Cannabis. Further progress was made when the receptors for Delta(9)-tetrahydrocannabinol were identified as part of an endocannabinoid system, that consists of specific cannabinoid receptors, endogenous ligands and their biosynthetic and degradative enzymes. Anatomical, physiological and pharmacological studies have shown that the endocannabinoid system is widely distributed throughout the gut, with regional variation and organ-specific actions. It is involved in the regulation of food intake, nausea and emesis, gastric secretion and gastroprotection, GI motility, ion transport, visceral sensation, intestinal inflammation and cell proliferation in the gut. Cellular targets have been defined that include the enteric nervous system, epithelial and immune cells. Molecular targets of the endocannabinoid system include, in addition to the cannabinoid receptors, transient receptor potential vanilloid 1 receptors, peroxisome proliferator-activated receptor alpha receptors and the orphan G-protein coupled receptors, GPR55 and GPR119. Pharmacological

agents that act on these targets have been shown in preclinical models to have therapeutic potential. Here, we discuss cannabinoid receptors and their localization in the gut, the proteins involved in endocannabinoid synthesis and degradation and the presence of endocannabinoids in the gut in health and disease. We focus on the pharmacological actions of cannabinoids in relation to GI disorders, highlighting recent data on genetic mutations in the endocannabinoid system in GI disease."

-Department of Experimental Pharmacology, University of Naples Federico II and Endocannabinoid Research Group, Naples, Italy.
https://pubmed.ncbi.nlm.nih.gov/20117132/

Gut feelings about the endocannabinoid system

"Stemming from the centuries-old and well known effects of Cannabis on intestinal motility and secretion, research on the role of the endocannabinoid system in gut function and dysfunction has received ever increasing attention since the discovery of the cannabinoid receptors and their endogenous ligands, the endocannabinoids. In this article, some of the most recent developments in this field are discussed, with particular emphasis on new data, most of which are published in Neurogastroenterology & Motility, on the potential tonic endocannabinoid control of intestinal motility, the function of cannabinoid type-1 (CB1) receptors in gastric function, visceral pain, inflammation and sepsis, the emerging role of cannabinoid type-2 (CB2) receptors in the gut, and the pharmacology of endocannabinoid-related molecules and plant cannabinoids not necessarily acting via cannabinoid CB1 and CB2 receptors. These novel data highlight the multi-faceted aspects of endocannabinoid function in the GI tract, support the feasibility of the future therapeutic exploitation of this signaling system for the treatment of GI disorders, and leave space for some intriguing new hypotheses on the role of endocannabinoids in the gut."

-Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Pozzuoli, Italy.
https://pubmed.ncbi.nlm.nih.gov/21481098/

See also Macrophages

Gastroparesis

"Gastroparesis is a long-term (chronic) condition where the stomach cannot empty in the normal way. Food passes through the stomach slower than usual. It's thought to be the result of a problem with the nerves and muscles that control how the stomach empties."

-National Health Service UK
https://www.nhs.uk/conditions/gastroparesis/

Impact of Cannabinoids on Symptoms of Refractory Gastroparesis: A Single-center Experience

"Cannabinoids are increasingly used for medicinal purposes, including neuropathy. Gastroparesis is a neuromuscular disorder and neuropathy plays a large role in its pathogenesis. It is thus reasonable that cannabinoids can serve a beneficial role in the management of gastroparesis. Our study evaluates the effect of cannabinoids on gastroparesis symptoms."…

Results

"A significant improvement in the GCSI total symptom composite score was seen with either cannabinoid treatment (mean score difference of 12.8, 95% confidence interval 10.4-15.2; p-value < 0. 001). Patients prescribed marijuana experienced a statistically significant improvement in every GCSI symptom subgroup. Significant improvement in abdominal pain score was also seen with either cannabinoid treatment (mean score difference of 1.6; p-value <0.001)."

Conclusions

"Cannabinoids dramatically improve the symptoms of gastroparesis. Furthermore, an improvement in abdominal pain with cannabinoids represents a breakthrough for gastroparesis-associated abdominal pain treatment, for which there are currently no validated therapies."

- Department of Gastroenterology, Bridgeport Hospital, Bridgeport, USA
- Department of Gastroenterology and Hepatology, Westchester Medical Center, Valhalla, USA
- Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, USA
- Department of Hospital Medicine, Bridgeport Hospital, Bridgeport, USA
- Division of Gastroenterology and Hepatobiliary Diseases, Westchester Medical Center/New York Medical College, Valhalla, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6970440/

Effect of ω-3 Fatty Acid on Gastrointestinal Motility after Abdominal Operation in Rats

"ω-3 [omega-3] fatty acid include Eicosapentaenoic acid (EPA), Ducosahexaenoic acid (DHA), and Alpha-linolenic acid (ALA), which play an important role in the regulation of inflammation [7]."…

"As we know, intestinal handling induces the secretion of IL-1, IL-6 and TNF-α, triggers mast cell activation and inflammation associated with prolonged postoperative ileus. COX-2 catalyzes the first step of conversion of its common substrate, arachidonic acid (AA), into a number of

biologically active derivatives, designated as prostaglandins (PGs, including PG-E2, PG-D2, PGF-2α, and PG-I2) and thromboxane (TX) A2, which are major participants in rodent postoperative ileus [8]. In our research, on POD 3, the serum IL-1, IL-6, TNF-α, COX-2 levels in ω-3 fatty acid group were lower than those in normal saline group and intralipid group, $P < .05$. This indicates that ω-3 fatty acid can decrease serum inflammatory factors and COX-2 levels. The possible reasons are as follows. (1) After consumption, ω-3 fatty acid can be incorporated into cell membranes and can reduce the amount of AA available for the synthesis of proinflammatory eicosanoids (e.g., PGs, leukotrienes (LTs)). Likewise, ω-3 fatty acid can also reduce the production of inflammatory cytokines, such as IL-1, IL-6, and TNF-α [9]. (2) With regard to inflammatory processes, the main fatty acids of interest are the AA, which is the precursor of inflammatory eicosanoids like PG-E2 and LT-B4, but ω-3 fatty acid gives rise to mediators (PG-E3, LT-B5) that are less inflammatory than those produced from AA [10]. (3) In addition to modifying the lipid mediator profile, ω-3 fatty acid exerts effects on other aspects of inflammation like leukocyte chemotaxis and inflammatory cytokine production. Some of these effects are likely due to changes in gene expression, as a result of altered transcription factor activity [10]. (4) COX-2 is the key enzyme of prostaglandin synthesis and ω-3 fatty acid can reduce the expression of COX-2 mRNA, in this respect, ω-3 fatty acid could inhibit inflammation [11, 12]. (5) Recently, resolvins and protectins, novel ω-3 fatty-acids-derived mediators were identified [13]. These mediators can signal for potent counter-regulatory effects on leukocyte functions, including preventing uncontrolled neutrophil swarming, decreasing the generation of cytokines, chemokines, and reactive oxygen species and promoting clearance of apoptotic neutrophils from inflamed tissues [14]. In this way, ω-3 fatty acids could reduce gastrointestinal inflammation.

Because postoperative inflammation inhibits gastrointestinal mobility significantly, ω-3 fatty acid could accelerate the recovery of gastrointestinal mobility after abdominal operation.

Our study showed that enteral nutrition with ω-3 fatty acid compared to intralipid could accelerate the recovery of gastrointestinal mobility after caecectomy in rats. The mechanism of action is that ω-3 fatty acid could decrease serum inflammatory facts levels and relieve postoperative inflammation. Hence, it can accelerate the recovery of gastrointestinal mobility."

Conclusion

"ω-3 fatty acid could accelerate the recovery of gastrointestinal mobility after abdominal operation in rats, mainly by decreasing serum levels of IL-1, IL-6, TNF-α, and COX-2 and by relieving postoperative inflammation."

-Department of General Surgery, Peking Union Medical College Hospital, Peking Union Medical College, No. 1 Shuaifuyuan Wangfujing, Beijing, China

-Department of Pathophysiology, Peking Union Medical College, No. 1 Shuaifuyuan Wangfujing, Beijing, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3086275/

Gender Differences

…"Our results suggest that sex differences in the medial amygdala are modulated by the endocannabinoid system during early development. Sex differences in play behavior are loosely correlated with differences in neuronal morphology."

Department of Pharmacology, University of Maryland School of Medicine, Baltimore, MD 21201
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5272923/

Genetically Modified Organisms (GMO)

GMO often refers to seeds which have been modified to not be affected by glyphosate herbicide. Glyphosate was invented to bind to metal, and minerals, ie metal ions / metal atoms. It was first patented in 1964 as a descaling agent to remove minerals and other elements from inside of industrial equipment. [patent #3160632] it was later purchased by monsanto and patented again as a herbicide in 1969 [patent # 3455675] In 1996 RoundUp Ready was on the market containing glyphosate. In 2005 a new use was found for RoundUp as a desiccant used to dry out the crop quicker before harvesting and also to eliminating any weeds before harvesting. In 2010 glyphosate was patented again as a powerful antibiotic at 1 part per million [patent # 7771736].

https://www.google.com/patents/US3160632

https://www.google.com/patents/US3455675

https://www.google.com/patents/US7771736

Metalloproteins

"Metalloproteins, or proteins that bind metal cofactors, make up a substantial portion of the human proteome and are essential for the viability of both individual cells and of the overall organism." By some estimates Metalloproteins make up one-third to one-half of all proteins,[59] thus glyphosate may make many proteins, enzymes, minerals in food bio-unavailable to humans.

Zinc

[59] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2861717/

Zinc deficiency in humans is associated with an increased risk of developing esophageal squamous cell carcinoma. Another mechanism by which zinc might prevent cancer is through its effect on angiogenesis and tumour progression. Since there are Zinc Metalloenzymes, glyphosate most likely also affects the bioavailability of these enzymes and many others due to how the glyphosate functions.[60,61]

Inflammatory Effects of Subacute Exposure of Roundup in Rat Liver and Adipose Tissue

"Roundup is a popular herbicide containing glyphosate as an active ingredient. The formulation of Roundup is speculated to have critical toxic effects, one among which is chronic inflammation. The present study analyzed adverse inflammatory effects in the liver and adipose tissue of rats after a subacute exposure of Roundup. Adult male rats were exposed to various doses of Roundup (0, 5, 10, 25, 50, 100 and 250 mg/kg bodyweight [bw] glyphosate) orally, everyday for 14 days. On day 15, liver and adipose tissues from dosed rats were analyzed for inflammation markers. C-reactive protein in liver, cytokines IL-1β, TNF-α, IL-6, and inflammatory response marker, and prostaglandin–endoperoxide synthase were upregulated in liver and adipose of rats exposed to higher (100 and 250 mg/kg bw/d) doses of Roundup. Cumulatively, our data suggest development of inflammation in lipid and hepatic organs upon exposure to Roundup. Furthermore, liver histological studies showed formation of vacuoles, fibroid tissue, and glycogen depletion in the groups treated with doses of higher Roundup. These observations suggest progression of fatty liver disease in Roundup-treated adult rats. In summary, our data suggest progression of multiorgan inflammation, liver scarring, and dysfunction post short-term exposure of Roundup in adult male rats."…

"The current study describes for the first time the effects of a subacute exposure of Roundup in developing multi-organ inflammation and non-alcoholic fatty liver (NAFL) condition. After a 2-week exposure of herbicide doses well below LD50, increased expression levels of inflammatory markers were seen in adipose and liver tissues of treated rats. Liver tissue showed signs of developing glycogen storage imbalance and fibrosis at higher doses. Taken together, the report presents dose-dependent adverse inflammatory effects of short-term exposure of Roundup on the liver and adipose tissues of treated rats."

-Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore, Karnataka, India

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[60] https://academic.oup.com/jn/article/130/5/1437S/4686409

[61] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3102454/

-Indian Institute of Science Education and Research, Mohali, Punjab, India
-Aparamita Pandey, Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6537504/

■■■

"Deficiencies in iron, cobalt, molybdenum, copper and other rare metals associated with celiac disease can be attributed to glyphosate's strong ability to chelate these elements. Deficiencies in tryptophan, tyrosine, methionine and selenomethionine associated with celiac disease match glyphosate's known depletion of these amino acids. Celiac disease patients have an increased risk to non-Hodgkin's lymphoma, which has also been implicated in glyphosate exposure. Reproductive issues associated with celiac disease, such as infertility, miscarriages, and birth defects, can also be explained by glyphosate. Glyphosate residues in wheat and other crops are likely increasing recently due to the growing practice of crop desiccation just prior to the harvest. We argue that the practice of “ripening” sugar cane with glyphosate may explain the recent surge in kidney failure among agricultural workers in Central America. We conclude with a plea to governments to reconsider policies regarding the safety of glyphosate residues in foods."

- Independent Scientist and Consultant
- Computer Science and Artificial Intelligence Laboratory, MIT
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945755

■■■

..."Taken together, our data suggest that exposure to GBH [Glyphosate based herbicide] from juvenile age through adulthood in mice leads to neurobehavioral changes that stem from the impairment of neuronal developmental processes."

-Laboratory of Pharmacology, Neurobiology and Behavior (URAC-37), Faculty of Sciences Semlalia, Cadi Ayyad University, Marrakech, Morocco.
https://www.ncbi.nlm.nih.gov/pubmed/28848410

■■■

…"Concerns about the carcinogenic properties of GBHs [glyphosate-based herbicides] have increased after the World Health Organization’s International Agency for Research on Cancer (IARC) re-classified glyphosate as “probably carcinogenic to humans””…

-Environmental Health Sciences, Charlottesville, VA, and Adjunct Professor, Carnegie Mellon University, Pittsburg, PA USA
-Department of Medical and Molecular Genetics, Faculty of Life Sciences and Medicine, King’s College London, London, UK
-Department of Developmental and Cell Biology, University of California, Irvine, CA USA

-The Endocrine Disruption Exchange, Paonia, CO USA
-L. Everett & Associates, Santa Barbara, CA USA
-Consumers Union, Yonkers, NY USA
-Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY USA
-Child & Family Research Institute, BC Children's Hospital, University of British Columbia, Vancouver, BC Canada
-Department of Environmental Health Sciences, School of Public Health and Health Sciences, University of Massachusetts – Amherst, Amherst, MA USA
-Division of Biological Sciences, University of Missouri, Columbia, MO USA
-Department of Biomedical Sciences, University of Missouri-Columbia, Columbia, MO USA
-Benbrook Consulting Services, Enterprise, OR, USA
-Environmental Health Sciences, Charlottesville, VA ,USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4756530

See Pesticides

Glaucoma

Cannabinoids in the treatment of glaucoma

"The leading cause of irreversible blindness is glaucoma, a disease normally characterized by the development of ocular hypertension and consequent damage to the optic nerve at its point of retinal attachment. This results in a narrowing of the visual field, and eventually results in blindness. A number of drugs are available to lower intraocular pressure (IOP), but, occasionally, they are ineffective or have intolerable side-effects for some patients and can lose efficacy with chronic administration. The smoking of marijuana has decreased IOP in glaucoma patients. Cannabinoid drugs, therefore, are thought to have significant potential for pharmaceutical development. However, as the mechanism surrounding their effect on IOP initially was thought to involve the CNS, issues of psychoactivity hindered progress. The discovery of ocular cannabinoid receptors implied an explanation for the induction of hypotension by topical cannabinoid applications, and has stimulated a new phase of ophthalmic cannabinoid research. Featured within these investigations is the possibility that at least some cannabinoids may ameliorate optic neuronal damage through suppression of N-methyl-D-aspartate receptor hyperexcitability, stimulation of neural microcirculation, and the suppression of both apoptosis and damaging free radical reactions, among other mechanisms. Separation of therapeutic actions from side-effects now seems possible through a diverse array of novel chemical, pharmacological, and formulation strategies."

-Department of Pharmaceutical Chemistry, University of Kuopio, Finland.
https://pubmed.ncbi.nlm.nih.gov/12182967/

Cannabinoid applications in glaucoma

"Introduction: Glaucoma is a slowly progressive optic neuropathy that is one of the leading causes of legal blindness throughout the world. Currently there is a limited group of topical drugs for the medical treatment of glaucoma is currently limited, and research needs to be focused on new therapeutic horizons, such as the potential usefulness of the cannabinoid agonists for the treatment of glaucoma.

Aim: To review the current scientific literature related to the beneficial effects derived from the different ways of administration of cannabinoids indicated for the glaucomatous optic neuropathy.

Development: Cannabinoid receptors have shown an intense expression in ocular tissues implicated in the regulation of the intraocular pressure, as well as inner layers of the retina. Through activation of CB1 and CB1 specific receptors and through other still unknown pathways, the cannabinoid agonists have shown both a clear hypotensive, as well as an experimentally proved neuroprotective effect on retinal ganglion cells.

Conclusions: Some cannabinoid agonists (WIN 55212-2, anandamide) have demonstrated, in experimental studies, to act as «ideal drugs» in the management of glaucoma, as they have been shown to have good tolerability after topical application, efficiently reduce intraocular pressure, and behave as neuroprotectors on retinal ganglion cells. Further studies as regards the safety and clinical assays must be carried out in order to examine the effectiveness of these drugs for the treatment of glaucoma in our daily clinical practice."

-Department of Cell Biology and Histology, Group of Ophthalmo-Experimental Biology (GOBE), Faculty of Medicine, University of the Basque Country (UPV / EHU), Leioa, Vizcaya, Spain.
https://pubmed.ncbi.nlm.nih.gov/21414525/

The Endocannabinoid System as a Therapeutic Target in Glaucoma

"Glaucoma is an irreversible blinding eye disease which produces progressive retinal ganglion cell (RGC) loss. Intraocular pressure (IOP) is currently the only modifiable risk factor, and lowering IOP results in reduced risk of progression of the disorder. The endocannabinoid system (ECS) has attracted considerable attention as a potential target for the treatment of glaucoma, largely due to the observed IOP lowering effects seen after administration of exogenous cannabinoids. However, recent evidence has suggested that modulation of the ECS may also be

neuroprotective. This paper will review the use of cannabinoids in glaucoma, presenting pertinent information regarding the pathophysiology of glaucoma and how alterations in cannabinoid signalling may contribute to glaucoma pathology. Additionally, the mechanisms and potential for the use of cannabinoids and other novel agents that target the endocannabinoid system in the treatment of glaucoma will be discussed."

-Department of Pharmacology, Dalhousie University, Halifax, NS, Canada.
-Department of Medical Neuroscience, Dalhousie University, Halifax, NS, Canada
-Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4737462/

Glial Cells

"Glial cells are integrated part of neurovascular unit of blood brain barrier (BBB). They undergo mitosis and mainly classified as astrocytes, oligodendrocytes, microglia, ependymal cells and nerve glial antigen 2 cells. Being a most versatile glial cell, astrocytes provide structural support to neurons, maintain brain homeostasis, take part in neuronal communication, and perform some housekeeping functions."…

-Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University, New Delhi. India.
-Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh. India.
https://www.ncbi.nlm.nih.gov/pubmed/28302022

■■■

"Microglia, immune cells in the brain, are regarded to play crucial roles in brain homeostasis and inflammation via phagocytosis and/or releasing pro- and anti- inflammatory mediators such as cytokines and chemokines (Block and Hong, 2005). Psychological stress is one of the most frequent triggers of suicide (Hawton and van Heeringen, 2009). Rodent studies have revealed that acute and chronic stress based on social defeat model and restraint model induce microglial activation in various brain regions (Sugama et al., 2007; Tynan et al., 2010; Hinwood et al., 2012; Ohgidani et al., 2016). Human microglia research is difficult to conduct because of difficulty in analysis of microglia in human subjects based on ethical and technical issues (Ohgidani et al., 2015). To our knowledge, human microglia analysis during the course of psychological stress has not been conducted, while our previous pharmacological study with healthy volunteers using minocycline, an antibiotic with suppressing microglial activation in rodents, has indirectly suggested that human social-decision making in stressful situations is unconsciously controlled by microglia (Kato et al., 2012, 2013b; Watabe et al., 2013). Postmortem brain analysis and PET imaging are two major methods to estimate microglial activation in human

subjects, and these studies have suggested activation of human microglia in the brain of patients with various psychiatric disorders (Kato et al., 2013b). Here, we introduce human biological studies using these techniques focusing on suicide and microglia."

-National Hospital Organization Shimofusa Psychiatric Medical Center, Chiba, Japan

-Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

-Neuropathology Department, Sainte-Anne Hospital, Paris, France

-Human Histopathology and Animal Models Laboratory, Institute Pasteur, Paris, France

-Department of Pathology and Forensic Medicine, Raymond Poincaré University Hospital, Garches, France

-Department of Clinical Chemistry and Laboratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

-Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

-Edited by: Jose Luis Venero, Universidad de Sevilla, Spain

-Reviewed by: Andrew Dwork, Columbia University, United States; Naguib Mechawar, McGill University, Canada; Ana María Espinosa Oliva, Universidad de Sevilla, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6381042/

Clinical Findings Documenting Cellular and Molecular Abnormalities of Glia in Depressive Disorders

"There is ample evidence that glial abnormalities are present in the brains of depressed individuals. These glial changes affect all major glial cell types, astrocytes, microglia and oligodendrocytes and are detectable at multiple levels: at molecular, cellular and network level. Notably, we could not find any clinical studies on NG2-psoitive glia in the context of depressive disorders. Here, we gathered the clinical observations and we did not consider the potential functional consequences, mainly because a number of recent excellent reviews discuss these issues. Astrocytes carry out a large number of vital cellular functions (e.g., Sofroniew and Vinters, 2010), their functional deficits can lead to various malfunctions, most prominently to disturbed glutamate and ion homeostasis, and to synaptic dysfunctions (see e.g., Rajkowska and Stockmeier, 2013; Jun et al., 2014; Verkhratsky and Parpura, 2016; Haroon et al., 2017; Sild et al., 2017; Wang et al., 2017). The main function of oligodendrocytes is to provide support and insulation to axons, thus, their dysfunction can lead to disrupted neuronal network connectivity and communication and consequently result in psychopathology (Menon, 2011; Edgar and Sibille, 2012). Plenty of evidences suggest neuroimmune etiology (Yirmiya et al., 2015; Miller and Raison, 2016; Haroon et al., 2017) or at least disturbed immune response regulation in a subgroup of depressed individuals (Mechawar and Savitz, 2016) and activated microglia is one player in this complex multifaceted process."

-Neurobiology of Stress Research Group, Szentágothai Research Center, University of Pécs, Pécs, Hungary

-Department of Laboratory Medicine, University of Pécs, Medical School, Pécs, Hungary

-Department of Neurosurgery, University of Pécs, Medical School, Pécs, Hungary

-MTA-PTE, Clinical Neuroscience MR Research Group, Pécs, Hungary
-Pécs Diagnostic Centre, Pécs, Hungary

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5835102/

See also Suicide

Glioblastomas

β-Caryophyllene Inhibits Cell Proliferation through a Direct Modulation of CB2 Receptors in Glioblastoma Cells

"Glioblastomas are aggressive cancers characterized by uncontrolled proliferation and inflammation. b-caryophyllene (BCP) is a cannabinoid receptor 2 (CB2) agonist that showed an important anti-inflammatory effect through the interaction of CB2 and peroxisome proliferator-activated receptor gamma (PPARg) receptors. BCP effects were investigated in an in vitro model of glioblastoma. "….

"These findings let us hypothesize that BCP may act as a tumor suppressor in glioblastoma, acting on CB2 receptor and modulating JNK."

-Department of Clinical and Experimental Medicine, University of Messina, c/o AOU Policlinico G. Martino, Via C. Valeria Gazzi, Messina, Italy.
-Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", University of Messina, c/o AOU Policlinico G. Martino, Via C. Valeria Gazzi, Messina, Italy.
-Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, c/o AOU Policlinico G. Martino, Via C. Valeria Gazzi, Messina, Italy.

https://pubmed.ncbi.nlm.nih.gov/32340197

Cannabidiol enhances the inhibitory effects of Δ9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival

"The cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptor agonist, Δ9-tetrahydrocannabinol (THC), has been shown to be a broad range inhibitor of cancer in culture and in vivo, and is currently being used in a clinical trial for the treatment of glioblastoma. It has been suggested that other plant-derived cannabinoids, which do not interact efficiently with CB1 and CB2 receptors, can modulate the actions of Δ9-THC. However, there are conflicting reports as to what extent other cannabinoids can modulate Δ9-THC activity, and most importantly, it is not clear whether other cannabinoid compounds can either potentiate or inhibit the actions of Δ9-

THC. We therefore tested cannabidiol (CBD), the second most abundant plant derived cannabiniod, in combination with Δ9-THC. In U251 and SF126 glioblastoma cell lines, Δ9-THC and CBD acted synergistically to inhibit cell proliferation. The treatment of glioblastoma cells with both compounds led to significant modulations of the cell cycle and induction of reactive oxygen species (ROS) and apoptosis as well as specific modulations of extracellular signal-regulated kinase (ERK) and caspase activities. These specific changes were not observed with either compound individually, indicating that the signal transduction pathways affected by the combination treatment were unique. Our results suggest that the addition of CBD to Δ9-THC may improve the overall effectiveness of Δ9-THC in the treatment of glioblastoma in cancer patients."…

-California Pacific Medical Center Research Institute, San Francisco, CA
-Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2806496/

See also Beta-caryophyllene (β-caryophyllene)

glossodynia (Burning Mouth Syndrome)

Ginger

Ginger on Human Health: A Comprehensive Systematic Review of 109 Randomized Controlled Trials

…"Ginger (Zingiber officinale Roscoe), a well-known herbaceous plant, has been widely used as a flavoring agent and herbal medicine for centuries. Furthermore, the consumption of the ginger rhizome is a typical traditional remedy to relieve common health problems, including pain, nausea, and vomiting [1]. Notably, a prominent number of randomized clinical trials (RCTs) have been conducted to examine ginger's antiemetic effect in various conditions such as motion sickness, pregnancy, and post-anesthesia [2,3,4]. More than approximately 100 compounds have reportedly been isolated from ginger [5]. Specifically, the major classes of ginger compounds are gingerol, shogaols, zingiberene, and zingerone, as well as other less common compounds, including terpenes, vitamins, and minerals [6]. Among them, gingerols are considered as the primary components, reported to possess several bioactivities [7]. As a result, many related

biological activities have been explored such as those of antioxidant, antimicrobial, and anti-neuroinflammation, just to name a few [8]. Moreover, in recent years, the role of ginger has been extended to anticancer, chemotherapy-induced nausea and vomiting (CINV), and fatigue, as well as improvements in the quality of life in daily human work [9,10].

These potential pharmacological and physiological activities have led to a significant increase in the number of investigations on the health benefits of ginger. Regarding clinical aspects, there has been a trend of accumulative evidence in terms of ginger efficacy on human health. Indeed, a remarkable number of RCTs that have aimed to discover the benefits of ginger by reducing symptoms have been conducted. For example, multiple RCTs evaluated the effectiveness of ginger supplementation in reducing CINV in cancer patients, as well as in dysmenorrhea [11]. Moreover, several systematic reviews and meta-analysis (SR–MA), which aimed to assess the clinical ginger effectiveness, have been completed. In particular, Chen et al. conducted an SR–MA of oral ginger intake and found that ginger could effectively control menstrual pain in dysmenorrhea [11]. Another SR–MA study revealed that ginger improved lipid profiles and benefited the glucose control, insulin sensitivity, and glycosylated hemoglobin of type 2 diabetes mellitus [12]. In addition, ginger's potency has been regularly proposed in arthritis, gastric dysfunction, and cancers [6,13,14]."…

-College of Pharmacy, Seoul National University, Korea
-School of Medicine, Vietnam National University, Vietnam
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7019938/

Gingerols: a novel class of vanilloid receptor (VR1) agonists

"Gingerols, the pungent constituents of ginger, were synthesized and assessed as agonists of the capsaicin-activated VR1 (vanilloid) receptor."…

"We conclude that gingerols represent a novel class of naturally occurring VR1 receptor agonists that may contribute to the medicinal properties of ginger, which have been known for centuries. The gingerol structure may be used as a template for the development of drugs acting as moderately potent activators of the VR1 receptor."…

…"Ginger (Zingiber officinale) has been used extensively for more than 2500 years in China for conditions including headaches, nausea and colds (Grant & Lutz, 2000) and in Ayurvedic (Sharma & Clark, 1998) and Western herbal medicine practice for the treatment of arthritis, rheumatological conditions and muscular discomfort (Blumenthal & Werner, 1998). Its use in inflammatory conditions is consistent with anti-inflammatory activities of its components in vitro (Kiuchi et al., 1982; Mascolo et al., 1989). The moderate pungency of ginger has been attributed to the mixture of gingerol derivatives in the oleoresin

fraction of processed ginger (Mustafa et al., 1993). Gingerols possess the vanillyl moiety (Figure 1, region A), which is considered important for activation of the VR1 receptor expressed in nociceptive sensory neurones (Walpole et al., 1993a). Recently it was found that molecules lacking the vanillyl structure also activate the VR1 receptor in DRG neurones. These molecules include N-arachidonoyl-dopamine and its 3-O-methyl analogue (Huang et al., 2002), **anandamide, an endogenous ligand of the neuronal cannabinoid receptor (CB1)** (Smart & Jerman, 2000; Smart et al., 2000; Zygmunt et al., 1999), lipoxygenase metabolites (Hwang et al., 2000; Craib et al., 2001; Piomelli, 2001), and the naturally occurring sesquiterpene dialdehydes (Szallasi et al., 1998). The VR1 receptor has recently been cloned and suggested to integrate chemical and thermal nociceptive stimuli (Tominaga et al., 1998; Caterina et al., 1997; 2000). Therefore, direct activation/deactivation of the VR1 receptor at the site where pain is generated during inflammation and other painful conditions provides a new strategy for the development of a new class of peripheral analgesics devoid of the well characterized side effects of currently available analgesics (Kress & Zeilhofer, 1999; Roufogalis & Dedov, 1999). Furthermore, VR1-expressing neurones have recently been found throughout the whole neuroaxis (Mezey et al., 2000), opening up a new and so far unexplored area of VR1-related drug development. We report here for the first time to our knowledge that the pungent principle of ginger, [6]-gingerol and [8]-gingerol, activate the VR1 receptor in capsaicin-sensitive neurones and that activation is blocked by the VR1 antagonist, capsazepine.“…

-Faculty of Pharmacy, University of Sydney, Sydney, Australia
-Department of Pharmacology, University of Sydney, Sydney, Australia
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1573550

Interaction Between the Cannabinoid and Vanilloid Systems on Anxiety in Male Rats

…”Acute neuropharmacological blockade of the TRPV1 receptor or stimulation of the CB1 receptor produced an anxiolytic effect. It seems that antagonism of the vanilloid system modulates cannabinoid gain that rises the anxiolytic effect. TRPV1 antagonism may amend generation of endocannabinoids, which in turn increases anxiolytic impact. These results suggest that two systems could act on or share a common signaling pathway affecting the expression of anxiety.”…

-Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran.
-Department of Biology, Hamadan Branch, Islamic Azad University, Hamadan, Iran.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440922/

Managing Rheumatoid Arthritis with Dietary Interventions

…"Ginger has been known for its therapeutic properties due to the presence of pungent phenolics such as shogaols and gingerols [122]. Turmeric, rich in phenolic curcuminoids, has also proved its beneficial effects against several malignancies [123]. In a study, a perfect mixture of blended ginger and turmeric were given to the adjuvant-induced arthritic rats. This mixture showed protective effects against extra-articular complications of RA [122]. In another study conducted by the same group, they found that ginger and turmeric administered at a dose of 200 mg/kg body weight could independently lower down the signs and symptoms of RA in the adjuvant-induced arthritic male Wistar albino rats. The results were significant with a p-value <0.05 as compared to the control group receiving only indomethacin [123].

Curcumin has also presented itself as a potent anti-inflammatory spice by blocking the expression of IL-1 and IL-6 in an in vitro study with RA patient-derived fibroblast-like synoviocytes [124]. Methotrexate is a widely prescribed antirheumatic drug for the treatment of RA but it increases oxidative stress, decreases NO levels, and leads to vascular endothelial dysfunction [124, 125]. Curcumin and folic acid co-administration was found to lower down methotrexate-induced vascular endothelial dysfunctions in male Wistar rats [126].

Bark of Cinnamomum zeylanicum (Cinnamon bark) is widely used in South-East Asian dishes. Rathi et al. treated RA animal models involving male Swiss albino mice and Wistar rats with polyphenolic fraction of cinnamon barks and found inhibitory effects on secretion of cytokines IL-2, IL-4, and IFN-γ and reduction in levels of TNF-α [127]."…

-Disease Biology Laboratory, School of Biotechnology, KIIT University, Bhubaneswar, Odisha, India Edited by: Marilia Seelaender, University of São Paulo, Brazil

Reviewed by: Dario Coletti, Sapienza Università di Roma, Italy; Emanuele Rinninella, Agostino Gemelli University Polyclinic, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5682732/

Ginger extract versus Loratadine in the treatment of allergic rhinitis: a randomized controlled trial

…."The ginger extract is as good as loratadine in improving nasal symptoms and quality of life in AR patients. However, ginger extract caused less side effects especially, drowsiness, fatigue, dizziness and constipation. Therefore, the ginger extract could be used as alternative treatment

for patients with AR."

-Department of Applied Thai Traditional Medicine, Faculty of Medicine, Thammasat University, Klongluang, Pathumthani, Thailand

-Department of Otolaryngology, Faculty of Medicine, Thammasat University, Klongluang, Pathumthani, 12120, Thailand

Center of Excellence on Applied Thai Traditional Medicine Research (CEATMR), Faculty of Medicine, Thammasat University, Klongluang, Pathumthani, 12120, Thailand

https://bmccomplementmedtherapies.biomedcentral.com/articles/10.1186/s12906-020-2875-z

Anti-Oxidative and Anti-Inflammatory Effects of Ginger in Health and Physical Activity: Review of Current Evidence

"The anticancer potential of ginger is well documented and its functional ingredients like gingerols, shogaol, and paradols are the valuable ingredients which can prevent various cancers. This review concludes to favor ginger but some ambiguities necessitate further research before claiming its efficacy."…

"Ginger has staring potential for treating a number of ailments including degenerative disorders (arthritis and rheumatism), digestive health (indigestion, constipation and ulcer), cardiovascular disorders (atherosclerosis and hypertension), vomiting, diabetes mellitus, and cancer. It also has anti-inflammatory and anti-oxidative properties for controlling the process of aging. Furthermore, it has antimicrobial potential as well which can help in treating infectious diseases.[2,4–6] Generation of free radicals or reactive oxygen species (ROS) during metabolism beyond the antioxidant capacity of a biological system results in oxidative stress,[7] which plays an essential role in heart diseases, neurodegenerative diseases, cancer, and in the aging process.[7,8] The bioactive molecules of ginger like gingerols have shown antioxidant activity in various modules.[9]

Inflammatory disorders such as gastritis, esophagitis, and hepatitis, which are caused not only by infectious agents such as viruses, bacteria, and parasites but also by physical and chemical agents like heat, acid, cigarette smoke, and foreign bodies, are recognized as risk factors for human cancer. Ginger consumption before exercise might reduce naturally occurring quadriceps muscle pain during moderate-intensity cycling exercise. This effect may be due to anti-inflammatory effect of ginger and further investigation need to prove it in human.[10]"…

-Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

-Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

-Department of Biochemistry, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3665023/

Glucocorticoids

“Cortisol, the stress hormone, is one of the many hormones responsible for this physiological change. Cortisol is a glucocorticoid hormone produced by the adrenal glands and released for a variety of reasons. The hypothalamus-pituitary-adrenal axis regulates its release and when not controlled, overproduction and underproduction of cortisol cause Cushing’s syndrome and Addison disease, respectively.“

- Lauren Thau; Sandeep Sharma, Mery Fitzgerald Hospital
https://www.ncbi.nlm.nih.gov/books/NBK538239/

Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System

…“Chronic exposure to glucocorticoids downregulates the eCB system.”…

-GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom; Department of Family Medicine, University of Vermont, Burlington, Vermont, USA.

-GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom.

-Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei, Pozzuoli, Napoli, Italy.
http://www.ncbi.nlm.nih.gov/pubmed/24622769

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..."Endocannabinoids have been found to mediate the nongenomic glucocorticoid-induced inhibition of the release of corticotrophin-releasing factor within the paraventricular nucleus of the hypothalamus. Altogether, these observations suggest that alterations of the endocannabinoid tone might be associated with the development of stress-related diseases, including anxiety, depression and obesity."

Department of Psychiatry, Obesity Research Center, Genome Research Institute, University of Cincinnati, Cincinnati, OH, USA.
https://www.ncbi.nlm.nih.gov/pubmed/18426497

G Protein-Coupled Receptors (GPCRs)

G protein-coupled receptors: signalling and regulation by lipid agonists for improved glucose homoeostasis

“G protein-coupled receptors (GPCRs) play a pivotal role in cell signalling, controlling many

processes such as immunity, growth, cellular differentiation, neurological pathways and hormone secretions. Fatty acid agonists are increasingly recognised as having a key role in the regulation of glucose homoeostasis via stimulation of islet and gastrointestinal GPCRs."…

-SAAD Centre for Pharmacy and Diabetes, School of Biomedical Sciences, University of Ulster, Cromore Road, Coleraine, BT52 1SA, Northern Ireland, UK.

-SAAD Centre for Pharmacy and Diabetes, School of Biomedical Sciences, University of Ulster, Cromore Road, Coleraine, BT52 1SA, Northern Ireland, UK

https://pubmed.ncbi.nlm.nih.gov/26739335/

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"The cannabinoid receptors are G protein-coupled receptors that are activated by endocannabinoids or exogenous agonists such as tetrahydrocannabinol [THC]. Upon agonist binding, cannabinoid receptors will activate Gi which in turn inhibits adenylyl cyclase. "…

-Tung M. Fong, in Methods in Enzymology, 2010

https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/cannabinoid-receptor

G-Protein Coupled Receptors

The Endocannabinoid System and Chronic Disease

"Pharmacodynamically, AEA [anandamide] and 2-AG [2-Arachidonoylglycerol] bind to the G-protein coupled receptors (GPCRs), CB1 [cannabinoid 1 receptor] and CB2 [cannabinoid 1 receptor], which are located in the CNS and the peripheral nervous system. The analgesic properties of AEA likely involve its partial agonism (moderate affinity, low efficacy) of the CB1 receptor, which, in turn, decreases the release of excitatory neurotransmitters.[51] It has also been shown to act as a weak agonist at the transient receptor potential vanilloid 1 (TRPV-1) receptors.[47,52] The TRPV-1 receptors are expressed in nociceptive sensory neurons and respond to noxious mechanical, thermal, and chemical stimuli. AEA and capsaicin share the same TRPV-1 binding site, but higher concentrations of AEA are required in order to activate TRPV-1.[47,52] Unlike AEA, 2-AG is found in much higher concentrations in the brain (up to 170-fold) and is thought to be a full agonist (low affinity, high efficacy) of the CB1 receptor.[47,51,52]"

-Book: Physical Activity and the Aging Brain - Effects of Exercise on Neurological Function

-A. Yoder, Edited by: Ronald Ross Watson

https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/endocannabinoid-system

GPR55

The endocannabinoids anandamide and virodhamine modulate the activity of the candidate cannabinoid receptor GPR55

..."Increasing amount of evidence suggests an important physiological role for GPR55 (Andradas et al. 2011) (Staton et al. 2008; Whyte et al. 2009; Huang et al. 2011; Pineiro et al. 2011). Recently GPR55 has been demonstrated to play significant role in inflammation where it interacts with the well characterized CB2 receptor (Balenga et al. 2011). While lysophosphatidylinositol, LPI, has been repeatedly reported as an endogenous ligand at GPR55 (Bondarenko et al. 2011; Kapur et al. 2009; Henstridge et al. 2009; Henstridge et al. 2010) the role of endocannabinoids, known activators of the well characterized cannabinoid receptors (CB1 and CB2), in regulating GPR55 is poorly understood. Moreover, no specific and selective antagonists have been identified at GPR55, thus preventing a more thorough understanding of GPR55's physiological role. The availability of high potency antagonists will facilitate the study of the biological roles of this receptor."...

-Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, USA.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3669693/

Advances Towards The Discovery of GPR55 Ligands

"The G-protein-coupled receptor 55 (GPR55) was identified in 1999. It was proposed as a novel member of the endocannabinoid system due to the fact that some endogenous, plant-derived and synthetic cannabinoid ligands act on GPR55. However, the complexity of the cellular downstream signaling pathways related to GPR55 activation delayed the discovery of selective GPR55 ligands. It was only a few years ago that the high throughput screening of libraries of pharmaceutical companies and governmental organizations allowed to identify selective GPR55 agonists and antagonists. Since then, several GPR55 modulator scaffolds have been reported. The relevance of GPR55 has been explored in diverse physiological and pathological processes revealing its role in inflammation, neuropathic pain, bone physiology, diabetes and cancer. Considering GPR55 as a new promising therapeutic target, there is a clear need for new selective and potent GPR55 modulators. This review will address a current structural update of GPR55 ligands."

-Instituto de Química Médica, Consejo Superior de Investigaciones Científicas, Calle Juan de la Cierva, 3, Madrid E-28230, Spain.
https://pubmed.ncbi.nlm.nih.gov/27109575/

Pharmacological characterization of GPR55, a putative cannabinoid receptor

"GPR55 has recently attracted much attention as another member of the cannabinoid family, potentially explaining physiological effects that are non-CB1/CB2 mediated. However, the data gathered so far are conflicting with respect to its pharmacology. We review the primary literature to date on GPR55, describing its discovery, structure, pharmacology and potential physiological functions. The CB1 receptor antagonist/inverse agonist AM251 has been shown to be a GPR55 agonist in all reports in which it was evaluated, as has the lysophospholipid, lysophosphatidylinositol (LPI). Whether GPR55 responds to the endocannabinoid ligands anandamide and 2-arachidonylglycerol and the phytocannabinoids, delta-9-tetrahydrocannabidiol and cannabidiol, is cell type and tissue-dependent. GPR55 has been shown to utilize G(q), G(12), or G(13) for signal transduction; RhoA and phospholipase C are activated. Experiments with mice in which GPR55 has been inactivated reveal a role for this receptor in neuropathic and inflammatory pain as well as in bone physiology. Thus delineating the pharmacology of this receptor and the discovery of selective agonists and antagonists merits further study and could lead to new therapeutics."

-Department of Anatomy and Cell Biology and Center for Substance Abuse Research, Temple University, Philadelphia, USA.

https://pubmed.ncbi.nlm.nih.gov/20298715

Grounding

Also known as Earthing

"Grounding or earthing refers to direct skin contact with the surface of the Earth, such as with bare feet or hands, or with various grounding systems. Subjective reports that walking barefoot on the Earth enhances health and provides feelings of well-being can be found in the literature and practices of diverse cultures from around the world.1 For a variety of reasons, many individuals are reluctant to walk outside barefoot, unless they are on holiday at the beach. Experience and measurements show that sustained contact with the Earth yields sustained benefits. Various grounding systems are available that enable frequent contact with the Earth, such as while sleeping, sitting at a computer, or walking outdoors. These are simple conductive systems in the form of sheets, mats, wrist or ankle bands, adhesive patches that can be used inside the home or office, and footwear. These applications are connected to the Earth via a cord

inserted into a grounded wall outlet or attached to a ground rod placed in the soil outside below a window. For the footwear applications, a conductive plug is positioned in the shoe sole at the ball of the foot, under the metatarsals, at the acupuncture point known as Kidney [1]. From a practical standpoint, these methods offer a convenient and routine, user-friendly approach to grounding or earthing. They can also be used in clinical situations, as will be described in the section entitled Summary of findings to date.[1]

Recently, a group of about a dozen researchers (including the authors of this paper) has been studying the physiological effects of grounding from a variety of perspectives. This research has led to more than a dozen studies published in peer-reviewed journals. While most of these pilot studies involved relatively few subjects, taken together, the research has opened a new and promising frontier in inflammation research, with broad implications for prevention and public health. The findings merit consideration by the inflammation research community, which has the means to verify, refute, or clarify the interpretations we have made thus far.

Grounding reduces or even prevents the cardinal signs of inflammation following injury: redness, heat, swelling, pain, and loss of function (Figures 1 and and2).2). Rapid resolution of painful chronic inflammation was confirmed in 20 case studies using medical infrared imaging (Figure 3).[2,3]"…

"Voluminous current research correlates inflammation with a wide range of chronic diseases. A search for "inflammation" in the National Library of Medicine database (PubMed) reveals over 400,000 studies, with more than 34,000 published in 2013 alone. The most common cause of death and disability in the United States is chronic disease. Seventy-five percent of the nation's health care spending, which surpassed US$2.3 trillion in 2008, is for treating chronic disease. Heart disease, cancer, stroke, chronic obstructive pulmonary disease, osteoporosis, and diabetes are the most common and costly chronic diseases.[61] Others include asthma, Alzheimer's disease, bowel disorders, cirrhosis of the liver, cystic fibrosis, multiple sclerosis, arthritis, lupus, meningitis, and psoriasis. Ten percent of all health care dollars are spent treating diabetes. Osteoporosis affects about 28 million aging Americans.[61,62] However, there are few theories on the mechanisms connecting chronic inflammation with chronic disease. The research on grounding or earthing summarized here provides a logical and testable theory based on a variety of evidence.

The textbook description of the immune response describes how large or small injuries cause neutrophils and other white blood cells to deliver highly ROS and RNS to break down pathogens and damaged cells and tissues. Classical textbook descriptions also refer to an "inflammatory barricade" that isolates injured tissues to hinder the movement of pathogens and debris from the damaged region into adjacent, healthy tissues. Selye described how the debris coagulates to form the inflammatory barricade (Figure 10). This barrier also hinders the movements of

antioxidants and regenerative cells into the blocked-off area. Repair can be incomplete, and this incomplete repair can set up a vicious inflammatory cycle that can persist for a long period of time, leading to so-called silent or smoldering inflammation that in turn, over time, can promote the development of chronic disease.

Remarkable as it may seem, our findings suggest that this classical picture of the inflammatory barricade may be a consequence of lack of grounding, and of a resultant "electron deficiency". Wounds heal very differently when the body is grounded (Figures 1 and and2).2). Healing is much faster, and the cardinal signs of inflammation are reduced or eliminated. The profiles of various inflammatory markers over time are very different in grounded individuals."

-Nature's Own Research Association, Dover, NH, USA
-Developmental and Cell Biology Department, University of California at Irvine, Irvine, CA, USA
-Human Physiology Department, University of Oregon, Eugene, OR, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4378297

Earthing: Health Implications of Reconnecting the Human Body to the Earth's Surface Electrons

"Environmental medicine generally addresses environmental factors with a negative impact on human health. However, emerging scientific research has revealed a surprisingly positive and overlooked environmental factor on health: direct physical contact with the vast supply of electrons on the surface of the Earth. Modern lifestyle separates humans from such contact. The research suggests that this disconnect may be a major contributor to physiological dysfunction and unwellness. Reconnection with the Earth's electrons has been found to promote intriguing physiological changes and subjective reports of well-being. Earthing (or grounding) refers to the discovery of benefits—including better sleep and reduced pain—from walking barefoot outside or sitting, working, or sleeping indoors connected to conductive systems that transfer the Earth's electrons from the ground into the body. This paper reviews the earthing research and the potential of earthing as a simple and easily accessed global modality of significant clinical importance."…

"Environmental medicine focuses on interactions between human health and the environment, including factors such as compromised air and water and toxic chemicals, and how they cause or mediate disease. Omnipresent throughout the environment is a surprisingly beneficial, yet overlooked global resource for health maintenance, disease prevention, and clinical therapy: the surface of the Earth itself. It is an established, though not widely appreciated fact, that the Earth's surface possesses a limitless and continuously renewed supply of free or mobile electrons. The surface of the planet is electrically conductive (except in limited ultradry areas such as

deserts), and its negative potential is maintained (i.e., its electron supply replenished) by the global atmospheric electrical circuit [1, 2].

Mounting evidence suggests that the Earth's negative potential can create a stable internal bioelectrical environment for the normal functioning of all body systems. Moreover, oscillations of the intensity of the Earth's potential may be important for setting the biological clocks regulating diurnal body rhythms, such as cortisol secretion [3].

It is also well established that electrons from antioxidant molecules neutralize reactive oxygen species (ROS, or in popular terms, free radicals) involved in the body's immune and inflammatory responses. The National Library of Medicine's online resource PubMed lists 7021 studies and 522 review articles from a search of “antioxidant+electron+free radical” [3]. It is assumed that the influx of free electrons absorbed into the body through direct contact with the Earth likely neutralize ROS and thereby reduce acute and chronic inflammation [4]. Throughout history, humans mostly walked barefoot or with footwear made of animal skins. They slept on the ground or on skins. Through direct contact or through perspiration-moistened animal skins used as footwear or sleeping mats, the ground's abundant free electrons were able to enter the body, which is electrically conductive [5]. Through this mechanism, every part of the body could equilibrate with the electrical potential of the Earth, thereby stabilizing the electrical environment of all organs, tissues, and cells.

Modern lifestyle has increasingly separated humans from the primordial flow of Earth's electrons. For example, since the 1960s, we have increasingly worn insulating rubber or plastic soled shoes, instead of the traditional leather fashioned from hides. Rossi has lamented that the use of insulating materials in post-World War II shoes has separated us from the Earth's energy field [6]. Obviously, we no longer sleep on the ground as we did in times past.

During recent decades, chronic illness, immune disorders, and inflammatory diseases have increased dramatically, and some researchers have cited environmental factors as the cause [7]. However, the possibility of modern disconnection with the Earth's surface as a cause has not been considered. Much of the research reviewed in this paper points in that direction.”…

“Eight healthy men ages 20–23 were put through a similar routine of toe raises while carrying on their shoulders a barbell equal to one-third of their body weight. Each participant was exercised individually on a Monday morning and then monitored for the rest of the week while following a similar eating, sleeping, and living schedule in a hotel. The group was randomly divided in half and either grounded or sham grounded with the use of a conductive patch placed at the sole of each foot during active hours and a conductive sheet at night. Complete blood counts, blood

chemistry, enzyme chemistry, serum and saliva cortisol, magnetic resonance imaging and spectroscopy, and pain levels (a total of 48 parameters) were taken at the same time of day before the eccentric exercise and at 24, 48, and 72 hours afterwards. Parameters consistently differing by 10 percent or more, normalized to baseline, were considered worthy of further study.

Parameters that differed by these criteria included white blood cell counts, bilirubin, creatine kinase, phosphocreatine/inorganic phosphate ratios, glycerolphosphorylcholine, phosphorylcholine, the visual analogue pain scale, and pressure measurements on the right gastrocnemius.

The results showed that grounding the body to the Earth alters measures of immune system activity and pain. Among the ungrounded men, for instance, there was an expected, sharp increase in white blood cells at the stage when DOMS is known to reach its peak and greater perception of pain (see Figure 3). This effect demonstrates a typical inflammatory response. In comparison, the grounded men had only a slight decrease in white blood cells, indicating scant inflammation, and, for the first time ever observed, a shorter recovery time. Brown later commented that there were “significant differences” in the pain these men reported [12].”....

-Developmental and Cell Biology Department, University of California at Irvine, Irvine, USA
-Earth FX Inc., Palm Springs, USA
-University of CT School of Medicine, c/o Optimum Health Building, CT, USA
-Nature's Own Research Association, Dover, USA
-Department of Ambulatory Cardiology, Military Clinical Hospital, Poland
-Department of Neurosurgery, Military Clinical Hospital, Poland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3265077/

The biologic effects of grounding the human body during sleep as measured by cortisol levels and subjective reporting of sleep, pain, and stress

“Results indicate that grounding the human body to earth ("earthing") during sleep reduces night-time levels of cortisol and resynchronizes cortisol hormone secretion more in alignment with the natural 24-hour circadian rhythm profile. Changes were most apparent in females. Furthermore, subjective reporting indicates that grounding the human body to earth during sleep improves sleep and reduces pain and stress.”

-Journal of Alternative and Complementary Medicine (New York, N.Y)
https://pubmed.ncbi.nlm.nih.gov/15650465

Can electrons act as antioxidants? A review and commentary

“A previous study demonstrated that connecting the human body to the earth during sleep (earthing) normalizes the daily cortisol rhythm and improves sleep. A variety of other benefits were reported, including reductions in pain and inflammation. Subsequent studies have confirmed these earlier findings and documented virtually immediate physiologic and clinical effects of grounding or earthing the body. It is well established, though not widely known, that the surface of the earth possesses a limitless and continuously renewed supply of free or mobile electrons as a consequence of a global atmospheric electron circuit. Wearing shoes with insulating soles and/or sleeping in beds that are isolated from the electrical ground plane of the earth have disconnected most people from the earth's electrical rhythms and free electrons. The most reasonable hypothesis to explain the beneficial effects of earthing is that a direct earth connection enables both diurnal electrical rhythms and free electrons to flow from the earth to the body. It is proposed that the earth's diurnal electrical rhythms set the biological clocks for hormones that regulate sleep and activity. It is also suggested that free electrons from the earth neutralize the positively charged free radicals that are the hallmark of chronic inflammation. A relationship between cortisol and inflammation was established in the pioneering work of H. Selye published in the 1950s. Current biomedical research has led to an inflammation hypothesis that is establishing chronic inflammation as the culprit behind almost every modern chronic illness. The research summarized here and in subsequent reports provides a basis for a number of earthing technologies that restore and maintain natural electrical contact between the human body and the earth throughout the day and night in situations where going barefoot on the earth is impractical. It is proposed that free or mobile electrons from the earth can resolve chronic inflammation by serving as natural antioxidants.”

-Nature's Own Research Association, Dover, USA.
https://pubmed.ncbi.nlm.nih.gov/18047442/

Earthing the Human Body Influences Physiologic Processes

“Earthing the human body influences human physiologic processes. This influence is observed during night relaxation and during physical activity. Effect of the earthing on calcium-phosphate homeostasis is the opposite of that which occurs in states of weightlessness. It also increases the activity of catabolic processes. It may be the primary factor regulating endocrine and nervous systems.”…

“Our experiments have shown that contact of the human body with moistened surface of the Earth via a copper conductor can influence calcium–phosphate homeostasis. The effect of

earthing of the human body in a recumbent position on calcium–phosphate homeostasis is opposite to that which occurs in states of weightlessness. It shows that contact with the Earth in a recumbent position leads to effects that have been noted during rhythmic, longitudinal compression of the skeleton in immobilized patients.5 The reduction of renal excretion of calcium and phosphorus, and the lowering of serum concentrations of total calcium, ionized calcium, and phosphorus can indicate that they are stored in the skeleton. This pool of calcium ions is readily exchangeable because it is in physicochemical equilibrium with extracellular fluid. The pool consists of calcium phosphate salts and provides an immediate reserve for sudden decreases of calcium ions in blood.[6] In the state of normocalcemia, the excitation–secretion processes of parathyroid glands are sensitive and immediate.5 Minimal changes of concentrations of calcium ions in the blood modulate the activity of nervous and endocrine systems.

Dynamics of changes in concentrations of ions (sodium, potassium, and chloride) could indicate an exchange of these ions with the intracellular environment. The contact of human organism with the Earth may change the conditions of intestinal absorption and excretion, renal excretion, and storage and transmission of ions through the cellular membrane.

Results of presented studies have shown that earthing from the defined surface of the Earth transmitted via a copper conductor onto the surface of an insulated human body is responsible for changes of iron and proteins in serum concentrations.

Earthing the human body during relaxation and during physical activity is responsible for the increasing glucose utilization by the cells in NIDDM. Lack of contact with the Earth may cause opposite effects and may be the reason for several disorders (diabetes, obesity, and hypertension).[7]"..

-Dr. Karol Sokal, MD, PhD
-Dr. Pawel Sokal, MD, PhD
-Department of Ambulatory Cardiology, Military Clinical Hospital, Poland.
-Department of Neurosurgery, Military Clinical Hospital, Bydgoszcz, Poland.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3154031/

Gum Disease (Periodontal Disease)

"Periodontal (gum) disease is an infection of the tissues that hold your teeth in place. It's typically caused by poor brushing and flossing habits that allow plaque—a sticky film of bacteria—to build up on the teeth and harden."

- National Institute of Dental and Craniofacial Research
https://www.nidcr.nih.gov/health-info/gum-disease/more-info

■■■

…"These findings suggest that endocannabinoid system may have an important role in periodontal healing."

-Department of Periodontology, Kagoshima University Graduate School of Medical and Dental Sciences, Japan.
https://www.ncbi.nlm.nih.gov/pubmed/20233580

See also Bone Loss & Fractures

Gut-Brain Axis (GBA)

Also referred to as Brain-Gut Axis

The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems

"The gut-brain axis (GBA) consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. Recent advances in research have described the importance of gut microbiota in influencing these interactions. This interaction between microbiota and GBA appears to be bidirectional, namely through signaling from gut-microbiota to brain and from brain to gut-microbiota by means of neural, endocrine, immune, and humoral links. In this review we summarize the available evidence supporting the existence of these interactions, as well as the possible pathophysiological mechanisms involved. Most of the data have been acquired using technical strategies consisting in germ-free animal models, probiotics, antibiotics, and infection studies. In clinical practice, evidence of microbiota-GBA interactions comes from the association of dysbiosis with central nervous disorders (i.e. autism, anxiety-depressive behaviors) and functional gastrointestinal disorders. In particular, irritable bowel syndrome can be considered an example of the disruption of these complex relationships, and a better understanding of these alterations might provide new targeted therapies."…

-Department of Internal Medicine and Medical Specialties, University Sapienza, Rome (Marilia Carabotti, Annunziata Scirocco, Carola Severi), Italy

-Experimental Pharmacology Laboratory, Scientific Institute of Gastroenterology S. de Bellis, Castellana Grotte, Bari (Maria Antonietta Maselli), Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4367209/

The role of the endocannabinoid system in the brain-gut axis

"The actions of cannabis are mediated by receptors that are part of an endogenous cannabinoid system. The endocannabinoid system (ECS) consists of the naturally occurring ligands N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), their biosynthetic and degradative enzymes, and the cannabinoid receptors CB1 and CB2. The ECS is a widely distributed transmitter system that controls gut functions peripherally and centrally. It is an important physiologic regulator of gastrointestinal motility. Polymorphisms in the gene encoding CB1 (CNR1) have been associated with some forms of irritable bowel syndrome. The ECS is involved in the control of nausea and vomiting and visceral sensation. The homeostatic role of the ECS also extends to the control of intestinal inflammation. We review the mechanisms by which the ECS links stress and visceral pain. CB1 in sensory ganglia controls visceral sensation, and transcription of CNR1 is modified through epigenetic processes under conditions of chronic stress. These processes might link stress with abdominal pain. The ECS is also involved centrally in the manifestation of stress, and endocannabinoid signaling reduces the activity of hypothalamic–pituitary–adrenal pathways via actions in specific brain regions—notably the prefrontal cortex, amygdala, and hypothalamus. Agents that modulate the ECS are in early stages of development for treatment of gastrointestinal diseases. Increasing our understanding of the ECS will greatly advance our knowledge of interactions between the brain and gut and could lead to new treatments for gastrointestinal disorders."…

Cannabis has been used for millennia to treat the symptoms of inflammatory and functional disorders of the gastrointestinal (GI) tract[1], including abdominal pain, cramps, diarrhea, nausea, and vomiting2-6. Currently, cannabis is used legally and illegally by patients seeking relief from a vast array of symptoms—many of GI origin. The availability and use of medical cannabis is increasing in the USA, Canada, and elsewhere, however, although cannabis is widely used for the treatment of nausea and abdominal pain, there is only limited evidence to support these uses[7].

About 25 years ago researchers discovered the cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). Activation of these receptors accounts for the majority of the actions of the main psychoactive constituent of cannabis Δ9-tetrahydrocannabinol (THC)[8, 9]. The CB1 and CB2, their ligands N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), and the enzymes that synthesize and degrade them are the major components of the endocannabinoid system (ECS)[9]. Our knowledge of the ECS has increased exponentially in recent years and we now appreciate its roles in the brain–gut axis and gut pathophysiology. The actions of the ECS appear to be largely homeostatic, contributing importantly to the regulation of motility and inflammation in the GI tract. However, activation of CB1 in the intestinal epithelium also contributes in what appears to be a maladaptive fashion to the development of metabolic

disease and obesity[10]. In the central nervous system (CNS), the ECS is involved in the pathophysiology of stress.[11, 12"]…

-Hotchkiss Brain Institute and Snyder Institute of Chronic Diseases, Department of Physiology and Pharmacology, University of Calgary, Canada

-Department of Internal Medicine, University of Michigan, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4961581/

Gut Health

…"Intestinal microbiota colonization is essential in balancing immune responses in a homeostatic manner: studies conducted on germ-free mice suggest that the absence of an intestinal microbiota leads to impaired immune function (for a review see Round and Mazmanian, 2009, [32]) and that microbiota influences the specific phenotypes and physiological functions of T and B cells in the gut mucosa layer (for a review see Honda and Littman, 2016, [33]). These cells play a pivotal role in immune homeostasis by defending against foreign antigens and by maintaining the integrity of the gut mucosal barrier. A balanced gut-microbiota stimulates resident macrophages to release large amounts of interleukin (IL)-10 and transforming growth factor (TGF)-beta [34], thus promoting the induction of regulatory T cells (Tregs) and preventing an increase in the number of proinflammatory T helper 17 (Th17) cells in the gut [35]. In fact, a peripheral tolerance is maintained by the correct balance between gut-bacteria population and responses by the host.

An altered microbiota, including a reduction in health-promoting bacteria such as Lactobacilli and Bifidobacteria, may lead to a dysbiotic condition generated by Gram-negative-bacteria producing immunogenic endotoxins such as lipopolysaccharide (LPS) which increase intestinal permeability [33,36,37]. This condition changes the microbiota taxa profile and switches Treg to T-inflammatory cells (i.e., Th17) triggering a toll-like receptor (TLRs) mediated inflammatory response [38]. Very recently, the intestinal microbiota has emerged as a potential triggering factor in central nervous system–specific auto-immunity disease, as demonstrated in an experimental animal model for MS [multiple sclerosis] [39,40,41]. Gut microbiota from patients with MS enabled a spontaneous experimental autoimmune encephalomyelitis in germ-free transgenic mice, devoid of resident microbes, demonstrating that the MS-derived microbiota has factors that may precipitate an MS-like autoimmune disease in a transgenic mouse model [39]. Brain autoimmunity critically depends on the presence of an intact gut flora. Some members of the intestinal microbiota may ignite innate immune responses with the activation of dormant brain-specific T cells within gut-associated lymphatic tissues. Upon activation, such lymphocytes travel

to the central nervous system (CNS) and trigger a cascade of events that culminate in the formation of brain-specific autoantibodies. Brain-specific autoantibodies together with T-cell activation produce demyelinating lesions, similar to active multiple sclerosis (MS) plaques [41].

As demonstrated in a recent pilot study conducted in our laboratory, dietary components, and in particular fruit, vegetables and fibers, allow the longtime maintenance of gut–microbiota homeostasis. It was observed that patients with MS who followed a controlled diet showed a significant decrease of Th1 and Th17 cells compared to those that followed a Western diet. This evidence correlated with an increase in the gut microbiota population of Lachnospiraceae family (phylum Firmicutes, see Figure 1), which are butyrate producers [15].

Therefore, these results link the gut microbiota to a variety of brain disorders. Studies of the mechanisms elucidating this transition could have important consequences both for developing new therapeutic strategies for treatment and the diagnosis of human neurodegenerative diseases [33]. It is still unclear whether a dysbiotic microbial profile exists a priori or whether changes in the composition of microbiota occur after the onset of disease [42].”…

-IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy;
-Department of Physiopathology and Transplants, University of Milano, Milan, Italy
-Department of Biology and Biotechnology, University of Pavia, Pavia, Italy;
-Istituto per lo Studio e la Cura del Diabete [ISCD], Casagiove, Caserta, Italy;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164598/

See also Gastrointestinal Diseases

Gynecologic Cancer

“Gynecologic cancer is any cancer that starts in a woman's reproductive organs. Cancer is always named for the part of the body where it starts. Gynecologic cancers begin in different places within a woman's pelvis, which is the area below the stomach and in between the hip bones.”

- Centers for Disease Control
https://www.cdc.gov/cancer/gynecologic/basic_info/what-is-gynecologic-cancer.htm

(Endo)Cannabinoids and Gynaecological Cancers

“Cancers of the female reproductive system are common and are responsible for a large number of deaths in women. The exact reasons why some of these cancers occur are unknown. It is, however, known that for most of these cancers, several factors interact for them to happen.

These interactions involve factors external and internal to the woman. An understanding of some of the internal factors involved in how these cancers arise will not only help drive preventive strategies, but will speed the development of new treatment approaches. The endocannabinoid system is a family including chemicals (known as endocannabinoids) produced in the body that are similar to those derived from the cannabis plant. This system, which is widely distributed in the body, has been shown to be involved in various functions. Its disruption has been shown to lead to various diseases, one of which is cancer. In this review, we summarize current knowledge of this system, its various constituents, and how they are involved in reproductive events and their pathologies, especially cancers. Furthermore, we discuss the role of the endocannabinoid system in these cancers and how targeting it could lead to new approaches to diagnosis and treatment of cancers of the female reproductive system."…

"A pivotal role of the ECS in gynaecological cancers has been demonstrated in recent years; in particular, the development, progression, and prognosis of female reproductive tract diseases seem to be associated with their dysregulation [12,30,38,56,57,95,105,108,112,113,118,119,120,122,141,179]. Due to manifold cellular and metabolic regulatory functions, the ECS represents an important therapeutic target that needs further investigation."….

-Endocannabinoid Research Group, Reproductive Sciences Section, Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester LE1 7RH, UK;
-Department of Molecular and Cell Biology, University of Leicester, Leicester, UK
-European Centre for Brain Research, IRCCS Santa Lucia Foundation, Rome, Italy;
-Gynaecology Oncology Cancer Centre, Liverpool Women's NHS Foundation Trust, Liverpool Women's Hospital, UK
-Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK
-Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7795647

H

Hematopoiesis

noun: haemopoiesis; noun: hemopoiesis
"The production of blood cells and platelets, which occurs in the bone marrow."
-Oxford Languages / Google

The role of endocannabinoids in haematopoiesis

"Endocannabinoids are blood borne and may also be secreted by the endothelium. Accordingly, there has been interest in the interactions between (endo)cannabinoids and blood cells. There is certainly evidence that (endo)cannabinoids may promote platelet activation, indicating that they may be thrombogenic. Platelets are involved both in the metabolism and release of endocannabinoids, and so it is possible that their circulating levels may be regulated by platelets. This process is altered in disease states such that platelet-derived endocannabinoids contribute towards hypotension in cardiovascular shock. Not only may endocannabinoids regulate platelet function and possibly lead to thrombogenesis, but they may also influence haematopoiesis. Given these emerging roles, the aim of this review is to examine the interactions between cannabinoids and blood."…

"The production of blood cells is a tightly regulated process and is designed to maintain physiological levels of cells but also to respond to pathophysiology. Valk et al. (1997), reported that in vitro anandamide (at low micromolar concentrations) acted via cannabinoid CB2 receptors to synergize with colony-stimulating factors (CSFs), interleukin-3 and erythropoietin to stimulate haematopoesis. This finding at low concentrations may suggest a role in the modulation of blood cell production, while the effects on white cells may contribute towards their established role in immune responses. More recently, the same group has also reported that 2-AG acts via cannabinoid CB2 receptors to cause haematopoietic cell migration and this effect was synergistic with interleukin-3 and granulocyte-CSF (Jorda et al., 2002). This may indicate that 2-AG is important in immune cell mobilization."

-School of Biomedical Sciences, University of Nottingham Medical School, Nottingham, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2190025/

thrombogenesis - the formation of a thrombus. - *Merriam-Webster / Google*
thrombus - a blood clot formed in situ within the vascular system of the body and impeding blood flow. - *Oxford Languages / Google*

Head Injury

See Traumatic Brain Injury

Headache (post-traumatic)

"Headache after concussion persists in a substantial portion of patients. Early inflammatory

sources activate trigeminal ganglia neurons to release excitatory neuropeptides and neurotransmitters. Centralized sources of inflammation after concussion may sensitize neurons at several regions along the trigeminal nuclei. Sensitized trigeminal neurons lead to a lowered threshold of activation, which more readily triggers a headache. The eCB system is believed to contribute to the homeostatic basis by which both the CNS and immune system respond to injury, while also being a main modulator of the pain system. Whether there is a deficiency in the eCB after concussion as proposed for migraine has yet to be evidenced. Exogenous modulators of the eCB, whether derived from the plant or synthetics, have been shown to alter pain in acute, chronic and neuropathic conditions, including migraine and are expected to play a large role in the headache and other pain conditions resulting from concussion."

-Department of Neurosurgery, Vickie & Jack Farber Institute for Neuroscience Thomas Jefferson University
-Department of Pharmacology, Lewis Katz School of Medicine, Temple University
-Department of Anatomy & Cell Biology, Lewis Katz School of Medicine, Temple University
-Department of Physiology Lewis Katz School of Medicine, Temple University
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6122691/

Headaches & Migraines - Food Triggers

Headaches: a Review of the Role of Dietary Factors

"Dietary triggers are commonly reported by patients with a variety of headaches, particularly those with migraines. The presence of any specific dietary trigger in migraine patients varies from 10 to 64 % depending on study population and methodology. Some foods trigger headache within an hour while others develop within 12 h post ingestion. Alcohol (especially red wine and beer), chocolate, caffeine, dairy products such as aged cheese, food preservatives with nitrates and nitrites, monosodium glutamate (MSG), and artificial sweeteners such as aspartame have all been studied as migraine triggers in the past. This review focuses the evidence linking these compounds to headache and examines the prevalence of these triggers from prior population-based studies. Recent literature surrounding headache related to fasting and weight loss as well as elimination diets based on serum food antibody testing will also be summarized to help physicians recommend low-risk, non-pharmacological adjunctive therapies for patients with debilitating headaches."

-Division of Neurology, University of British Columbia, 8219-2775 Laurel Street, Vancouver, BC, Canada.
https://pubmed.ncbi.nlm.nih.gov/27714637/

Effect of exclusion of frequently consumed dietary triggers in a cohort of children with chronic primary headache

…"Results: One hundred patients attended follow-up. Of these 13 (13%) did not respond to dietary exclusion; 87 (87%) achieved complete resolution of headaches by exclusion of 1-3 of the identified food(s). Caffeine was the most common implicated trigger (28), followed by monosodium glutamate (25), cocoa (22), aspartame (13), cheese (13), citrus (10) and nitrites (six). One patient was sensitive to tomatoes.

Conclusions: This study demonstrates the potential scale and significance of seven frequently consumed foods or food additives as triggers for primary headache in children. Also this is the first study to show that headaches can be triggered by the cumulative effect of a food that is frequently consumed, rather than by single time ingestion."

-Children's Hospital of Western Ontario, Department of Academic Paediatrics, London, Canada.
https://pubmed.ncbi.nlm.nih.gov/28298151/

Diet and Headache: Part 1

…"Results: Caffeine withdrawal and administration of MSG [monosodium glutamate] (dissolved in liquid) has the strongest evidence for triggering attacks of headache as evidenced by multiple positive provocation studies. Aspartame has conflicting evidence with two positive and two negative provocation studies. Observational studies provide modest evidence that gluten- and histamine-containing foods as well as alcohol may precipitate headaches in subgroups of patients. Two of three randomized controlled trials reported that an elimination diet of IgG positive foods significantly decreased frequency of headache/migraine during the treatment as compared to baseline time period.

Conclusions: Certain foods, beverages, and ingredients within foods may trigger attacks of headache and/or migraine in susceptible individuals. Elimination diets can prevent headaches in subgroups of persons with headache disorders."

-Department of Internal Medicine & Department of Neurology, University of Cincinnati College of Medicine, Cincinnati, OH,
https://pubmed.ncbi.nlm.nih.gov/27699780/

The diet factor in pediatric and adolescent migraine

"Diet can play an important role in the precipitation of headaches in children and adolescents with migraine. The diet factor in pediatric migraine is frequently neglected in favor of preventive drug therapy. The list of foods, beverages, and additives that trigger migraine includes cheese,

chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer. Underage drinking is a significant potential cause of recurrent headache in today's adolescent patients. Tyramine, phenylethylamine, histamine, nitrites, and sulfites are involved in the mechanism of food intolerance headache. Immunoglobulin E-mediated food allergy is an infrequent cause. Dietary triggers affect phases of the migraine process by influencing release of serotonin and norepinephrine, causing vasoconstriction or vasodilatation, or by direct stimulation of trigeminal ganglia, brainstem, and cortical neuronal pathways. Treatment begins with a headache and diet diary and the selective avoidance of foods presumed to trigger attacks. A universal migraine diet with simultaneous elimination of all potential food triggers is generally not advised in practice. A well-balanced diet is encouraged, with avoidance of fasting or skipped meals."…

-Division of Neurology, Children's Memorial Hospital, Chicago, Illinois, USA.

https://pubmed.ncbi.nlm.nih.gov/12657413/

Diet and migraine

"Some foods in our diet can spark off migraine attacks in susceptible individuals. Some foods can bring an attack on through an allergic reaction. A certain number such as citrus fruits, tea, coffee, pork, chocolate, milk, nuts, vegetables and cola drinks have been cited as possible allergens associated with migraine. This mechanism has however been criticized: an improvement in symptoms by eliminating some food(s) from our diet does not necessarily mean an immunologically based allergic reaction. The high IgE incidence rate is not greater in such patients than in the population at large. Other allergic reactions unrelated to diet may also be associated with migraine attacks. On the other hand substances in food may be the cause of modifications in vascular tone and bring migraine on in those so prone. Among such substances are tyramine, phenylalanine, phenolic flavonoids, alcohol, food additives (sodium nitrate, monosodium glutamate, aspartame) and caffeine. Another recognized trigger for migraine is hypoglycemia. Such foods as chocolate, cheese, citrus fruits, bananas, nuts, 'cured' meats, dairy products, cereals, beans, hot dogs, pizza, food additives (sodium nitrate, monosodium glutamate in Chinese restaurant food, aspartame as a sweetener), coffee, tea, cola drinks, alcoholic drinks such as red wine, beer or whisky distilled in copper stills, all may bring on a migraine attack. For every patient we have to assess which foodstuffs are involved in the attack (not necessarily produced by consuming the product concerned) in order to try to avoid their consumptions as a means of prophylaxis for migraine."

-Neurology Service, Hospital General de Galicia Clinico Universitario, Santiago de Compostela.

https://pubmed.ncbi.nlm.nih.gov/8681169/

Foods and supplements in the management of migraine headaches

"Objective: Although a wide range of acute and preventative medications are now available for the treatment of migraine headaches, many patients will not have a significant improvement in the frequency and severity of their headaches unless lifestyle modifications are made. Also, given the myriad side effects of traditional prescription medications, there is an increasing demand for "natural" treatment like vitamins and supplements for common ailments such as headaches. Here, we discuss the role of food triggers in the management of migraines, and review the evidence for supplements in migraine treatment.

Methods: A review of the English language literature on preclinical and clinical studies of any type on food triggers, vitamins, supplements, and migraine headaches was conducted.

Results: A detailed nutritional history is helpful in identifying food triggers. Although the data surrounding the role of certain foods and substances in triggering headaches is controversial, certain subsets of patients may be sensitive to phenylethylamine, tyramine, aspartame, monosodium glutamate, nitrates, nitrites, alcohol, and caffeine. The available evidence for the efficacy of certain vitamins and supplements in preventing migraines supports the use of these agents in the migraine treatment.

Conclusions: The identification of food triggers, with the help of food diaries, is an inexpensive way to reduce migraine headaches. We also recommend the use of the following supplements in the preventative treatment of migraines, in decreasing order of preference: magnesium, Petasites hybridus, feverfew, coenzyme Q10, riboflavin, and alpha lipoic acid."

-The New York Headache Center, New York, NY
https://pubmed.ncbi.nlm.nih.gov/19454881/

Headaches

Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been ….

"The literature suggests that the medicinal use of cannabis may have a therapeutic role for a multitude of diseases, particularly chronic pain disorders including headache. Supporting literature suggests a role for medicinal cannabis and cannabinoids in several types of headache disorders including migraine and cluster headache, although it is primarily limited to case based,

anecdotal, or laboratory-based scientific research. Cannabis contains an extensive number of pharmacological and biochemical compounds, of which only a minority are understood, so many potential therapeutic uses likely remain undiscovered. Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms ofaction, and opiate pathways, suggesting potential synergistic or similar benefits. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for many new classes of medications. Despite the limited evidence and research suggesting a role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are lacking and necessary for confirmation and further evaluation."

-Department of Neurology, Headache Center, Cleveland Clinic Neurological Institute, Cleveland, OH, USA.
https://www.ncbi.nlm.nih.gov/pubmed/26015168

Diet-induced changes in n-3 and n-6 derived endocannabinoids and reductions in headache pain and psychological distress

"Omega-3 and omega-6 fatty acids are biosynthetic precursors to endocannabinoids with antinociceptive, anxiolytic, and neurogenic properties. We recently reported that targeted dietary manipulation—increasing omega-3 fatty acids while reducing omega-6 linoleic acid (the H3-L6 intervention)—reduced headache pain and psychological distress among chronic headache patients. It is not yet known whether these clinical improvements were due to changes in endocannabinoids and related mediators derived from omega-3 and omega-6 fatty acids." …

"Diet-induced changes in these endocannabinoid derivatives of omega-3 docosahexaenoic acid, but not omega-6 arachidonic acid, correlated with reductions in physical pain and psychological distress. These findings demonstrate that targeted dietary manipulation can alter endocannabinoids derived from omega-3 and omega-6 fatty acids in humans, and suggest that 2-docosahexaenoylglycerol and docosahexaenoylethanolamine could have physical and/or psychological pain modulating properties."

-Section on Nutritional Neurosciences, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

-Department of Physical Medicine and Rehabilitation, Program on Integrative Medicine, University of North Carolina, Chapel Hill, NC,USA

-Center for Drug Discovery and Departments of Chemistry and Chemical Biology and Pharmaceutical Sciences, Northeastern University, Boston, MA, USA

-Department of Neurology, Program on Integrative Medicine, University of North Carolina, Chapel Hill, USA

-Nutrition Research and Metabolism Core, North Carolina Translational Clinical Sciences Institute, University of North Carolina, Chapel Hill, USA

-Anesthesia Section, Department of Perioperative Medicine, Clinical Center, National Institutes of Health, Bethesda, MD, USA

-Nutrition Department, Clinical Center, National Institutes of Health (NIH), Bethesda, MD 20892, USA

-Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4522350/

See also Omega Ratio

Healing

Involvement of the endocannabinoid system in periodontal healing.

"Endocannabinoids including anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are important lipid mediators for immunosuppressive effects and for appropriate homeostasis via their G-protein-coupled cannabinoid (CB) receptors in mammalian organs and tissues, and may be involved in wound healing in some organs. The physiological roles of endocannabinoids in periodontal healing remain unknown. We observed upregulation of the expression of CB1/CB2 receptors localized on fibroblasts and macrophage-like cells in granulation tissue during wound healing in a wound-healing model in rats, as well as an increase in AEA levels in gingival crevicular fluid after periodontal surgery in human patients with periodontitis. In-vitro, the proliferation of human gingival fibroblasts (HGFs) by AEA was significantly attenuated by AM251 and AM630, which are selective antagonists of CB1 and CB2, respectively. CP55940 (CB1/CB2 agonist) induced phosphorylation of the extracellular-regulated kinases (ERK) 1/2, p38 mitogen-activated protein kinase (p38MAPK), and Akt in HGFs. Wound closure by CP55940 in an in-vitro scratch assay was significantly suppressed by inhibitors of MAP kinase kinase (MEK), p38MAPK, and phosphoinositol 3-kinase (PI3-K). These findings suggest that endocannabinoid system may have an important role in periodontal healing."

-Department of Periodontology, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima , Japan.

https://www.ncbi.nlm.nih.gov/pubmed/20233580

[Endocannabinoids as molecular instruments of health promotion].

"Endocannabinoids may be a physiological model for our self-healin capacities, since they are part of a complex system of natural auto-regulatory processes. This system has been examined

via neurobiology, where the experimental invertebrate model is useful. Endocannabinoids, as well as endogenous morphine, activate constitutive nitric oxide (NO) release, which exerts a variety of positive physiological effects. By doing so, we surmise endogenous stress reduction emerges. Therefore, in the context of endocannabinoid auto-regulation, it seems adequate to speak of "health promotion on a molecular level". The convergence of endogenous auto-regulation on NO pathways critically relies upon common or overlapping neurobiological molecular components, as they are represented by limbic reward and motivation mechanisms. To our knowledge, endogenous auto-regulation--involving deep limbic brain activities--plays a crucial role in successful modern strategies of applied and integrative health promotion. More research, however, is necessary before the different aspects of neurobiological science and clinical medicine in the field of prevention may be integrated extensively and with profound reason."

-Studiengang der Integrierenden Gesundheitsförderung, Hochschule für Angewandte Wissenschaften Coburg, Friedrich-Streib-Str. 2, Coburg.

https://www.ncbi.nlm.nih.gov/pubmed/17131686

■■■

…"Together, these results demonstrate that Ω-3+ LEs [Omega-3 enriched lipid emulsions] control key innate protective mechanism during the onset and resolution of acute inflammation and promote to tissue repair and regeneration."

-Department of Anesthesiology and Intensive Care Medicine, University Hospital Tübingen, Eberhard-Karls University, Tübingen, Germany

-Center for Proteomics and Metabolomics, Leiden University Medical Center (LUMC), Leiden, The Netherlands

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5762854/

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…"Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), lower blood triglyceride concentrations but likely exert additional atheroprotective properties at higher doses. Omega-3 fatty acids modulate T-cell differentiation and give rise to various prostaglandins and specialized proresolving lipid mediators that promote resolution of tissue injury and inflammation. "…

-From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (R.P.M., P.L., D.L.B.)

-Elucida Research LLC, Beverly, MA (R.P.M.).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7176343/

Arachidonic acid promotes skin wound healing through induction of human MSC migration by MT3-MMP-mediated fibronectin degradation

"Arachidonic acid (AA) is largely released during injury, but it has not been fully studied yet how AA modulates wound repair with stem cells. Therefore, we investigated skin wound-healing effect of AA-stimulated human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) in vivo and its molecular mechanism in vitro."…

" In conclusion, AA enhances skin wound healing through induction of hUCB-MSCs motility by MT3-MMP-mediated fibronectin degradation, which relies on GPR40-dependent mTORC2 signaling pathways."…

"Skin wound healing is a dynamic process that involves inflammation, re-epithelization, granulation, vascularization, and tissue remodeling, in which various types of cells migrate into the wound.[1] Many treatment modalities are applicable to improve skin recovery after injury including cytokines/growth factors and cell-based therapies."…

-Department of Veterinary Physiology, College of Veterinary Medicine, Research Institute for Veterinary Science, and PLUS Creative Veterinary Research Center, Seoul National University, Seoul, Korea

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4669694/

Health Condition Prevalence

Condition	Rank	Rank
Depression	6	1
Obesity	2	2
Arthritis	4	3
Back and neck pain	9	4
Anxiety	7	5
GERD	5	6
Allergy	1	7
Other cancers	19	8
Other chronic pain	17	9
Hypertension	3	10

Asthma	8
Migraine	10
Sleeping problem	11
Irritable bowel	12
Fatigue	13
Headache	14

"Prevalence of health conditions causing major USA health care costs. The 25 most prevalent conditions in a large occupational medicine study [67] are shown with the ten having the most annual cost ranked in order. The overall annual costs include expenses from medical, pharmacy, absenteeism, and presenteeism aspects."…

Omega-3 [n-3] nutrients play an important role in moderating the inherent propensity for arachidonic acid cascade overreactions when n-6 [omega-6 (Arachidonic Acid)] mediators dominate. The unintended consequences of eating foods that create such conditions can be prevented by combining knowledge about the explicit balance of n-3 and n-6 nutrients in each food item with knowledge of the dynamics of fatty acid metabolism and the different intensities of n-3 and n-6 eicosanoid actions. Tools are freely available for making informed food choices that can prevent serious health conditions caused by cascade overreactions.

- Professor Bill Lands (Professor of Biochemistry)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537720

Hearing Loss

…"Cannabinoids and their receptors are increasingly being studied because of their high potential for clinical use. As a hyperspecialized portion of the peripheral nervous system, study of the expression and function of cannabinoid receptors in the hearing organ is of high interest. Stria vascularis and inner hair cells express CB2 receptor, as well as neurites and cell bodies of the spiral ganglion. Cellular types such as supporting cells and outer hair cells, in which the expression of other types of functional receptors has been reported, do not significantly express CB2 receptors in this study. An up-regulation of CB2 gene expression was detected after an ototoxic event such as cisplatin treatment, probably due to pro-inflammatory events triggered by the drug. That fact suggests promising potential of CB2 receptor as a therapeutic target for new treatments to palliate cisplatin-induced hearing loss and other ototoxic events which triggers

inflammatory pathways."

-Ear Research Group, Universitary Hospital Puerta de Hierro Majadahonda- Health Research Institute Puerta de Hierro, Madrid, Spain

-Sequencing and Molecular Biology Unit, Universitary Hospital Puerta de Hierro Majadahonda, Health Research Institute Puerta de Hierro, Madrid, Spain

- Neuroimmunology Unit, Universitary Hospital Puerta de Hierro Majadahonda- Health Research Institute Puerta de Hierro, Madrid, Spain

-Confocal Microscopy Unit, Universitary Hospital Puerta de Hierro Majadahonda, Health Research Institute Puerta de Hierro, Madrid, Spain

-Department of Medical Oncology, Universitary Hospital Puerta de Hierro Majadahonda- Health Research Institute Puerta de Hierro, Madrid, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5001640/

Fish and fatty acid consumption and the risk of hearing loss in women

"Conclusion: Regular fish consumption and higher intake of long-chain omega-3 PUFAs are associated with lower risk of hearing loss in women."

-From the Channing Division of Network Medicine (SGC, MW, EBR, and GCC) and the Renal Division (GCC), Department of Medicine, Brigham and Women's Hospital, Boston, MA; Vanderbilt Bill Wilkerson Center for Otolaryngology and Communication Sciences, Vanderbilt University School of Medicine, Nashville, TN (RDE); and the Departments of Biostatistics (MW) and Epidemiology (MW, EBR, GCC), Harvard School of Public Health, Boston, MA.

corresponding authorCorresponding author.

-Supported by NIH [National Institute of Health] grants DC010811; and UM1 CA176726 and by grants from Vanderbilt University School of Medicine.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4196487/

Consumption of omega-3 fatty acids and fish and risk of age-related hearing loss

…"Dietary intervention with n-3 PUFAs could prevent or delay the development of age-related hearing loss."

-Centre for Vision Research, Department of Ophthalmology, and Westmead Millennium Institute, University of Sydney

https://pubmed.ncbi.nlm.nih.gov/20534742/

Heart Disease

"Several studies over the past 20 years have demonstrated that subjects on diets composed of

substances with high levels of n-3 [omega-3] polyunsaturated fatty acids (PUFAs) (e.g. fish) have a decreased incidence of heart disease. On this basis, a recent report from the Department of Health has advised UK consumers to decrease the proportion of saturated as opposed to unsaturated fats in their diet and to increase the ratio of n-3 to n-6 PUFAs. "…

-Reproduction and Development Group, Department of Veterinary Basic Sciences, Royal Veterinary College, London, UK.
https://pubmed.ncbi.nlm.nih.gov/10670689

■■■

"**Recent studies showed that a low ratio between the levels of eicosapentaenoic acid and those of arachidonic acid (EPA/AA) is associated with higher incidence of coronary artery disease and poor prognosis of heart failure, arrhythmia, and cardiac sudden death**. However, the clinical implications of EPA/AA in adult patients with congenital heart disease remain unclear. We aimed to assess the prognostic value of EPA/AA regarding cardiac events in adult patients with congenital heart disease. We measured the serum levels of eicosapentaenoic acid and arachidonic acid in 130 adult patients (median age, 31 years) stratified into two groups according to their EPA/AA (low, ≤0.22; high, >0.22). We prospectively analyzed the association between EPA/AA and incidence of cardiac events during a mean observation period of 15 months, expressed in terms of hazard ratio (HR) with 95% confidence interval (95% CI). In the subgroup of patients with biventricular circulation (2VC) (n = 76), we analyzed the same clinical endpoints. In our study population, EPA/AA was not associated with the incidence of arrhythmic events (HR, 1.52; 95% CI, 0.82-2.85; p = 0.19), **but low EPA/AA was a predictor of heart failure hospitalization** (HR, 2.83; 95% CI, 1.35-6.30; p < 0.01). Among patients with 2VC, an EPA/AA of ≤0.25 was associated with a significantly higher risk of arrhythmic events (HR, 2.55; 95% CI, 1.11-6.41; p = 0.03) and heart failure hospitalization (HR, 5.20; 95% CI, 1.78-18.1; p < 0.01). **EPA/AA represents a useful predictor of cardiac events in adult patients with congenital heart disease.**"

-Division of Adult Congenital Heart Disease Pathophysiology and Life-long Care, Department of Pediatric Cardiology, Tokyo Women's Medical University, 8-1 Kawadacho, Shinjukuku, Tokyo, Japan.
https://pubmed.ncbi.nlm.nih.gov/28681101

Heart Failure

"Recent studies showed that a low ratio between the levels of eicosapentaenoic acid [omega-3] and those of arachidonic acid [omega-6] (EPA/AA) is associated with higher incidence of coronary artery disease and poor prognosis of heart failure, arrhythmia, and cardiac sudden

death. "…

…"EPA/AA was not associated with the incidence of arrhythmic events (HR, 1.52; 95% CI, 0.82-2.85; p = 0.19), **but low EPA/AA** [ratio] [eicosapentaenoic acid (omega-3) / arachidonic acid (omega-6)] **was a predictor of heart failure hospitalization** (HR, 2.83; 95% CI, 1.35-6.30; p < 0.01)."…

-Division of Adult Congenital Heart Disease Pathophysiology and Life-long Care, Department of Pediatric Cardiology, Tokyo Women's Medical University, 8-1 Kawadacho, Shinjukuku, Tokyo, Japan.
https://pubmed.ncbi.nlm.nih.gov/28681101

Risk stratification by the "EPA+DHA level" and the "EPA/AA ratio" focus on anti-inflammatory and antiarrhythmogenic effects of long-chain omega-3 fatty acids

"The identification of risks associated with sudden cardiac death requires further investigations. The question was addressed whether parameters can be established which not only describe an increased risk for an enhanced electrical instability of the heart but also of inflammatory events underlying plaque rupture. Emphasis is placed on dose-dependent effects of the long-chain omega-(omega-)3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Since free acids of EPA and DHA are required for most of their biological effects, it appears essential not only to build up stores in the body for release of these fatty acids, but also to provide a sustained uptake of EPA and DHA in the form of ethyl esters. In contrast to rapidly absorbed triacylglycerols from fish, ethyl esters are taken up more slowly within 24 h. For the administration of 1 g/day highly purified EPA+DHA ethyl esters (Omacor) to healthy volunteers, it is shown that EPA is increased from 0.6% to 1.4% within 10 days, while DHA is increased from 2.9% to 4.3%. After withdrawal, EPA and DHA approach baseline values within 10 days. A gas chromatographic procedure was established which requires only 10 microl of whole blood for the identification of more than 35 fatty acids. Evidence is summarized strengthening the concept that a low "EPA+DHA level" presents a risk for sudden cardiac death and that the administration of 840 mg/day of EPA+DHA ethyl esters raises the "EPA+DHA level" to approximately 6% that is associated with a marked protection from sudden cardiac death. For reducing pro-inflammatory eicosanoids and cytokines, a higher "EPA+DHA level" is required which can be achieved with an intake of 2-4 g/day of 84% EPA+DHA ethyl esters. For assessing influences from pro-inflammatory eicosanoids and cytokines, the EPA/arachidonic acid ratio ("EPA/AA ratio") was identified as diagnostic parameter. To assess the dietary EPA+DHA intake, fatty acids were determined in fish dishes of the cafeteria of the Philipps University Hospital Marburg, Germany.

The EPA+DHA content of the popular Alaska Pollock was 125 +/- 70 mg/100 g. A once daily fish dish can thus not provide the 840 mg/day EPA+DHA administered in the GISSI Prevention Study in the form of ethyl ester which markedly reduced the risk of sudden cardiac death in postmyocardial infarction patients. Nonetheless, at least two preferably oily fish meals per week should be consumed as preventive measure by persons without coronary artery disease. With documented coronary heart disease, it was advised to consume approximately 1 g/day of EPA+DHA."

-Molecular Cardiology Laboratory, Department of Internal Medicine and Cardiology, Philipps University of Marburg, Marburg, Germany.

https://pubmed.ncbi.nlm.nih.gov/15580322/

Hepatic Encephalopathy (HE)

"Hepatic encephalopathy is a decline in brain function that occurs as a result of severe liver disease. In this condition, your liver can't adequately remove toxins from your blood. This causes a buildup of toxins in your bloodstream, which can lead to brain damage."

-Heathline

https://www.healthline.com/health/hepatic-encephalopathy-2

Curcumin prevents cognitive deficits in the bile duct ligated rats

…"These findings demonstrate the beneficial effect of curcumin on cognitive function in BDL rats of the HE model. The curcumin effect may be related to mitochondrial function improvement in the HE [Hepatic Encephalopathy]."

-Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

-Department of Biology, Faculty of Sciences, University of Zanjan, Zanjan, Iran.

-Department of Pharmacology School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

-Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran.

-Department of Neuroendocrinology, Endocrinology, and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran.

-Cognitive and Neuroscience Research Center (CNRC), Tehran Medical Sciences, Amir-Almomenin Hospital, Islamic Azad University, Tehran,

-Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

https://pubmed.ncbi.nlm.nih.gov/32761362/

Reducing Peripheral Inflammation with Infliximab Reduces Neuro-inflammation and Improves Cognition in Rats with Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome present in patients with liver disease with symptoms ranging from mild cognitive impairment to coma. Around 40% of patients with liver cirrhosis show minimal HE (MHE), with mild cognitive impairment, psychomotor slowing, and attention deficits (Weissenborn et al., 2005; Felipo et al., 2012a) which are not evident but can be unveiled using psychometric tests. MHE affects several million people around the world and impairs their quality of life and the ability to perform daily tasks (Leevy and Phillips, 2007; Bajaj, 2008; Felipo, 2013). Hyperammonemia and inflammation act synergistically to induce the neurological alterations in MHE and in HE. In cirrhotic patients, hyperammonemia impairs performance in psychometric tests during inflammation but not after its resolution (Shawcross et al., 2004). The serum levels of the pro-inflammatory cytokines IL-6 and IL-18 are higher in cirrhotic patients with MHE than in those without MHE and show a good correlation with the grade of cognitive impairment (Montoliu et al., 2009). The joint presence of certain levels of inflammation and hyperammonemia is enough to induce mild cognitive impairment, even in the absence of liver failure, as shown in a report analyzing neurological impairment in patients with different hepatic or dermatological diseases associated with different grades of inflammation and hyperammonemia (Felipo et al., 2012b).

The mechanisms leading to cognitive impairment in HE seem to involve induction of neuroinflammation which would alter neurotransmission resulting in reduced cognitive function.

Rats with porta-cava shunts (PCS), a main model of HE recommended by the International Society for Hepatic Encephalopathy (Butterworth et al., 2009), show impaired cognitive function and neuroinflammation (Cauli et al., 2007; Agusti et al., 2011). Reducing neuroinflammation with ibuprofen or with inhibitors of MAP kinase p38 improves cognitive function in rats with HE due to PCS (Cauli et al., 2007; Agusti et al., 2011).

An in vivo PET study in cirrhotic patients with HE show that they have increased binding in brain of [11C](R)-PK11195, a marker of neuroinflammation, correlating with the grade of cognitive impairment (Cagnin et al., 2006). This suggests that patients with HE also show neuroinflammation.

Hyperammonemia per se induces neuroinflammation (Rodrigo et al., 2010), but peripheral inflammation may also induce neuroinflammation (Biesmans et al., 2013; Murta et al., 2015). A main aim of this work was to assess whether peripheral inflammation contributes to neuroinflammation and cognitive impairment in rats with HE.

Neuroinflammation would impair cognitive function by altering neurotransmission. Spatial learning and memory are modulated by AMPA and NMDA receptors in hippocampus (Sanderson et al., 2008; Keifer and Zheng, 2010; Wiltgen et al., 2010). Membrane expression of AMPA and NMDA receptors in

hippocampus may be altered by neuroinflammation. Exposure to IL-1b reduces membrane expression of GluR1 subunit of AMPA receptors in hippocampal neurons and this seems to be mediated by NMDA receptors (Lai et al., 2006). TNF-a also alters AMPA receptors membrane expression in hippocampus (Ogoshi et al., 2005). These effects of IL-1b and TNF-a would result in altered neurotransmission which would lead to cognitive impairment.

An association between peripheral inflammation and mild cognitive impairment is also present in other diseases leading to chronic inflammation as diabetes, rheumatoid arthritis, obesity or chronic kidney disease (Umemura et al., 2011; Shin et al., 2013; da Matta et al., 2014; Díaz-Gerevini et al., 2014; Nguyen et al., 2014). To reduce peripheral inflammation patients with some of these diseases are being treated with compounds directed to inhibit TNF-a, which plays a pivotal role in the initiation and amplification of the inflammatory cascade (Cheng et al., 2014). In patients with sarcoidosis or rheumatoid arthritis, anti-TNF-a improves cognitive function (Elfferich et al., 2010; Raftery et al., 2012). Anti-TNF-a has been also suggested as a potential treatment against cognitive impairment in Alzheimers disease (Cheng et al., 2014)."...

-Neurobiology Laboratory, Príncipe Felipe Research Center, Valencia, Spain

-Valencian Institute of Pathology, Mixed Unit of Molecular Pathology, Prince Felipe Research Center / Catholic University of Valencia, Valencia, Spain

-Multiple Sclerosis and Neuroregeneration Mixed Unit, Neurology Service, Hospital la Fe Research Foundation, Valencia, Spain

-Laboratory of Comparative Neurobiology, Institut Cavanilles de Biodiversitat i Biologia-University of Valencia, Valencia, Spain

-Institute for Health Research-INCLIVA, Valencia, Spain

-Edited by: Detlev Boison, Legacy Health, USA

-Reviewed by: Munjal M. Acharya, University of California, Irvine School of Medicine,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5089983

"Treatment with infliximab reduces peripheral inflammation in PCS rats, normalizing prostaglandin E2, IL-17, IL-6, and IL-10 levels in serum. Infliximab also prevents neuroinflammation, reduces microglial activation, translocates NF-kB into nucleoli and normalizes TNF-a and IL-1b content in hippocampus."

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5089983/

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See also Prostaglandins which discusses the consequences of synthetically inhibiting prostaglandin's which can lead to prostaglandin deficiency.

Hepatocellular Carcinoma

“Hepatocellular carcinoma is a cancer that starts in your liver. It's different from "secondary" liver cancers, which have spread to the liver from other organs.”…

-WebMD

https://www.webmd.com/cancer/hepatocellular-carcinoma#1

■■■

“Chronic inflammation is a common theme in a variety of disease pathways, including autoimmune diseases. The pathways of chronic inflammation are well illustrated by nonalcoholic steatohepatitis (NASH), which is of a serious concern due to its increasing prevalence in the westernized world and its direct correlation with lifestyle factors, particularly diet. Importantly, NASH may ultimately lead to the development of hepatocellular carcinoma.”….

-Department of Diagnostic Pathology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan.

https://www.ncbi.nlm.nih.gov/pubmed/18178378

■■■

“Hepatocellular carcinoma (HCC) is linked to inflammation and immunosuppression. Chemerin is highly expressed in the liver and implicated in the regulation of inflammation. However, the role of chemerin in HCC remains unclear. In this study, we aimed to investigate whether chemerin is able to influence HCC progression by regulating tumor-associated inflammation. Here we demonstrated that chemerin significantly decreased in blood and tumor tissues of HCC patients, and tumor chemerin levels were inversely associated with the prognosis. In an orthotopic mouse model of HCC, Rarres2-/- mice exhibited aggressive tumor growth and lung metastasis, whereas chemerin overexpression greatly inhibited tumor growth. The tumor-inhibitory effect of chemerin was accompanied by a shift in tumor-infiltrating immune cells from myeloid-derived suppressive cells (MDSCs) to interferon-γ+T cells and decreased tumor angiogenesis. Furthermore, we demonstrated that the tumor-inhibitory effect of chemerin was partly dependent on T cells, as chemerin overexpression could inhibit tumor growth, albeit to a lesser extent, in Rag1-/- mice when compared with wild-type controls. Mechanistically, chemerin inhibited nuclear factor-κB activation and the expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-6) by tumor cells and tumor-associated endothelial cell, respectively, via its receptors, and consequently, MDSC induction was impaired, leading to restoration of antitumor T-cell response and decreased tumor angiogenesis. Clinically,

systemic and tumor levels of chemerin were found to inversely correlate with circulating concentrations of GM-CSF or IL-6 and tumor-infiltrating myeloid cells, respectively, in HCC patients. Moreover, neutralization of GM-CSF and IL-6 abrogated HCC progression and MDSC accumulation in Rarres2-/- mice. In conclusion, our study reveals the tumor-inhibitory effect of chemerin by suppressing inflammatory tumor microenvironment with therapeutic implications for inflammation-associated cancer-like HCC."

-Department of Immunology and Key Laboratory of Medical Molecular Virology of Ministries of Education and Health, School of Basic Medical Sciences, Shanghai, People's Republic of China.

-Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Department of Liver Surgery, Liver Cancer Institute, Zhongshan Hospital, Shanghai, People's Republic of China.

-Department of Immunology, Biotherapy Research Center, Fudan University, Shanghai, People's Republic of China.

https://pubmed.ncbi.nlm.nih.gov/28166197/

Hericium Erinaceus

See Lion's Mane (Hericium erinaceus)

Homeostasis

Also referred to as Homeostatic

Homeostasis as the Mechanism of Evolution

…"Homeostasis is defined as the property of a system in which variables are regulated so that internal conditions remain stable and relatively constant. Examples of homeostasis include the regulation of body temperature, and the balance between acidity and alkalinity. It is a process that maintains the stability of the organism's internal environment in response to fluctuations in external environmental conditions."…

-John S. Torday

-Harbor-UCLA Medical Center

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588151/#

Endocannabinoids in nervous system health and disease: the big picture in a nutshell

"The psychoactive component of the cannabis resin and flowers, delta9-tetrahydrocannabinol

(THC), was first isolated in 1964, and at least 70 other structurally related 'phytocannabinoid' compounds have since been identified. The serendipitous identification of a G-protein-coupled cannabinoid receptor at which THC is active in the brain heralded an explosion in cannabinoid research. Elements of the endocannabinoid system (ECS) comprise the cannabinoid receptors, a family of nascent lipid ligands, the 'endocannabinoids' and the machinery for their biosynthesis and metabolism. The function of the ECS is thus defined by modulation of these receptors, in particular, by two of the best-described ligands, 2-arachidonoyl glycerol and anandamide (arachidonylethanolamide). Research on the ECS has recently aroused enormous interest not only for the physiological functions, but also for the promising therapeutic potentials of drugs interfering with the activity of cannabinoid receptors. Many of the former relate to stress-recovery systems and to the maintenance of homeostatic balance. Among other functions, the ECS is involved in neuroprotection, modulation of nociception, regulation of motor activity, neurogenesis, synaptic plasticity and the control of certain phases of memory processing. In addition, the ECS acts to modulate the immune and inflammatory responses and to maintain a positive energy balance. This theme issue aims to provide the reader with an overview of ECS pharmacology, followed by discussions on the pivotal role of this system in the modulation of neurogenesis in the developing and adult organism, memory processes and synaptic plasticity, as well as in pathological pain and brain ageing. The volume will conclude with discussions that address the proposed therapeutic applications of targeting the ECS for the treatment of neurodegeneration, pain and mental illness."

-Department of Pharmaceutical Sciences, University of Padua, Italy
-Endocannabinoid Research Group, Institute of Biomolecular Chemistry, National Research Council, Naples, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481537/

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"The main pharmacological functions of the endocannabinoid system include neuromodulation, controlling motor functions, cognition, emotional responses, homeostasis and motivation. However, in the periphery, this system is an important modulator of autonomic nervous system, the immune system and microcirculation."…

"Thus, anandamide and 2-AG can be released from both neuronal and non-neuronal cells whenever the need arises, and they utilize analogous but distinct receptor-dependent pathways regulating the effects of primary messengers, such as neurotransmitters and hormones. In certain disorders such as multiple sclerosis, cancer, intestinal disorders, cardiovascular disorders, pain, Parkinson's disease and excitotoxicity, the tissue concentration of endocannabinoids,

cannabinoid receptor density and the cannabinoid receptor coupling efficiency increases resulting in the reduction of symptoms of these disorders. The endocannabinoid system has been shown to be involved in various physiological processes like lipogenesis, inflammation, food intake and nociception."….

-Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, United State
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044336

Homeostasis, Inflammation, and Disease Susceptibility

"While modernization has dramatically increased lifespan, it has also witnessed the increasing prevalence of diseases such as obesity, hypertension and type 2 diabetes. Such chronic, acquired diseases result when normal physiologic control goes awry and may thus be viewed as failures of homeostasis. However, while nearly every process in human physiology relies on homeostatic mechanisms for stability, only some have demonstrated vulnerability to dysregulation. Additionally, chronic inflammation is a common accomplice of the diseases of homeostasis, yet the basis for this connection is not fully understood. Here we review the design of homeostatic systems and discuss universal features of control circuits that operate at the cellular, tissue and organismal levels. We suggest a framework for classification of homeostatic signals that is based on different classes of homeostatic variables they report on. Finally, we discuss how adaptability of homeostatic systems with adjustable set points creates vulnerability to dysregulation and disease. This framework highlights the fundamental parallels between homeostatic and inflammatory control mechanisms and provides a new perspective on the physiological origin of inflammation."….

"These modern human diseases seem to have two features in common: they involve disruption of homeostasis and they are nearly universally associated with chronic inflammation. Despite this well-documented connection between inflammation and diseases of homeostasis, the underlying evolutionary and mechanistic bases remain obscure. In most complex diseases, in contrast to rare Mendelian diseases, the pathological state has a normal, physiological counterpart. The etiology of modern human diseases may therefore point to the physiological rationale connecting inflammation and homeostasis.

Most physiological processes can only operate under a narrow range of conditions, which are maintained by specialized homeostatic mechanisms in the face of variations in the environment, and adjusted in response to changes in functional demands and biological priorities. Interestingly, only some of these processes are vulnerable to dysregulation and disease. For example, lipid and glucose metabolism can be derailed, leading to dyslipidemia, diabetes and obesity, while amino

acid metabolism seems resistant to homeostatic dysregulation. Here we present a view that may help explain the differential susceptibility of physiological processes to diseases of homeostasis. We explore the fundamental connections between homeostasis and inflammation and discuss an evolutionary perspective on homeostatic diseases."…

Inflammation and homeostatic circuits

"Inflammation is a protective response to extreme challenges to homeostasis, such as infection, tissue stress, and injury. Inflammatory signals - including cytokines, chemokines, biogenic amines and eicosanoids, induce myriad changes in diverse biological processes, ranging from local vascular responses to alterations of body temperature. Despite this complexity and diversity of functions, all the activities of inflammatory signals can be described in terms of their effects on homeostatic circuits: First, inflammatory signals can directly stimulate or inhibit the flows of various homeostatic systems. For example, TNF and IL-1β activate lipolysis, inhibit gluconeogenesis and increase vascular permeability to fluids and solutes, while IL-6 changes hepatic protein synthesis (Medzhitov, 2008). Second, in addition to directly affecting the flows, inflammatory signals can change the sensitivity of the Plants to homeostatic signals. For example, TNF makes liver, fat and skeletal muscle less sensitive to insulin (Hotamisligil et al., 1993; Weisberg et al., 2003). Third, inflammatory signals can change the gain of the Controllers. For example TNF and IL-1β suppress expression of GLUT2 and glucokinase in pancreatic β-cells, thus making them less sensitive to the blood glucose level (Park et al., 1999). Consequently, β-cells produce less insulin given the same amount of plasma glucose – an example of gain tuning of the Controller. As discussed above, homeostatic signals also operate by directly regulating flows, by changing sensitivity of Plants to other homeostatic signals, and by gain-tuning of Controllers. Thus homeostatic and inflammatory signals employ identical methods to change the same homeostatic variables (Figure 5).

Importantly, the inflammatory mediators are both antagonistic to and dominant over homeostatic signals. They are antagonistic because normal homeostasis is often incompatible with the goals of the inflammatory response, and the former has to be temporarily disengaged. Inflammatory signals are dominant because they have higher physiological priority as they orchestrate the protective response to life threatening insults of infection and injury. Thus, homeostatic control of body temperature (thermogenesis or sweating) is normally induced by changes in ambient temperature. However, acute inflammation overrides this control by raising the set point of body temperature, thereby inducing thermogenesis and fever regardless of ambient temperature. Likewise, acute inflammation-induced anorexia suppresses caloric intake regardless of the adiposity, circulating nutrient concentrations, or body weight.

It is increasingly appreciated that chronic inflammation is an important component of numerous

disease states including obesity, type 2 diabetes, atherosclerosis, asthma, and neurodegenerative diseases. One potential mechanism by which inflammation may initiate or perpetuate disease is through set point changes. In obesity, for example, macrophages and other cells of the immune system infiltrate adipose tissue in response to the increased burden of lipid accumulation and adipocyte stress (Hotamisligil and Erbay, 2008; Weisberg et al., 2003). These cells produce inflammatory cytokines that are capable of shifting homeostatic set points in states of chronic inflammation, just as they do in acute inflammatory states. The rationale for transiently adjusting the insulin responsiveness in acute inflammation is presumed to be in shifting nutrient allocation from tissues that have lower priority during infection (adipose and skeletal muscle) towards the higher priority immune defenses (Hotamisligil and Erbay, 2008). In obesity, chronic inflammation may contribute to the shift of insulin sensitivity to an alternative set point.

Inflammation is a protective response that is engaged to defend and restore physiological functions when homeostatic mechanisms are insufficient. The inflammatory response can only achieve this goal by overriding or suppressing incompatible homeostatic controls. However, in its attempts to restore homeostasis, inflammation may enforce and propagate homeostatic set point changes that are detrimental and can result in chronic pathological states. This happens when a persistent change in the set point itself creates a problem sufficient to promote inflammation. For example, hyperglycemia can lead to glucose toxicity and tissue damage, which in turn can lead to secondary inflammation. Similarly, the abnormal accumulation of harmful lipid mediators (lipotoxicity) in adipocytes, liver, and muscle in obesity leads to cellular stress and tissue dysfunction, and consequently to inflammation (DeFronzo, 2010; Samuel and Shulman, 2012; Summers, 2006). Thus, a homeostatic perturbation initially induced by lipotoxicity may be further perpetuated by inflammation. In such scenarios, a vicious cycle can ensue that may explain the chronicity of some homeostatic diseases and their perpetuation by inflammation. Such a model is consistent with data demonstrating that inflammation is dispensable for the initial induction of insulin resistance, but contributes to maintaining and even worsening insulin resistance in states of chronic obesity (Oh et al., 2012).

Successful inflammatory response is followed by the resolution phase that restores homeostasis. However, because inflammation is induced by loss of homeostasis, but also intentionally disrupts incompatible homeostatic processes, the system has the potential to become locked in a state of a chronic inflammation that fails to resolve. The non-resolving inflammation may, in turn, account for the persistence of chronic diseases (Nathan and Ding, 2010; Serhan et al., 2007). It is therefore important to identify the mechanisms responsible for physiological shifts between alternative stable states of the homeostatic systems, as the same mechanisms could be employed therapeutically to reverse pathological states in chronic diseases of homeostasis."

-Department of Immunobiology, Yale University School of Medicine, New Haven, CT USA
-Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4369762/

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"The endocannabinoid system is involved in a host of homeostatic and physiologic functions, including modulation of pain and inflammation. "…

-Professor of Anesthesiology, Pain Research and Management Centers, Department of Anesthesiology, School of Medicine, University of Utah, Salt Lake City, Utah, USA
-Chief Executive Officer, ISA Scientific, Draper, Utah, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3820295/

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"The endocannabinoid system (ECS) has lately been proven to be an important, multifaceted homeostatic regulator, which influences a wide-variety of physiological processes all over the body."…

-Department of Physiology, Faculty of Medicine, University of Debrecen, Hungary
-Department of Immunology, Faculty of Medicine, University of Debrecen, Hungary
-HCEMM Nonprofit Ltd., Hungary
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429381/

Lipid homeostasis and regulated cell death

"Modern lipidomics analysis paints a dynamic picture of membrane organizations, as changing and adapting lipid assemblies that play an active role in cellular function. This article highlights how the lipid composition of membranes determines specific organelle functions, how homeostatic mechanisms maintain these functions by regulating physical properties of membranes, and how cells disrupt lipid homeostasis to bring about regulated cell death (RCD). These are broad phenomena, and representative examples are reviewed here. In particular, the mechanisms of ferroptosis – a form of RCD brought about by lipid peroxidation – are highlighted, demonstrating how lipid metabolism drives cells' lipid composition towards states of increased sensitivity to lipid oxidation. An understanding of these interactions has begun to give rise to lipid-based therapies. This article reviews current successes of such therapies, and suggests directions for future developments."…

"Lipidomics analyses have transformed our understanding of cell membranes, from the more

static conceptualization of the fluid mosaic model [1], to a more complex conceptualization in which different stable and transient microdomains coexist in the same membrane [2–4]. Compositions are continuously remodeled through regulatory metabolic processes, and networks of lipid sensors and pipelines traffic membranes between organelles. Organelle membrane compositions are fine-tuned by homeostatic mechanisms to fit their required function, whether acting as barriers, regulating permeation, facilitating signal transduction, trafficking membranes, or storing energy. These in turn contribute to cellular viability by maintaining properties such as ionic and redox homeostasis, and protein function.

In turn, membranes are increasingly recognized as parts of complex mechanisms that regulate growth, development, and cellular homeostasis – mechanisms that, when altered, can lead to membrane degradation, cellular dysfunction, and ultimately cell death. By understanding lipid organization and dynamics more completely, we gain a deeper appreciation for lipids' role in in cell biology and in disease. With this knowledge, researchers have come to control cellular dysfunction with new types of lipid-based therapies that target organelles based on their lipid compositions. This article outlines these developments."

-Department of Biological Sciences, Columbia University, New York, NY
-Department of Chemistry, Columbia University, New York, NY
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5581689/#R37

Host-versus-Graft Disease (HvGD)

"Immune cells have been shown to express cannabinoid receptors and to produce endogenous ligands. Moreover, activation of cannabinoid receptors on immune cells has been shown to trigger potent immunosuppression. Despite such studies, the role of cannabinoids in transplantation, specifically to prevent allograft rejection, has not, to our knowledge, been investigated previously. In the current study, we tested the effect of THC on the suppression of HvGD as well as rejection of skin allografts. To this end, we studied HvGD by injecting H-2k splenocytes into H-2b mice and analyzing the immune response in the draining ingLNs. THC treatment significantly reduced T cell proliferation and activation in draining LNs of the recipient mice and decreased early stage rejection-indicator cytokines, including IL-2 and IFN-γ. THC treatment also increased the allogeneic skin graft survival. THC treatment in HvGD mice led to induction of MDSCs. Using MDSC depletion studies as well as adoptive transfer experiments, we found that THC-induced MDSCs were necessary for attenuation of HvGD. Additionally, using pharmacological inhibitors of CB1 and CB2 receptors and CB1 and CB2 knockout mice, we found that THC was working preferentially through CB1. Together, our research shows, for the first

time to our knowledge, that targeting cannabinoid receptors may provide a novel treatment modality to attenuate HvGD and prevent allograft rejection."

-Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, Columbia, South Carolina, USA;
-William Jennings Bryan Dorn Veterans Affairs Medical Center, Columbia, South Carolina, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4541500/

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"Nuclear warfare at the end of World War II inspired Dick W. van Bekkum to study total-body irradiation (TBI) in animal models. After high-dose TBI, mice died from "primary disease" or bone marrow (BM) aplasia. Intravenous administration of allogeneic BM cells delayed mortality but did not prevent it. Initially the delayed deaths were said to be caused by "secondary disease," which was later renamed graft-versus-host disease (GvHD). GvHD is caused by donor T lymphocytes that destroy recipient cells in skin, intestinal mucosa, bile ducts, and lymph nodes. GvHD is opposed by host-versus-graft disease (HvGD), in which host T lymphocytes destroy the administered allogeneic BM cells, including the administered T lymphocytes of the BM donor. In 1960, van Bekkum became the director of the Radiobiological Institute of the Dutch Organization for Applied Scientific Research TNO, Rijswijk, The Netherlands, where he built a multidisciplinary team that defined the variables controlling the outcome of a BM transplant. The team published their early results in the Journal of Experimental Hematology [1981;9:904-916 and 1956;4:482-488]. Later, protocols were established for BM transplantation (BMT) in patients with severe combined immunodeficiency disease, leukemia, lymphoma, and other diseases of the hematopoietic system. This review honors the scientific contributions made by Dick van Bekkum and his team in defining the four dominant variables for improving the therapeutic ratio of allogeneic BMT and in fostering the international collaboration necessary to translate this knowledge into current clinical practice."

https://www.ncbi.nlm.nih.gov/pubmed/27235758

Human Disease

"The modern Western diet (MWD) has dramatically changed the nutritional content of ingested foods in developed countries, and given the rapid nature of these nutritional transitions, mal-adaptations and related human diseases are a likely outcome of our current nutritional environment [1,2]. For example, up to 72% of dietary calories consumed presently in the MWD did

not exist in hunter-gatherer diets [3]. Changes in food type (quality) and quantity in the MWD have been largely driven by technological changes in food production and processing to provide high-calorie and appealing food (high in sugars, refined grains and oils) to large urban populations [1,4]. These have led to detrimental shifts in nutrient metabolism leading to gene-diet interactions responsible for more obesity and localized and systemic inflammation [2]. In turn, this inflammation contributes to the pathogenesis of a variety of disease states, including cardiovascular disease, diabetes and insulin resistance, cancer, autoimmunity, hypersensitivity disorders such as asthma and allergies, chronic joint disease, skin and digestive disorders, dementia and Alzheimer's disease [5,6,7,8,9,10,11,12,13,14]. As challenging as these changes are for overall populations of developed countries such as the US, they are more negative for certain populations and ethnic groups [15,16,17,18,19,20], in whom a disproportionate burden of preventable disease, death, and disability now exists. However, the emergence of the field of precision nutrition that factors in individual- and population-based genetic variability in the context of human diets offers the promise to provide more specific and individualized dietary and supplement interventions that may prevent and mitigate many of the pro-inflammatory effects of the MWD [21].

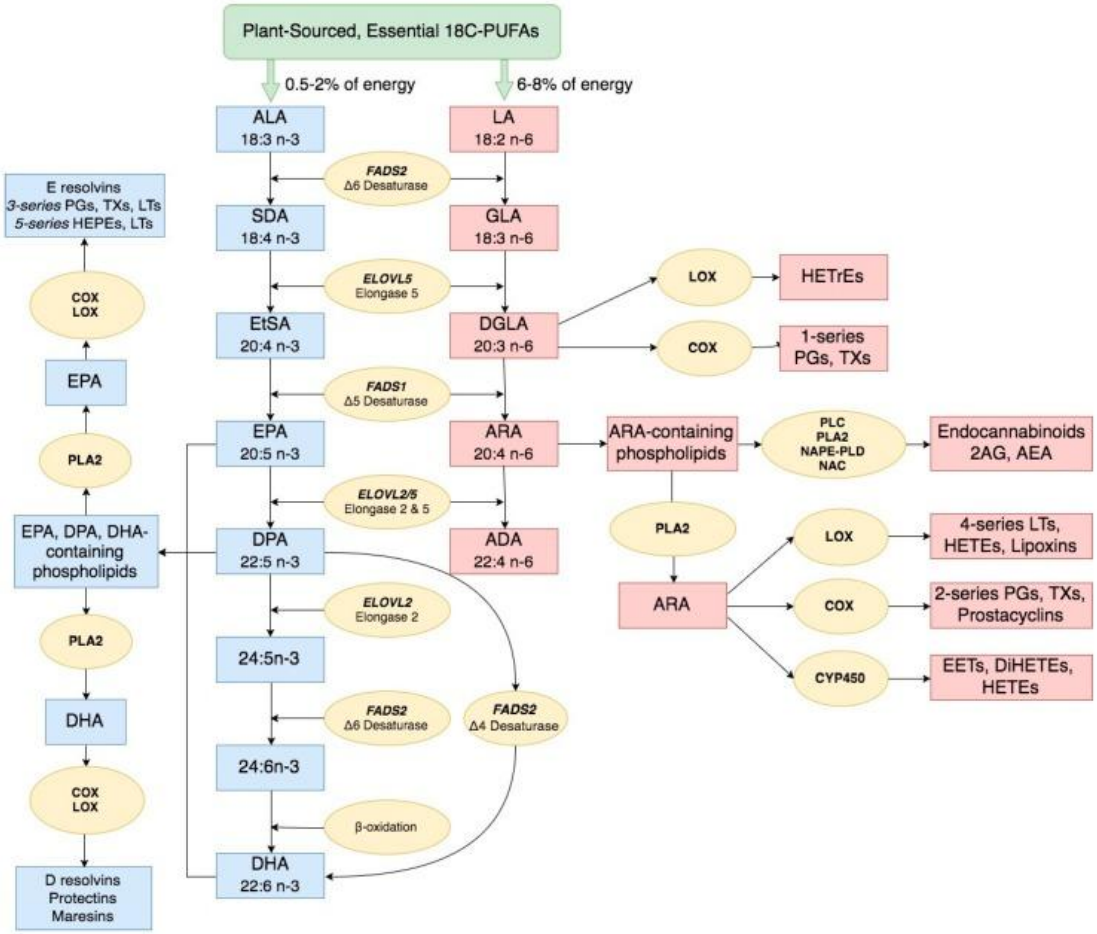
With regard to fatty acid (FA) intake, there has been marked shift (due largely to recommendations from health agencies) to reduce levels of saturated fatty acids and replace them with polyunsaturated fatty acids (PUFAs) in an attempt to lower serum total cholesterol and LDL lipoproteins [22,23]. From a practical perspective, this meant a replacement of sources of saturated fat such as lard and butter with PUFA-containing vegetable oils (soybean, corn, and canola oils, as well as margarine and shortenings), which are rich in the 18 carbon (18C) omega-6 (n-6) PUFA linoleic acid (18:2n-6, LA) and poor in both the omega-3 (n-3) 18C-PUFA, α-linolenic acid (18:3n-3, ALA) and monounsaturated fatty acids. In fact, it has been estimated that soybean oil consumption alone (which contains 58 g LA/100 g oil) increased >1000-fold from 1909 to 1999 and now contributes to ~7% of daily energy of the MWD [1]. Over time, this progressive increase in the ingestion of vegetable oils has led to a 3-fold increase (to 6–8% energy) in dietary LA content of the MWD [1,3,24,25,26], as well as an estimated 40% reduction in total n-3 long chain (≥20 carbon; LC-) PUFA levels, and a large shift in the ratio of dietary n-6/n-3 C18 PUFAs consumed from ~5:1 to >10:1 [1,27].

The objectives of this review are first to point out how lifestyle variables and specifically our current dietary PUFA exposure together with ancestral-based genetic variation in the LC-PUFA biosynthetic pathway gives rise to distinct molecular profiles (levels of LC-PUFAs, LC-PUFA metabolites, inflammatory and other disease biomarkers) that enhance disease risk for certain individuals and populations. These gene-diet interactions may be particularly important to health

in western countries as dietary n-6 and n-3 18C PUFAs comprise almost 10% of daily calories in the MWD. The second objective of the review is to describe how an understanding of PUFA-based gene-diet interactions can provide a scientific basis for the development of specific dietary and supplement strategies with n-3 LC-PUFAs to prevent and manage human diseases."

Long Chain Polyunsaturated Fatty Acid Biosynthesis and Biological Activities

"From the work of George and Mildred Burr almost 100 years ago [28,29], which was extended by the studies of Ralph Holman [30,31], it became clear that n-3 and n-6 18C-PUFAs were essential for human health. Furthermore, these 18C-PUFAs originated from the diet and were not synthesized from acetyl and malonyl CoA ester condensations catalyzed by fatty acid synthase. The two essential dietary PUFAs of shortest (18C) chain length, ALA and LA, are the key substrates that enter the biosynthetic pathways leading to biologically-active n-3 and n-6 LC-PUFAs, respectively. Figure 1 highlights the LC-PUFA biosynthetic pathway and genes known to encode for enzymes that play key roles in the two parallel and competing pathways that synthesize n-3 and n-6 LC-PUFAs. Two desaturation enzymes encoded by fatty acid desaturase 1 and 2 (FADS1 and FADS2) and one elongation enzyme encoded by ELOVL5 synthesize eicosapentaenoic acid (20:5n-3, EPA) and arachidonic acid (20:4n-6, ARA) from ALA and LA, respectively [32,33,34,35,36]. The n-3 LC-PUFA, docosapentaenoic acid (22:5n-3; DPA) and the n-6 LC-PUFA, adrenic acid (22:4n-6; ADA) can be generated from EPA and ARA, respectively, using an additional elongation enzyme (encoded by ELVOL 5/2), and finally docosahexaenoic acid (22:6n-3; DHA) can be produced from DPA with a Δ-4 desaturation enzyme also encoded by FADS2 [37]. EPA may also be converted to DHA utilizing three additional biosynthetic steps (2 elongation, 1 desaturation and 1 β-oxidation). Smaller quantities of LC-PUFAs can be obtained directly from the diet. For example, preformed ARA is found in organ meats, eggs, poultry, and fish, and various types of seafood such as cold-water fish are rich in preformed n-3 LC-PUFAs, EPA, DPA and DHA [26]." Figure 1



"Once formed, LC-PUFAs have many roles as free fatty acids and esterified in complex lipids (Figure 1). These include biophysical properties essential for proper plasma membrane function, energy production by β-oxidation and specific biochemical roles as precursors of bioactive lipids [38,39]. For example, in the central nervous system, the n-3 LC-PUFA DHA is the most abundant FA in complex lipids constituting approximately 50% of the weight of neuronal plasma membranes. Its membrane status and signaling capacity directly impact brain development and function via several mechanisms, including maintaining membrane integrity, neurotransmission, neurogenesis, membrane receptor function and signal transduction [38,40,41,42,43,44].

Importantly, both n-6 and n-3 LC-PUFAs are also converted to a diverse family of metabolites including multiple forms of prostaglandins, thromboxanes, hydroxyeicosatetraenoic acids, epoxyeicosatrienoic acids, leukotrienes, lipoxins, resolvins, protectins, maresins and endocannabinoids (Figure 1) [45,46,47,48,49,50,51,52]. LC-PUFAs and their metabolites, along with their cellular receptors, are present in practically all cells and tissues of the body and act as potent signaling molecules that impact a wide range of physiologic and pathophysiologic processes

[45,46,47,48,49,50,51,52].

Most evidence to date indicates that n-6 and n-3 LC-PUFAs and their metabolic products have not only different, but often opposing effects on immunity and inflammation [53,54,55,56,57]. In general, n-6 LC-PUFA metabolites and particularly ARA act as local hormones to promote acute and chronic inflammation [46,51,52]. In contrast to ARA, n-3 LC-PUFAs, such as EPA, DPA, and DHA, can be metabolized to anti-inflammatory mediators that have "pro-resolution" properties [47,58]. An exception to this principle are the ARA-derived lipoxins that exert anti-inflammatory, pro-resolution bioactions [59].

Over the past 20 years, one of the most fascinating areas of science has been the discovery of the pleiotropic effects of the endocannabinoid system [60,61,62]. Endocannabinoids have been shown to be complex lipids (such as 2-arachidonoyl glycerol and arachidonyl ethanolamide) derived from the n-6 LC-PUFA, ARA [60,61,62]. More recent studies have demonstrated that n-3 LC-PUFA derivatives of endocannabinoids also exist [63,64,65]. Endocannabinoid action via cannabinoid 1 and 2 receptors impacts a wide range of biological functions including energy balance and metabolism, mood, memory, sleep, reproduction, thermoregulation and immune function [63,64,65,66,67,68,69,70,71,72,73,74,75]. Endocannabinoids can also be metabolized by cyclooxygenases, lipoygenases, and p450 epoxygenases to form other biologically-active complex lipids [65,76,77].

It is clear from the aforementioned studies that n-6 and n-3 LC-PUFAs and their metabolites have structural and/or signaling roles throughout the human body (Figure 1). Additionally, maintaining a proper balance of n-6 and n-3 LC-PUFAs and their metabolites is critical to homeostasis in virtually every physiologic system. Consequently, environmental and genetic mechanisms that influence their levels and balance will impact human health and disease."…

-Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, USA
-Department of Urology, Wake Forest School of Medicine, Winston-Salem, USA;
-Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, USA;
-Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, NC, USA;
-GeneSTAR Research Program, General Internal Medicine, Johns Hopkins University School of Medicine, USA;
-Department of Internal Medicine, Section on Molecular Medicine, Wake Forest School of Medicine, Winston-Salem, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707637/

Human Immunodeficiency Virus (HIV)

“A CD4 count is a blood test to check the amount of CD4 cells in the body. CD4 cells are a type of white blood cell (WBC). They play a key role in the immune system. They alert other immune cells to the presence of infections such as bacteria and other viruses in the body. CD4 cells are also a subset of immune cells called T cells.

When a person is living with HIV, the virus attacks the CD4 cells in their blood. This process damages CD4 cells and causes the number of them in the body to drop, making it difficult to fight infections.

CD4 counts show the robustness of the immune system. A healthy immune system normally has a CD4 count ranging from 500 to 1,600 cells per cubic millimeter of blood (cells/mm3), according to HIV.gov. When a CD4 count is lower than 200 cell/mm3, a person will receive a diagnosis of AIDS.

When a CD4 count is lower than 200 cell/mm3, a person will receive a diagnosis of AIDS. AIDS occurs in stage 3 of HIV. At this stage, the body’s immune system is weak due to the low number of CD4 cells available to fight disease.”

-Healthline
https://www.healthline.com/health/hiv-aids/cd4-viral-count

“Well, the the war on AIDS this year as a result of pressure from President Clinton, is now costing the US taxpayer just through the federal government alone, $7 billion, that's a lot of money. And it's a lot of power. That money is being spent through four or five federal agencies primarily, or maybe six federal agencies. And the research money is coming mostly through the National Institutes of Health, and the Centers for Disease Control, and a couple of other agencies. And this money has bought scientists, scientists do not necessarily search for truth anymore. In fact, mostly, scientists will research and come to whatever conclusions they can get grant for and money. And in 1984, it was declared by the federal government at a press conference that aids the AIDS epidemic and the AIDS disease was caused by a particular virus that we now call HIV that was announced at a press conference by a scientist who then that afternoon, got the patent on the virus and on the test for the virus and has become very wealthy since that time selling the test for the virus. But there had been no scientific studies at that point that showed that this virus was the cause of AIDS. And indeed, we're saying that since then, no studies have ever emerged to show that HIV is actually the cause of AIDS and other words that are now there's no good reason to believe that we found the wrong cause of AIDS and that the $7 billion spent this year in the war on AIDS. The $30 billion spent up to this date on the war on AIDS, which is all being spent to study this virus is a barking up the wrong tree. It's it's actually a wild goose chase.

Designed for political reasons to chase this virus when in fact something else causes AIDS."

Alcohol dependence and CD4 cell count: is there a relationship?

"Alcohol and other drugs use seem to be common among people infected with HIV on antiretroviral treatment (ART). Their effects on HIV progression is still in debate. This study aimed to assess the association between alcohol and drug use and an HIV disease progression biomarker (CD4 cell count) among patients on ART."…."Alcohol dependents were nine times ($p < 0.01$) more likely to have CD4 cell count ≤200/mm(3), and this association was independent of ART adherence. In conclusion, alcohol dependence seems to be associated with low CD4 cell count in HIV-positive patients. **Based on these data, HIV health care workers should always assess alcohol consumption in the treatment setting, and patients should be advised that alcohol dependence may be linked to low CD4**."

-Department of Psychiatry, Medical School , University of São Paulo , São Paulo , Brazil.
https://pubmed.ncbi.nlm.nih.gov/25179410

Cannabinoids and inflammation: implications for people living with HIV

"Thanks to the success of modern antiretroviral therapy (ART), people living with HIV (PLWH) have life expectancies which approach that of persons in the general population. However, despite the ability of ART to suppress viral replication, PLWH have high levels of chronic systemic inflammation which drives the development of comorbidities such as cardiovascular disease, diabetes and non-AIDS associated malignancies. Historically, cannabis has played an important role in alleviating many symptoms experienced by persons with advanced HIV infection in the pre-ART era and continues to be used by many PLWH in the ART era, though for different reasons. Δ-Tetrahydrocannabinol (Δ-THC) and cannabidiol (CBD) are the phytocannabinoids, which have received most attention for their medicinal properties. Due to their ability to suppress lymphocyte proliferation and inflammatory cytokine production, there is interest in examining their therapeutic potential as immunomodulators. CB2 receptor activation has been shown in vitro to reduce CD4 T-cell infection by CXCR4-tropic HIV and to reduce HIV replication. Studies involving SIV-infected macaques have shown that Δ-THC can reduce morbidity and mortality and has favourable effects on gut mucosal immunity. Furthermore, ΔTHC administration was associated with reduced lymph node fibrosis and diminished levels of SIV proviral DNA in spleens of rhesus macaques compared with placebo-treated macaques. In

humans, cannabis use does not induce a reduction in peripheral CD4 T-cell count or loss of HIV virological control in cross-sectional studies. Rather, cannabis use in ART-treated PLWH was associated with decreased levels of T-cell activation, inflammatory monocytes and pro-inflammatory cytokine secretion, all of which are related to HIV disease progression and comorbidities. Randomized clinical trials should provide further insights into the ability of cannabis and cannabinoid-based medicines to attenuate HIV-associated inflammation. In turn, these findings may provide a novel means to reduce morbidity and mortality in PLWH as adjunctive agents to ART."

-Chronic Viral Illness Service, Division of Infectious Diseases, Department of Medicine, McGill University Health Centre, Montreal

-Infectious Diseases and Immunity in Global Health Program, Research Institute of McGill University Health Centre

-McGill Research Centre for Cannabis and the Mark Wainberg Centre for Viral Diseases
-Department of Microbiology and Immunology, McGill University
-Department of Biological Sciences, University of Quebec at Montreal (UQAM)
-Department of Microbiology, Infectiology and Immunology, Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada.
https://pubmed.ncbi.nlm.nih.gov/31764093

■■■

"Things other than the HIV virus can affect how high or low your CD4 count is, too. An infection like the flu, pneumonia, or a herpes simplex virus (including cold sores) can make your CD4 count go down for a while. Your CD4 count will go way down when you're getting chemotherapy for cancer.

To get the most accurate and helpful results for your CD4 count, try to:

- Use the same lab each time..
- Wait for at least 2 weeks after you've been sick or gotten a shot before you get a test."

-WebMD
https://www.webmd.com/hiv-aids/qa/what-else-can-affect-your-cd4-count

■■■

…"After receiving chemotherapy, radiotherapy or both, people with a baseline CD4 count above 500 cells/mm3 experienced a steep decrease of 203 cells/mm3 soon after treatment. Among those with fewer than 350 cells/mm3 at baseline, the decrease was smaller at 45 cell/mm3. A similar drop was not seen among those who received surgery, other modalities or no cancer treatment."…

-Liz Highleyman
https://www.aidsmap.com/news/dec-2019/cancer-treatment-can-suppress-immune-function-people-hiv

Injecting drug use is associated with a more rapid CD4 cell decline among treatment naïve HIV-positive patients in Indonesia

"Among 284 HIV-positive ART naïve patients, the majority were male (56%) with a history of IDU (79% among men). People with a history of IDU had a statistically significant faster decline in CD4 cells ($p<0.001$). Based on our data, patients with a history of IDU would have an average 33% decline in CD4 cells after one year without ART, compared with a 22% decline among non-users. At two years, the decline would average 66 and 40%, respectively. No other factor was significantly associated with CD4 cell decline.

Conclusions

We show that a history of IDU is associated with a more rapid CD4 cell natural decline among HIV-positive individuals in Indonesia. These findings have implications for monitoring ART naïve patients with a history of IDU and for starting ART in this group."

-Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
-Department of Internal Medicine, Medical Faculty, Universitas Padjadjaran and Hasan Sadikin Hospital, Bandung, Indonesia
-Department of Psychiatry Medical Faculty, Universitas Padjadjaran and Hasan Sadikin Hospital, Bandung, Indonesia
-Department of Internal Medicine, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880941

■■■

…"Drug use has shown to associate with increased inflammation [21, 22]. HIV infected drug users experience neurocognitive dysfunction mediated by increased systemic and local inflammation, as well as accelerated HIV disease progression [23-27]. Morphine, cocaine, methamphetamine, heroin, and amphetamine are the most frequently abused illicit drugs; and illicit drug use is associated with increased rate of HIV infection, comorbidities, HIV transcription and replication, immune dysfunction, and disease progression compared to HIV+ non-drug users [28-31]. Drug use/abuse has been shown to associate with low CD4+ T cell counts in HIV-infected patients, most likely due to loss of adherent to ART treatment and uncontrolled viremia [32, 33]. The link of drug use/abuse to CD4+ T cell reconstitution in the setting of long-term viral suppression on ART treatment is unknown."....

"Thus, our results suggest that drug use may play a role in blunted immune restoration in virologically suppressed patients with HIV infection."

-Department of Microbiology and Immunology, Medical University of South Carolina, Charleston, USA
-Divison of Infectious Diseases, Department of Medicine, Medical University of South Carolina, Charleston, USA
-Department of Population and Quantitative Health Science, Case Western Reserve University, Cleveland, OH
-Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, USA
-Department of Microbiology and Immunology, Tulane University School of Medicine, New Orleans, LA; Tulane National Primate Research Center, New Orleans, LA
-Division of Infectious Diseases, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA,
-Ralph H. Johnson VA Medical Center, Charleston, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6115301

Heroin Abuse and/or HIV Infection Dysregulate Plasma Exosomal miRNAs

"Exosomes play an important role in cell-to-cell communication as they can transfer functional molecules such as microRNAs (miRNAs) from one cell to another, exerting biological and immunological functions. Here, we investigated the impact of HIV infection and/or heroin use on the expression of the miRNAs in plasma exosomes. We found that HIV infection or heroin use upregulated the majority (98%) of a panel of plasma exosomal miRNAs associated with immune regulation and inflammation. We also observed the enhanced effect of HIV infection and heroin use on some of these upregulated miRNAs. Our further investigation showed that the levels of four of neuro-inflammation-related miRNAs (146a, 126, 21, and let-7a) were higher in HIV-infected heroin users as compared with the control subjects. These findings indicate that the dysregulations of the plasma exosomal miRNAs support further studies to determine the role of the miRNAs in HIV and/or heroin use-mediated immune modulation and neuro-inflammation."

"HIV infection is common among injecting drug users (IDUs), as a result of collective use of contaminated needle (Moore et al., 2004; Mathers et al., 2008). In the United States, 9% (3425 cases) of HIV-infected individuals (39,782 cases) were attributed to IDUs (https://www.cdc.gov/hiv/group/hiv-idu.html). In a nationwide retrospective cohort study in China (1989–2016), the injecting drug use (IDU) route of HIV infection was 70.7 % among HIV long term non progressors (LTNP) compared to only 37.1 % of non LTNP. Injection of opioid use contributes significantly to HIV transmission among drug users (Degenhardt et al., 2017; Chen et al., 2018; Paquette and Pollini, 2018; Christensen et al., 2019; Singh et al., 2019; Su et al., 2019). Although the role of opiate in promoting HIV disease progression remains to be determined, overwhelming evidence supports the notion that use of heroin or other opiate-derived substances impairs host immune system and induces inflammation (Alcabes and Friedland, 1995; Zhang et al., 2006; Wang et al., 2008; Dennis et al., 2014; Chan et al., 2015; Piepenbrink et al., 2016). Chronic inflammation is an indicator of HIV disease progression and comorbidities (Bosinger et al., 2011).

Although much of studies have been focused on protein regulators in immune modulation and inflammation (Dickens et al., 2017), the recent investigations have shown that certain miRNAs participate in regulation of immune activation and inflammation (Lee et al., 2016; Huang et al., 2017; Jin et al., 2017). miRNAs have an important role in regulating gene expression in the immune systems (Contreras and Rao, 2012). Several laboratories have documented that the LPS treatment of immune cells could induce the expression of a number of miRNAs (miRNA-146a, −132, −155, −21, −27b, −9 and −147 (Taganov et al., 2006a; Bazzoni et al., 2009; Liu et al., 2009; Sheedy et al., 2010; Sheedy, 2015). These miRNAs are implicated in inflammation and neurotoxicity."…

-Department of Pathology and Laboratory Medicine, Temple University Lewis Katz School of Medicine, Philadelphia, PA, USA

-Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, Nanning, China

-Guangxi Key Laboratory of AIDS Prevention and Treatment School of Public Health, Guangxi Medical University, Nanning, China

-Wuhan Centers for Disease Prevention & Control, Wuhan, China

https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7286798/

Huntington's Disease

The endocannabinoid system as a target for the treatment of neurodegenerative disease

"One of the first detectable signs of cellular dysfunction in human HD brains is the loss of CB1 from GABAergic efferent terminals and somata. In HD patients with early symptoms but without gross neuropathology (Grade zero (Vonsattel et al., 1985)), there is a significant decrease in CB1 density in the internal and external globus pallidus and substantia nigra (Glass et al., 2000). While CB1 loss in the external segment of the globus pallidus is likely due to the degeneration of the terminals of the GABA/enkephalin efferents lost first in HD (Reiner et al., 1988), in the internal segment significant CB1 loss is seen prior to changes in co-localized receptors or GABA/substance P neuronal pathology (Glass et al., 2000; Allen et al., 2009). Contrary to findings with CB1, CB2 has recently been demonstrated to be up-regulated in post-mortem HD striatum (Palazuelos et al., 2009), consistent with marked gliosis in this region.

Recently, it was reported that lymphocyte preparations from HD patients contained levels of AEA that were sixfold greater than those of control patient lymphocytes (Battista et al., 2007). This was attributed to an inhibition of function of FAAH in AEA metabolism. While the relationship between the peripheral and central endocannabinoid systems remains unclear, in the same study a corresponding reduction in FAAH activity was also detected in the cerebral cortex of

post-mortem HD brains."

-Centre for Brain Research and Department of Pharmacology, University of Auckland, Auckland, New Zealand

-Department of Anatomy and Cell Biology, Centre for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931550/

Treating the whole body in Huntington's disease.

"Huntington's disease is a genetic neurodegenerative disorder with symptoms that are linked to the progressive dysfunction and neuronal death in **corticostriatal circuits**. The causative gene (mutated HTT) is widely expressed outside the CNS and several peripheral signs of disease, including weight loss and increased proinflammatory signalling, are often seen; however, their importance in the pathophysiology of Huntington's disease is not clear. Studies in animals have shown that features of the disease involving the CNS, including synapse loss and behavioural alterations, are susceptible to modulation by treatments that target tissues and organs outside the CNS. Links between peripheral biology and neurodegeneration have also been shown in other chronic neurodegenerative diseases, suggesting that modulation of these peripheral targets can offer new approaches to therapeutic development. Treatments targeted to tissues and organs outside the CNS might therefore substantially improve the quality of life of patients with Huntington's disease, even in the absence of disease-modifying effects."

-Behavioral Neuroscience Program, Department of Psychology, Western Washington University, Bellingham, WA,

-Department of Medical and Molecular Genetics, King's College London, London, UK.

-Department of Psychiatry and Human Behavior, University of California at Irvine, Irvine, CA, USA.

-Department of Neurology, Huntington Center NRW, Ruhr-University Bochum, St Josef-Hospital, Bochum, Germany.

-Department of Neurodegenerative Disease, University College London Institute of Neurology, London, UK.

https://www.ncbi.nlm.nih.gov/pubmed/26466780

CB1 Cannabinoid Receptor Expression in the Striatum: Association with Corticostriatal Circuits and Developmental Regulation

"Corticostriatal circuits mediate various aspects of goal-directed behavior and are critically important for basal ganglia-related disorders. Activity in these circuits is regulated by the endocannabinoid system via stimulation of CB1 cannabinoid receptors."…

-Department of Cellular and Molecular Pharmacology, The Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

-Edited by: Joseph F. Cheer, University of Maryland School of Medicine, USA

-Reviewed by: David M. Lovinger, National Institutes of Health, USA; Jason B. Wu, Cedars-Sinai Medical Center, USA;

Miles Herkenham, National Institutes of Health, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298893/

Cannabinoid Receptors in the Central Nervous System: Their Signaling and Roles in Disease

…"Dysregulation of the ECS is also reported in experimental models and patients with HD [Huntington's disease]. The CB1 receptor expression is reduced, at least somewhat (e.g., 27% decrease in the striatum of the CB1 receptor mRNA), prior to symptoms of neurodegenerative HD in mice (McCaw et al., 2004). Losing the CB1 receptor expression decreases motor performance and increases the amount of aggregates in the striatum of HD mice (Mievis et al., 2011). Major loss of CB1 receptors is also reported in patients with HD (Glass et al., 2000). Interestingly, activation of the CB1 receptor may help reduce the progression of HD. For example, preclinical evidence suggested the use of CBs such as Sativex® for neuroprotection in patients with progressive neurodegenerative conditions like HD (Valdeolivas et al., 2012). Furthermore, selected receptor agonists have neuroprotective potential in a cell culture model of HD (Scotter et al., 2010; Laprairie et al., 2016). "…

-Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, USA
-Department of Anatomy and Neurobiology, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico
-Institute of Neurobiology, University of Puerto Rico, San Juan, Puerto Rico
-Edited by: Hansen Wang, University of Toronto, Canada
-Reviewed by: Carla Cannizzaro, University of Palermo, Italy; Eilís Dowd, National University of Ireland, Galway, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209363/

Cannabinoid Receptors in the Central Nervous System: Their Signaling and Roles in Disease

"Dysregulation of the ECS is also reported in experimental models and patients with HD. The CB1 receptor expression is reduced, at least somewhat (e.g., 27% decrease in the striatum of the CB1 receptor mRNA), prior to symptoms of neurodegenerative HD in mice (McCaw et al., 2004). Losing the CB1 receptor expression decreases motor performance and increases the amount of aggregates in the striatum of HD mice (Mievis et al., 2011). Major loss of CB1 receptors is also reported in patients with HD (Glass et al., 2000). Interestingly, activation of the CB1 receptor may help reduce the progression of HD. For example, preclinical evidence suggested the use of CBs such as Sativex® for neuroprotection in patients with progressive neurodegenerative conditions like HD (Valdeolivas et al., 2012). Furthermore, selected receptor agonists have neuroprotective potential in a cell culture model of HD (Scotter et al., 2010; Laprairie et al.,

2016). "…

-Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, USA

-Department of Anatomy and Neurobiology, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico

-Institute of Neurobiology, University of Puerto Rico, San Juan, Puerto Rico

-Edited by: Hansen Wang, University of Toronto, Canada

-Reviewed by: Carla Cannizzaro, University of Palermo, Italy; Eilís Dowd, National University of Ireland, Galway, Ireland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209363/

HU-210 (Synthetic Cannabinoid)

"Cannabinoid refers to a pharmacological class of about 60 naturally occurring compounds (phytocannabinoids) found in plants of the genus Cannabis (i.e. marijuana and hemp) and structurally related synthetic analogues (e.g. Δ3,4-tetrahydrocannabinol and HU-210, which is 100–800 times more potent psychoactively than natural THC[22]). "…

-Professor of Anesthesiology, Pain Research and Management Centers, Department of Anesthesiology, School of Medicine, University of Utah, Salt Lake City, Utah, USA

-Chief Executive Officer, ISA Scientific, Draper, Utah, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3820295

HU-331 (synthesized from cannabidiol)

"Anthracyclines, a large group of quinonoid compounds, are used to treat some forms of cancer. Although highly effective in cancer therapy, the mechanism of action of these compounds is not specific; they act on cancer and other cells by numerous mechanisms. A new anticancer quinone (HU-331) was synthesized from cannabidiol. It shows significant high efficacy against human cancer cell lines in vitro and against in vivo tumor grafts in nude mice. In this study, we investigated its mode of action and present evidence on its unique mechanism. HU-331 does not cause cancer cell cycle arrest, cell apoptosis, or caspase activation. HU-331-caused cell death of human cancer cell lines is not mediated by reactive oxygen intermediates/species, as exposure to HU-331 failed to elicit the generation of reactive oxygen species. HU-331 inhibits DNA topoisomerase II even at nanomolar concentrations but has only a slight nonsignificant effect on DNA topoisomerase I action. The cannabinoid quinone HU-331 is a highly specific inhibitor of

topoisomerase II, compared with most known anticancer quinones. It might represent a new potent anticancer drug."

-Department of Medicinal Chemistry and Natural Products, School of Pharmacy, The Hebrew University, Jerusalem, Israel.

https://pubmed.ncbi.nlm.nih.gov/17237277

Hypercalcemia

"Hypercalcemia is a condition in which the calcium level in your blood is above normal. Too much calcium in your blood can weaken your bones, create kidney stones, and interfere with how your heart and brain work. Hypercalcemia is usually a result of overactive parathyroid glands."

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/hypercalcemia/symptoms-causes/syc-20355523

■■■

…"One might presume that omega-3 supplementation could be beneficial for hypercalcemia-associated bone resorption because it was observed that, in an animal model of apical periodontitis, omega-3 supplementation reduced bone resorption by the downregulation of the inflammatory cells influx [147]. Moreover, the combination of omega-3 supplementation and exercise in postmenopausal healthy women promoted diminished serum PTH levels, leading to an improvement of skeletal health [148]. Nevertheless, there is no evidence linking paraneoplastic tumor-induced hypercalcemia and omega-3, as well as in relation to other kinds of paraneoplastic endocrine syndromes."…

-Centro de Pesquisa em Toxicologia e Farmacologia, Escola de Ciências da Saúde, Brazil;
-Programa de Pós-graduação em Medicina e Ciências da Saúde, Escola de Medicina, Brazil
-Programa de Pós-graduação em Odontologia, Escola de Ciências da Saúde, Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6566772/

Hypertension

"High blood pressure (HBP or **hypertension**) is when your blood pressure, the force of your blood pushing against the walls of your blood vessels, is consistently too high."

- American Heart Association

https://www.heart.org/en/health-topics/high-blood-pressure/the-facts-about-high-blood-pressure/what-is-high-blood-pressure

■■■

Vasoconstriction

"Vasoconstriction is the narrowing or closing (constriction) of a blood vessel."

-WebMD
https://www.webmd.com/migraines-headaches/qa/what-is-the-definition-of-vasoconstriction

■■■

Vasodilators are medications used for vasodilation

"Vasodilators are medications that open (dilate) blood vessels. They affect the muscles in the walls of your arteries and veins, preventing the muscles from tightening and the walls from narrowing. As a result, blood flows more easily through your vessels."

…."Doctors prescribe vasodilators to prevent, treat or improve symptoms in a variety of conditions, such as:

- High blood pressure
- High blood pressure during pregnancy or childbirth (preeclampsia or eclampsia)
- Heart failure
- High blood pressure that affects the arteries in your lungs (pulmonary hypertension)"

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/high-blood-pressure-medication/art-20048154

■■■

…"Wagner et al. also demonstrated that both HU-210 *[a synthetic cannabinoid]* and anandamide produce major vasodilation in the coronary and cerebral circulation,"…

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda MD
https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/16596789/

■■■

"The endocannabinoid anandamide exerts neurobehavioral, cardiovascular, and immune-

regulatory effects through cannabinoid receptors (CB). Fatty acid amide hydrolase (FAAH) is an enzyme responsible for the in vivo degradation of anandamide. Recent experimental studies have suggested that targeting the endocannabinergic system by FAAH inhibitors is a promising novel approach for the treatment of anxiety, inflammation, and **hypertension**. "

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

-The Skaggs Institute for Chemical Biology and Department of Cell Biology, The Scripps Research Institute, La Jolla, California

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225481/

Anandamide acts as a vasodilator of dural blood vessels in vivo by activating TRPV1 receptors

…"The study demonstrates that anandamide acts as a TRPV1 [vanilloid type 1] receptor agonist in the trigeminovascular system, activating TRPV1 receptors that promote CGRP [calcitonin gene-related peptide] release and **cause vasodilation independent of any action at the CB1 receptor**. Anandamide has been shown previously to inhibit trigeminovascular neurons and prevent vasodilation, through an action at CB1 receptors."…

-Headache Group, Institute of Neurology, Queen Square, London

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1575202/

Hypothalamic-pituitary-adrenal (HPA) Axis Hyperactivity

"HPA (hypothalamic-pituitary-adrenal) axis hyperactivity is commonly seen in people with depression and is associated with increased glucocorticoid levels in both the central nervous system (CNS) and peripherally. HPA axis activity is also activated by environmental and social stressors which are common triggers of depressive episodes [33,34]. Glucocorticoids have been shown to have a biphasic influence on mitochondrial function. Acute exposure to either low or high levels of glucocorticoids to cultured neurons increased mitochondrial activity [35]. However, prolonged exposure to excess glucocorticoids can cause respiratory chain dysfunction, increased ROS generation, mitochondrial structural abnormalities, apoptosis, and cell death in skeletal muscle cells and hippocampal neurons. Stress also increases the levels of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-, which can suppress mitochondrial activity and induce mitochondrial damage [14,36]"

-Adrian L. Lopresti B.A, M.A., PhD

-Neurobiology of Depression, 2019

https://www.sciencedirect.com/topics/neuroscience/hypothalamic-pituitary-adrenal-axis/pdf

■■■

"Deficiency in the long-chain omega-3 fatty acid, docosahexaenoic acid (DHA) has been associated with increased corticotropin releasing hormone and may contribute to hypothalamic pituitary axis (HPA) hyperactivity."….

-National Institutes of Health, National Institutes on Alcoholism and Alcohol Abuse, Laboratory of Membrane Biophysics and Biochemistry, Bethesda, MD 20814, USA.

https://www.ncbi.nlm.nih.gov/pubmed/16959481

Hypothyroidism

See Endocrine system

Hypoxic-ischemic Brain Injury

"Hypoxic-ischemic brain injury is a diagnostic term that encompasses a complex constellation of pathophysiological and molecular injuries to the brain induced by hypoxia, ischemia, cytotoxicity, or combinations of these conditions (Busl and Greer 2010). The typical causes of hypoxic-ischemic brain injury – cardiac arrest, respiratory arrest, near-drowning, near-hanging, and other forms of incomplete suffocation, carbon monoxide and other poisonous gas exposures, and perinatal asphyxia – expose the entire brain to potentially injurious reductions of oxygen (i.e., hypoxia) and/or diminished blood supply (ischemia)."…

-David B. Arciniegas, MD, FANPA, CBIST

-International Brain Injury Association

https://www.internationalbrain.org/articles/hypoxicischemic-brain-injury/

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"Hypoxic-ischemic brain injury continues to be the third leading cause of death in the United States, affecting over half a million new victims each year. Of these, nearly one-third will die and another third will be left with severe and permanent disability. Unlike ischemic injury to many other tissues, the severity of disability is not predicted well by the amount of brain tissue lost. For example, damage to a small area in the medial temporal lobe may lead to severe disability, such as loss of speech, while damage to a greater volume elsewhere has little effect on function.

The degree of disability does not simply reflect the severity or distribution of impaired blood supply. Populations of cells lying side by side in the brain can display dramatically different vulnerabilities to equivalent degrees of ischemia. Although a great deal has been learned about how nervous system anatomy, physiology and biochemistry interact to modify hypoxic-ischemic brain injury, much remains to be learned about what features contribute to the special vulnerability of the brain to stroke and of specific cell populations to hypoxic-ischemic injury during stroke."

-Laura L Dugan and Dennis W Choi.
-Washington University, Department of Neurology, St. Louis, Missouri.
https://www.ncbi.nlm.nih.gov/books/NBK28046/

The cannabinoid WIN55212-2 promotes neural repair after neonatal hypoxia-ischemia

"Background and purpose: The endocannabinoid system has been involved in the modulation of neural stem cells proliferation, survival and differentiation as well as in the generation of new oligodendrocyte progenitors in the postnatal brain. The present work aims to test the effect of the synthetic Type 1 and Type 2 cannabinoid receptor agonist WIN55212-2 on these processes in the context of neonatal rat brain hypoxia-ischemia (HI)."…

"Conclusions: Our results suggest that the activation of the endocannabinoid system promotes white and gray matter recovery after neonatal HI injury."

-Unidad de Investigación Neurovascular, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/21115947/

Omega-3 Fatty Acids: Possible Neuroprotective Mechanisms in the Model of Global Ischemia in Rats

"Omega-3 (ω3) administration was shown to protect against hypoxic-ischemic injury. The objectives were to study the neuroprotective effects of ω3, in a model of global ischemia."
…"*Conclusion*. This study showed a neuroprotective effect of ω3, in great part due to its anti-inflammatory properties, stimulating translational studies focusing on its use in clinic for stroke managing."
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4895039/

Hyperbaric oxygen induces endogenous neural stem cells to proliferate and differentiate in hypoxic-ischemic brain damage in neonatal rats

"Background and purpose: Studies suggest that after brain injury, hyperbaric oxygen (HBO2) is neuroprotective by stimulating cell proliferation. We examine whether HBO2 promotes neural stem cells (NSC) to proliferate and differentiate in neonatal hypoxic-ischemic (HI) rats."…

Conclusions: This study suggests that HBO2 treatment may promote neurogenesis of the endogenous NSC in neonatal HI rats, contributing to repair of the injured brain."

-Division of Neonatology, Department of Pediatrics, Xiang Ya Hospital, Central South University.
https://pubmed.ncbi.nlm.nih.gov/18500076/

Hypoxic Pulmonary Vasoconstriction (HPV)

Endocannabinoid anandamide mediates hypoxic pulmonary vasoconstriction

"Hypoxic pulmonary vasoconstriction (HPV) is an important physiological reflex, which is only found in the lung and adapts perfusion to ventilation. HPV is potentially involved in hypoxia-induced pulmonary hypertension (PH) occurring in respiratory disorders. In this study we show that the endocannabinoid anandamide (AEA) via its fatty acid amide hydrolase (FAAH)-dependent metabolites is involved in HPV and PH. We have identified pulmonary arterial smooth muscle cells as the source of hypoxia-induced AEA synthesis. Our results illustrate that the onset of PH is prevented in FAAH−/− mice or by treating wild-type mice with a FAAH antagonist for 3 wk of hypoxia. Thus, we demonstrate a previously undescribed signaling pathway underlying HPV and an alternative strategy for the treatment of common pulmonary diseases."…

…"Endocannabinoids are emerging as unique mediators of organ homeostasis, and this concept also applies to the cardiovascular system. In fact, experimental evidence indicates their involvement in the regulation of systemic blood pressure [19] and cardiac output [2] and in atherosclerosis [20]. Herein, we demonstrate that AEA mediates hypoxic pulmonary vasoconstriction and is also involved in pulmonary hypertension via its degradation to FAAH-dependent metabolites."…

-Institutes of Physiology I and Molecular Psychiatry, Life and Brain Center, University of Bonn, Bonn, Germany
-Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3831960

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Icilin

"Icilin is a synthetic super-agonist of the transient receptor potential M8 (TRPM8) ion channel. Although structurally not related with menthol it produces an extreme sensation of cold both in humans and animals. It is almost 200 times more potent than menthol and 2.5 times more efficacious."

-Referenced on Wikipedia

https://en.wikipedia.org/wiki/Icilin

https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/15190109/

See also TRP Channels (Transient receptor potential channels)

Idiopathic Angioedema (IAE)

Life Threatening Idiopathic Recurrent Angioedema Responding to Cannabis

"Idiopathic angioedema (IAE) is defined as recurrent episodes of angioedema without urticaria for which no explanation can be found after full evaluation [4]. Currently recommended therapy is largely empiric. Available treatment modalities include a trial of nonsedating antihistamines, combination of nonsedating antihistamines with a leukotriene receptor antagonist, systemic corticosteroids, and immunosuppressant therapies. Plasmapheresis or intravenous immunoglobulin has also been used [5]. None of these treatments is universally successful."

-General Intensive Care Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba, Israel

-Infection Control and Hospital Epidemiology Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba, Israel

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4519555/

See Also : Angioedema (Hives)

Immune System

The Immune Endocannabinoid System of the Tumor Microenvironment

"Leukocytes are part of the tumor microenvironment (TME) and are critical determinants of tumor progression. Because of the immunoregulatory properties of cannabinoids, the endocannabinoid system (ECS) may have an important role in shaping the TME. Members of the ECS, an entity that consists of cannabinoid receptors, endocannabinoids and their synthesizing/degrading enzymes, have been associated with both tumor growth and rejection. Immune cells express cannabinoid receptors and produce endocannabinoids, thereby forming an "immune endocannabinoid system". Although in vitro effects of exogenous cannabinoids on immune cells are well described, the role of the ECS in the TME, and hence in tumor development and immunotherapy, is still elusive. This review/opinion discusses the possibility that the "immune endocannabinoid system" can fundamentally influence tumor progression. The widespread influence of cannabinoids on immune cell functions makes the members of the ECS an interesting target that could support immunotherapy."

-Division of Pharmacology, Otto Loewi Research Center, Medical University of Graz, Austria;
-BioTechMed, 8010 Graz, Austria
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7728085/

The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Inflammatory Cytokine Storms

"Inflammation is important in treating infections and wounds as it promotes tissue healing and the killing of pathogens. The omega-6 fat linoleic acid, and arachidonic acid (AA) formed from it, are important in responses such as redness, swelling, heat, and pain.[1] However, acute inflammatory responses are meant to be quickly suppressed by resolvins formed from the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Thus, a balance in the dietary omega-6/3 ratio may be important for ensuring that an excessive and prolonged inflammatory response does not occur, which could lead to tissue damage and potentially to autoimmune disease.

Up until about 100 years ago, the omega-6/3 ratio had been around 4:1 or less.[2] However, the typical Western diet now provides an omega-6/3 ratio approximately 20-fold higher in favor of omega-6.2 While foods such as nuts, seeds, and eggs are high in omega-6, the increase in the omega-6/3 ratio is primarily due to an increase in the intake of industrial seed oils (soybean, corn, safflower, cottonseed, and canola). Additionally, there has been a reduction in the intake of long-

chain omega-3s, which can primarily be found in fatty fish and shellfish. A high omega-6/3 ratio predisposes to supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation.[3] The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of EPA and DHA, has been proposed to put the population in a pro-inflammatory and pro-thrombotic state.[3, 4]"…

"A higher omega-6/3 ratio is also associated with lower immune cell function, which may result in lower immunity.[24] …

This research paper continues at COVID-19

-MSMA member since 2003, Saint Luke's Mid America Heart Institute, Kansas City, Missouri.
-Dr James J. DiNicolantonio
-Dr. James O'Keefe, MD
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7721408

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"Advances in understanding the physiology and pharmacology of the endogenous cannabinoid system have potentiated the interest of cannabinoid receptors as potential therapeutic targets. Cannabinoids have been shown to modulate a variety of immune cell functions and have therapeutic implications on central nervous system (CNS) inflammation, chronic inflammatory conditions such as arthritis, and may be therapeutically useful in treating autoimmune conditions such as multiple sclerosis. Many of these drug effects occur through cannabinoid receptor signalling mechanisms and the modulation of cytokines and other gene products. Further, endocannabinoids have been found to have many physiological and patho-physiological functions, including mood alteration and analgesia, control of energy balance, gut motility, motor and co-ordination activities, as well as alleviation of neurological, psychiatric and eating disorders. Plants offer a wide range of chemical diversity and have been a growing domain in the search for effective cannabinoid ligands. Cannabis sativa L. with the known plant cannabinoid, Delta(9-)tetrahydrocannabinol (THC) and Echinacea species with the cannabinoid (CB) receptor-binding lipophilic alkamides are the best known herbal cannabimimetics. This review focuses on the state of the art in CB ligands from plants, as well their possible therapeutic and immunomodulatory effects. "

- Institute of Pharmaceutical Sciences, Department of Pharmacognosy, Karl-Franzens-University Graz, Austria.
https://pubmed.ncbi.nlm.nih.gov/18289087

Defensive and damaging inflammation: basic characteristics

“Immune system is the integral part of the complex body response, inflammation, which is raised either by the exposure to external signals, predominantly pathogens or by damage of own structures. Predominantly innate immunity is equiped by the receptors recognizing pathogenic PAMPs or signals of own damage DAMPs. The inflammatory response is reflecting the actual demand of our body. The potential of the inflammatory response is so powerful that its intensity and extent have to be carefully regulated on many levels.”

-Jan Krejsek

https://pubmed.ncbi.nlm.nih.gov/30909696/

Endocannabinoids and the Immune System in Health and Disease

“Endocannabinoids are bioactive lipids that have the potential to signal through cannabinoid receptors to modulate the functional activities of a variety of immune cells. Their activation of these seven-transmembranal, G protein-coupled receptors sets in motion a series of signal transductional events that converge at the transcriptional level to regulate cell migration and the production of cytokines and chemokines. There is a large body of data that supports a functional relevance for 2-arachidonoylglycerol (2-AG) as acting through the cannabinoid receptor type 2 (CB2R) to inhibit migratory activities for a diverse array of immune cell types. However, unequivocal data that supports a functional linkage of anandamide (AEA) to a cannabinoid receptor in immune modulation remains to be obtained. Endocannabinoids, as typical bioactive lipids, have a short half-life and appear to act in an autocrine and paracrine fashion. Their immediate effective action on immune function may be at localized sites in the periphery and within the central nervous system. It is speculated that endocannabinoids play an important role in maintaining the overall "fine-tuning" of the immune homeostatic balance within the host.”

-Department of Microbiology and Immunology, Virginia Commonwealth University, Richmond, VA, USA.
-Department of Clinical Laboratory Sciences, Virginia Commonwealth University, Richmond, VA, USA.
https://pubmed.ncbi.nlm.nih.gov/26408161

Unraveling the Complexities of Cannabinoid Receptor 2 (CB2) Immune Regulation in Health and Disease

“It has become clear that the endocannabinoid system is a potent regulator of immune responses, with the cannabinoid receptor 2 (CB2) as the key component due to its high expression by all immune subtypes. CB2 has been shown to regulate immunity by a number of mechanisms including development, migration, proliferation and effector functions. In addition,

CB2 has been shown to modulate the function of all immune cell types examined to date. CB2 is a Gi-protein coupled receptor and thus exhibits a complex pharmacology allowing both stimulatory and inhibitory signaling that depends on receptor expression levels, ligand concentration and cell lineage specificities. Here, we discuss both in vitro and in vivo experimental evidence that CB2 is a potent regulator of immune responses making it a prime target for the treatment of inflammatory diseases."...

-Blood Research Institute, BloodCenter of Wisconsin, Milwaukee
-Department of Microbiology and Molecular Genetics, Medical College of Wisconsin
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624216/

Cannabinoids as novel anti-inflammatory drugs

"Cannabinoids are a group of compounds that mediate their effects through cannabinoid receptors. The discovery of Δ9-tetrahydrocannabinol (THC) as the major psychoactive principle in marijuana, as well as the identification of cannabinoid receptors and their endogenous ligands, has led to a significant growth in research aimed at understanding the physiological functions of cannabinoids. Cannabinoid receptors include CB1, which is predominantly expressed in the brain, and CB2, which is primarily found on the cells of the immune system. **The fact that both CB1 and CB2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system.** Recent studies demonstrated that administration of THC into mice triggered marked apoptosis in T cells and dendritic cells, resulting in immunosuppression. In addition, several studies showed that cannabinoids downregulate cytokine and chemokine production and, in some models, upregulate T-regulatory cells (Tregs) as a mechanism to suppress inflammatory responses. The endocannabinoid system is also involved in immunoregulation. For example, administration of endocannabinoids or use of inhibitors of enzymes that break down the endocannabinoids, led to immunosuppression and recovery from immune-mediated injury to organs such as the liver. Manipulation of endocannabinoids and/or use of exogenous cannabinoids in vivo can constitute a potent treatment modality against inflammatory disorders. This review will focus on the potential use of cannabinoids as a new class of anti-inflammatory agents against a number of inflammatory and autoimmune diseases that are primarily triggered by activated T cells or other cellular immune components."

-Department of Pathology, Microbiology and Immunology, University of South Carolina, School of Medicine, Columbia, SC , USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2828614/

Effects of Omega-3 Fatty Acids on Immune Cells

…"Both omega-3 and omega-6-derived metabolites have important immune-regulatory functions. These metabolites are generally known as pro-resolving mediators (SPMs) and can be classified in different families—prostaglandins, leukotrienes, thromboxanes, maresins, protectins, and resolvins. Their synthesis is orchestrated by cyclooxygenase, lipoxygenase, or cytochrome P450 enzymes [10]. A summary of the metabolites produced from omega-3 fatty acids and the enzymes regulating their synthesis is found in Figure 1. Omega-3 and omega-6 substrates compete for these enzymes [11], as well as for the above mentioned elongases and elastases. Therefore, in the presence of omega-3 fatty acids, the competition for the enzymes reduces the synthesis of omega-6-derived metabolites, which also have effects on immune cells. This competition constitutes an additional level of immune-regulation by omega-3 fatty acids."…

-Department of Physiology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6834330/

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…"Accumulating evidence indicates that the endocannabinoid system is a key modulator of gastrointestinal physiology, influencing satiety, emesis, **immune function**, mucosal integrity, motility, secretion, and visceral sensation." …

-College of Pharmacy, Pusan National University, Busan, Korea

-Section of Inflammatory Bowel Disease & Inflammatory Bowel Disease Center, Division of Digestive Diseases, David Geffen School of Medicine, UCLA, Los Angeles, California.

-College of Pharmacy, Pusan National University, Busan, Korea;

https://pubmed.ncbi.nlm.nih.gov/27538961

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…"Omega-3 (n-3) and omega-6 (n-6) fatty acids are major components of immune and neuronal cell membranes35 and the biosynthetic precursors to several families of lipid autacoids posited to modulate physical pain and psychological distress (e.g. eicosanoids, endovanilloids, endocannabinoids)[8-10, 20, 32, 38, 42]. Humans lack the enzymatic machinery needed for de novo biosynthesis of n-3 and n-6 fatty acids. Therefore, targeted dietary manipulation is a promising strategy for altering bioactive lipid autacoids in a manner that could reduce pain and comorbid conditions. "…

-Section on Nutritional Neurosciences, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

-Department of Physical Medicine and Rehabilitation, Program on Integrative Medicine, University of North Carolina,

Chapel Hill, NC,USA

-Center for Drug Discovery and Departments of Chemistry and Chemical Biology and Pharmaceutical Sciences, Northeastern University, Boston, MA, USA

-Department of Neurology, Program on Integrative Medicine, University of North Carolina, Chapel Hill, USA

-Nutrition Research and Metabolism Core, North Carolina Translational Clinical Sciences Institute, University of North Carolina, Chapel Hill, USA

-Anesthesia Section, Department of Perioperative Medicine, Clinical Center, National Institutes of Health, Bethesda, MD, USA

-Nutrition Department, Clinical Center, National Institutes of Health (NIH), Bethesda, MD, USA

-Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4522350/

Endocannabinoids and immune regulation

"Cannabinoid pharmacology has made important advances in recent years after the discovery of the cannabinoid receptors. These discoveries have added to our understanding of exogenous and endogenous cannabinoid signaling along with exploring the various pathways of their biosynthesis, molecular structure, inactivation, and anatomical distribution of their receptors throughout the body. The endocannabinoid system is involved in immunoregulation and neuroprotection. In this article, we have reviewed the possible mechanisms of the regulation of the immune response by endocannabinoids which include modulation of immune response in different cell types, effect on cytokine network, induction of apoptosis in immune cells and downregulation of innate and adaptive immune response. Studies from our laboratory have suggested that administration of endocannabinoids or use of inhibitors of enzymes that breakdown the endocannabinoids, leads to immunosuppression and recovery from immune-mediated injury to organs such as the liver. Thus, manipulation of endocannabinoids in vivo may constitute a novel treatment modality against inflammatory disorders."…

"Mammalian tissues are known to express primarily two types of cannabinoid receptors which are G-protein coupled. These include CB1 receptors, cloned in Tom Bonner's laboratory in 1990 and CB2 receptors, cloned by Sean Munro in 1993. Both CB1 and CB2 receptors regulate the release of chemical messengers, where CB1 receptors are found mainly on neurons (and in some non-neuronal tissues like pituitary gland, immune cells and reproductive tissues), and CB2 receptors are found primarily on immune cells. Anandamide binds to the brain CB1 with high affinity and mimics the behavioral actions of exogenous cannabinoid, Δ9-tetrahydrocannabinol (Δ9-THC) when injected into rodents. 2-AG has similar affinities for both CB1 and CB2 receptors comparable to those of anandamide but it exhibits higher efficacy than anandamide. Other pharmacological targets for anandamide, other than cannabinoid receptors, have also been described. The most accepted receptor to be activated by anandamide and other synthetic

analogs of endocannabinoids (methanamide, arachidonyl-2′-chloroethylamide) is TRPV1 (vanilloid VR1) receptor [6,7]. These findings have triggered an exponential growth in studies describing the endocannabinoid synthesis, their release [8], transport [9] and degradation [10], constituting the new ubiquitous "endogenous cannabinoid system"….

"**Endocannabinoids are believed to control immune functions and play a role in immune homeostasis.** Immune cells express both CB1 and CB2 receptors, secrete endocannabinoids and have functional cannabinoid transport and breakdown mechanisms [15,16]. Human peripheral blood immune cells are reported to have different degrees of cannabinoid receptor expression with the following rank order: B cells > NK cells > monocytes > polymorphonuclear neutrophils > CD8 lymphocytes > CD4 lymphocytes [17]. The CB1 receptors are densely expressed in the central nervous system and mediate neurobehavioral effects. The expression levels of CB2 receptors in immune cells are 10–100 times greater than CB1 receptors. Moreover, CB2 receptor mRNA was also detected in the cortex of lymph nodes and the nodular corona of Peyer's patches [18]."…

"There is significant biochemical evidence to suggest that biosynthesis, uptake and degradation of endocannabinoids occur in macrophages and leukocytes [15,16,19]. **This finding supports the role of endocannabinoids as local modulators of immune and inflammatory reactions**."…

"Endocannabinoids have important effects on immune functions. They modulate T- and B-lymphocytes proliferation and apoptosis, macrophage-mediated killing of sensitized cells, inflammatory cytokine production, immune cell activation by inflammatory stimuli, chemotaxis and inflammatory cell migration [44,45]. The immunosuppressive effect of endocannabinoids on immune cells is primarily considered to be mediated through CB2 receptors by the inhibition of the cAMP/protein kinaseA (PKA) pathway (by decreasing the expression of cAMP-responsive genes). Endocannabinoids also act at nuclear level, e.g. phosphorylation of IκB-α that enhances the transcription of several apoptotic genes regulated by NF-κB, by peroxisome proliferator-activated receptor gamma (PPAR-γ dependent inhibition of nuclear factor of activated T cells (NF-AT) and interference of cell cycle by activation of p21waf-1/cip-1 and induction of G1/S phase arrest [37]."

-Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, United State

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044336

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…."Outside the brain, the endocannabinoid system is one of the crucial modulators of the autonomic nervous system, the immune system and microcirculation."…

-Fundación IMABIS, Hospital Carlos Haya de Málaga, Avenida Carlos Haya 82, 29010 Málaga, Spain.

https://pubmed.ncbi.nlm.nih.gov/15550444/

CB2: a cannabinoid receptor with an identity crisis

"CB2 [cannabinoid receptor 2] was first considered to be the 'peripheral cannabinoid receptor'. This title was bestowed based on its abundant expression in the immune system and presumed absence from the central nervous system. However, multiple recent reports question the absence of CB2 from the central nervous system. For example, it is now well accepted that CB2 is expressed in brain microglia during neuroinflammation. However, the extent of CB2 expression in neurons has remained controversial. There have been studies claiming either extreme-its complete absence to its widespread expression-as well as everything in between. This review will discuss the reported tissue distribution of CB2 with a focus on CB2 in neurons, particularly those in the central nervous system as well as the implications of that presence. As CB2 is an attractive therapeutic target for pain management and immune system modulation without overt psychoactivity, defining the extent of its presence in neurons will have a significant impact on drug discovery. Our recommendation is to encourage cautious interpretation of data that have been presented for and against CB2's presence in neurons and to encourage continued rigorous study."

-The Gill Center and the Department of Psychological & Brain Sciences, Indiana University, Bloomington, IN, USA
-University of Washington, Program of Neurobiology and Behavior, Seattle, WA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931549/

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"It is well accepted that cannabinoids play a role in immune function. The exact nature of this involvement has not been resolved. As previously mentioned, NAGly suppresses inflammatory pain independent of CB1 and CB2 (Huang et al., 2001). In 2006 a group of investigators suggested that NAGly is the endogenous ligand for GPR18 (Kohno et al., 2006). In a recent report, NAGly was found to induce apoptosis of pro-inflammatory macrophages, further supporting the role of NAGly in inflammation (Takenouchi et al., 2012). Attentuation of apoptosis following knock-down of GPR18 expression by siRNA supports a role for GPR18 in immune function. The finding that abn-CBD, AEA and NAGly act as full agonists at GPR18 suggests that the "abn-CBD receptor" is in fact the GPR18 receptor (McHugh et al., 2010; McHugh et al., 2011)."...

-Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA
-Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378782/

Emerging importance of omega-3 fatty acids in the innate immune response: molecular mechanisms and lipidomic strategies for their analysis

"The beneficial health properties of dietary omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have long been known and their metabolic dysfunction has been linked to a range of diseases including various inflammatory disorders, cardiovascular diseases, and cancer. However, the molecular mechanisms underlying their health benefits have remained unclear. Recent technological advances in lipidomic analytical strategies have resulted in the discovery of a range of bioactive mediators derived from EPA and DHA that possess potent anti-inflammatory and pro-resolving properties and that may be responsible, at least in part, for the beneficial effects observed. These mediators include resolvins, protectins and maresins, as well as EPA derivatives of classical arachidonic acid derived eicosanoids, such as prostaglandin E3 . The aim of this review is to provide an overview of the biosynthetic pathways and biological properties of these omega-3 mediators, with a particular focus on the emerging importance of the counter-regulatory role of omega-3 and -6 fatty acids in the spatial and temporal regulation of the inflammatory response. It will also provide an insight into a range of lipidomic approaches, which are currently available to analyse these fatty acids and their metabolites in biological matrices."

-Lipidomics Research Facility, Department of Diabetes and Cardiovascular Science, University of the Highlands and Islands, Inverness, UK

https://pubmed.ncbi.nlm.nih.gov/23417926/

Targeting Cannabinoid Signaling in the Immune System: "High"-ly Exciting Questions, Possibilities, and Challenges

"It is well known that certain active ingredients of the plants of Cannabis genus, i.e., the "phytocannabinoids" [pCBs; e.g., (−)-trans-Δ9-tetrahydrocannabinol (THC), (−)-cannabidiol, etc.] can influence a wide array of biological processes, and the human body is able to produce endogenous analogs of these substances ["endocannabinoids" (eCB), e.g., arachidonoylethanolamine (anandamide, AEA), 2-arachidonoylglycerol (2-AG), etc.]. These ligands, together with multiple receptors (e.g., CB1 and CB2 cannabinoid receptors, etc.), and a complex enzyme and transporter apparatus involved in the synthesis and degradation of the ligands constitute the endocannabinoid system (ECS), a recently emerging regulator of several physiological processes. The ECS is widely expressed in the human body, including several members of the innate and adaptive immune system, where eCBs, as well as several pCBs were shown to deeply influence immune functions thereby regulating inflammation, autoimmunity, antitumor, as well as antipathogen immune responses, etc. Based on this knowledge, many in

vitro and in vivo studies aimed at exploiting the putative therapeutic potential of cannabinoid signaling in inflammation-accompanied diseases (e.g., multiple sclerosis) or in organ transplantation, and to dissect the complex immunological effects of medical and "recreational" marijuana consumption. Thus, the objective of the current article is (i) to summarize the most recent findings of the field; (ii) to highlight the putative therapeutic potential of targeting cannabinoid signaling; (iii) to identify open questions and key challenges; and (iv) to suggest promising future directions for cannabinoid-based drug development."….

"Research efforts of the past few decades have unambiguously evidenced that ECS is one of the central orchestrators of both innate and adaptive immune systems, and that pure pCBs [phytocannabinoids] as well as complex cannabis-derivatives can also deeply influence immune responses. Although, many open questions await to be answered, pharmacological modulation of the (endo)cannabinoid signaling, and restoration of the homeostatic eCB tone of the tissues augur to be very promising future directions in the management of several pathological inflammation-accompanied diseases. Moreover, in depth analysis of the (quite complex) mechanism-of-action of the most promising pCBs is likely to shed light to previously unknown immune regulatory mechanisms and can therefore pave new "high"-ways toward developing completely novel classes of therapeutic agents to manage a wide-variety of diseases."

-Department of Physiology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

-Department of Internal Medicine, Division of Rheumatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

-Department of Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5686045

The Immune Endocannabinoid System of the Tumor Microenvironment

"Leukocytes are part of the tumor microenvironment (TME) and are critical determinants of tumor progression. Because of the immunoregulatory properties of cannabinoids, the endocannabinoid system (ECS) may have an important role in shaping the TME. Members of the ECS, an entity that consists of cannabinoid receptors, endocannabinoids and their synthesizing/degrading enzymes, have been associated with both tumor growth and rejection. Immune cells express cannabinoid receptors and produce endocannabinoids, thereby forming an "immune endocannabinoid system". Although in vitro effects of exogenous cannabinoids on immune cells are well described, the role of the ECS in the TME, and hence in tumor development and immunotherapy, is still elusive. This review/opinion discusses the possibility that the "immune endocannabinoid system" can fundamentally influence tumor progression. The widespread influence of cannabinoids on immune cell functions makes the members of the

ECS an interesting target that could support immunotherapy."

-Division of Pharmacology, Otto Loewi Research Center, Medical University of Graz, Universitätsplatz 4, 8010 Graz, Austria

-BioTechMed, 8010 Graz, Austria

https://www.mdpi.com/1422-0067/21/23/8929/

Cannabinoids and the immune system: an overview

"Cannabinoids can influence the immune network. Data on the impact of exogenous cannabinoid ligands on immune function serve not only to understand how the endocannabinoid system modulates immune phenomena associated with infection or inflammation, but also to identify therapeutic targets for immune diseases. Cannabinoids can modulate immune reactions in the periphery but also in the brain, influence T cell subset balance and cytokine expression and play a role in the balance between neuroinflammation and neurodegeneration. Immune cells can synthesize endocannabinoids and also be influenced by cannabinoid analogues. Cannabinoid receptors show different expression on immune cells depending on activation status and stimuli. The complexity of relation between cannabinoid ligands of various classes and cannabinoid receptors brought the need to refine the simple conceptual frame of agonist-antagonists and offered potential implications for understanding interactions in pathological conditions. The immune influence of cannabinoid ligands is not fully elucidated. However, aspects of their immunomodulatory effects provide the basis for a context-dependent targeted therapeutic approach, thus leading to the possibility for the use of cannabinoids in the treatment of inflammatory disease."

-Department of Neurology, Colentina Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

https://pubmed.ncbi.nlm.nih.gov/20153077

The Endocannabinoid System in Pediatric Inflammatory and Immune Diseases

"Endocannabinoid system consists of cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors, their endogenous ligands, and the enzymes responsible for their synthesis and degradation. CB2, to a great extent, and CB1, to a lesser extent, are involved in regulating the immune response. They also regulate the inflammatory processes by inhibiting pro-inflammatory mediator release and immune cell proliferation. This review provides an overview on the role of the endocannabinoid system with a major focus on cannabinoid receptors in the pathogenesis

and onset of inflammatory and autoimmune pediatric diseases, such as immune thrombocytopenia, juvenile idiopathic arthritis, inflammatory bowel disease, celiac disease, obesity, neuroinflammatory diseases, and type 1 diabetes mellitus. These disorders have a high social impact and represent a burden for the healthcare system, hence the importance of individuating more innovative and effective treatments. The endocannabinoid system could address this need, representing a possible new diagnostic marker and therapeutic target."…

-Department of Experimental Medicine, University of Campania Luigi Vanvitelli, , Italy;

-Department of Women, Child, and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6928713/

The cannabinoid system and immune modulation

"Studies on the effects of marijuana smoking have evolved into the discovery and description of the endocannabinoid system. To date, this system is composed of two receptors, CB1 and CB2, and endogenous ligands including anandamide, 2-arachidonoyl glycerol, and others. CB1 receptors and ligands are found in the brain as well as immune and other peripheral tissues. Conversely, CB2 receptors and ligands are found primarily in the periphery, especially in immune cells. Cannabinoid receptors are G protein-coupled receptors, and they have been linked to signaling pathways and gene activities in common with this receptor family. In addition, cannabinoids have been shown to modulate a variety of immune cell functions in humans and animals and more recently, have been shown to modulate T helper cell development, chemotaxis, and tumor development. Many of these drug effects occur through cannabinoid receptor signaling mechanisms and the modulation of cytokines and other gene products. It appears the immunocannabinoid system is involved in regulating the brain-immune axis and might be exploited in future therapies for chronic diseases and immune deficiency."

-University of South Florida, College of Medicine, Department of Medical Microbiology and Immunology, USA.

https://pubmed.ncbi.nlm.nih.gov/12960289

The CB2 receptor and its role as a regulator of inflammation

"The CB2 receptor is the peripheral receptor for cannabinoids. It is mainly expressed in immune tissues, highlighting the possibility that the endocannabinoid system has an immunomodulatory role. In this respect, the CB2 receptor was shown to modulate immune cell functions, both in cellulo and in animal models of inflammatory diseases. In this regard, numerous studies have reported that mice lacking the CB2 receptor have an exacerbated inflammatory phenotype. This

suggests that therapeutic strategies aiming at modulating CB2 signaling could be promising for the treatment of various inflammatory conditions. Herein, we review the pharmacology of the CB2 receptor, its expression pattern, and the signaling pathways induced by its activation. We next examine the regulation of immune cell functions by the CB2 receptor and the evidence obtained from primary human cells, immortalized cell lines, and animal models of inflammation. Finally, we discuss the possible therapies targeting the CB2 receptor and the questions that remain to be addressed to determine whether this receptor could be a potential target to treat inflammatory disease."…

-Quebec University Institute of Cardiology and Pulmonology Research Center, Department of Medicine, Faculty of Medicine, Laval University, Quebec, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5075023/

■■■

"As we discussed above, several lines of evidence demonstrate that cutaneous cannabinoid signaling profoundly influences the immunogenic behavior of skin resident non-immune cells. Unfortunately, albeit effects of cannabinoid signaling on immune cells in general are well documented [31,33,141,142,212,213], much less data are available about their skin-relevant aspects."

-Department of Physiology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-Department of Immunology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-HCEMM Nonprofit Ltd., Szeged, Hungary
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429381/

Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression

"Cannabinoids are a group of compounds present in Cannabis plant (Cannabis sativa L.). They mediate their physiological and behavioral effects by activating specific cannabinoid receptors. With the recent discovery of the cannabinoid receptors (CB1 and CB2) and the endocannabinoid system, research in this field has expanded exponentially. Cannabinoids have been shown to act as potent immunosuppressive and anti-inflammatory agents and have been shown to mediate beneficial effects in a wide range of immune-mediated diseases such as multiple sclerosis, diabetes, septic shock, rheumatoid arthritis, and allergic asthma. Cannabinoid receptor 1 (CB1) is mainly expressed on the cells of the central nervous system as well as in the periphery. In contrast, cannabinoid receptor 2 (CB2) is predominantly expressed on immune cells. The precise mechanisms through which cannabinoids mediate immunosuppression is only now beginning to be understood and can be broadly categorized into four pathways: apoptosis, inhibition of

proliferation, suppression of cytokine and chemokine production and induction of T regulatory cells (T regs). Studies from our laboratory have focused on mechanisms of apoptosis induction by natural and synthetic cannabinoids through activation of CB2 receptors. In this review, we will focus on apoptotic mechanisms of immunosuppression mediated by cannabinoids on different immune cell populations and discuss how activation of CB2 provides a novel therapeutic modality against inflammatory and autoimmune diseases as well as malignancies of the immune system, without exerting the untoward psychotropic effects."….

-Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, SC, USA

https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.660.6260&rep=rep1&type=pdf

See also Macrophages

Immunoglobulin A nephropathy

'Consumption of n-3 polyunsaturated fatty acids (PUFAs) found in fish oil suppresses inflammatory processes making these fatty acids attractive candidates for both the prevention and amelioration of several organ-specific and systemic autoimmune diseases. Both pre-clinical and clinical studies have been conducted to determine whether fish oils containing the n-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) can be used in the prevention and treatment of immunoglobulin A nephropathy (IgAN) and lupus nephritis. In a toxin-induced mouse model that mimics the early stages of IgAN, n-3 PUFA consumption suppresses aberrant interleukin (IL)-6-driven IgA production and mesangial IgA immune complex deposition by impairing phosphorylation of upstream kinases and activation of transcription factors essential for IL-6 gene transcription. n-3 PUFAs can also suppress production of anti-double-stranded DNA IgG antibodies and the resultant development of lupus nephritis in the NZBW F1 mouse and related models. These effects have been linked in part to impaired expression of proinflammatory cytokines and adhesion molecules as well as increases in antioxidant enzymes in kidney and immune organs. Several recent clinical trials have provided compelling evidence that n-3 PUFA supplementation could be useful in treatment of human IgAN and lupus nephritis, although some other studies suggest such supplementation might be without benefit. Future investigations employing genomics/proteomics and novel genetically altered mice should provide further insight into how n-3 PUFAs modulate these diseases as well

help to identify clinically relevant biomarkers. The latter could be employed in future well-designed, long-term clinical studies that will resolve current controversies on n-3 PUFA efficacy in autoimmune-mediated glomerulonephritis."

-James J. Pestka, Department of Food Science and Human Nutrition, Department of Microbiology and Molecular Genetics, Center for Integrative Toxicology, Michigan State University, East Lansing, MI 48824, USA;
-Address correspondence to 234 G.M. Trout Building, Michigan State University, East Lansing, MI
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2885141/

Infants

"The clinical implications of the metabolism of the 2 essential fatty acids, linoleic and alpha-linolenic acid, are most clearly related to the membrane phospholipid concentrations of their elongation and desaturation products, arachidonic, eicosapentaenoic, and docosahexaenoic acid. Levels of these very long chain polyunsaturated fatty acids can be altered by diet, prematurity, and disease which can affect growth (nutritional repletion) and the intensity and character of systemic inflammation as well as cognitive and visual function in infants."

-Laboratory of Nutrition and Infection, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA.
https://pubmed.ncbi.nlm.nih.gov/12757109/

Polyunsaturated fatty acids in the low-birth-weight infant

https://pubmed.ncbi.nlm.nih.gov/395645/

Infertility

Relationship of omega-3 and omega-6 fatty acids with semen characteristics, and anti-oxidant status of seminal plasma: a comparison between fertile and infertile men

"**Background & aims**: Fatty acid (FA) composition of the spermatozoa may be an important determinant of fertility. The aim was to evaluate polyunsaturated fatty acid (PUFA) composition of the blood plasma and spermatozoa in infertile men with idiopathic oligoasthenoteratozoospermia (OAT).

Results: **Proven fertile men had higher blood and spermatozoa levels of omega-3 FAs compared with the infertile patients. The ratio of serum omega-6/omega-3 fatty acids was significantly higher in infertile** (14.8+/-4.3) patients compared to fertile controls (6.3+/-2.2) (P=0.001).

Additionally, levels of AA were higher and the omega-3 index (EPA+DHA) was lower in infertile subjects than in fertile controls (all P values<0.05). Infertile men had higher mean AA:DHA ratio and AA:EPA (6.4+/-2.9 and 12.0+/-4.9, respectively) than fertile men (3.3+/-1.8 and 6.7+/-2.6, respectively) (both P=0.001). A strong negative correlation was found between the AA:DHA and AA:EPA ratios and total sperm count (r=-0.62, P=0.001 and r=-0.64, P=0.001, respectively), sperm motility (r=-0.63, P=0.001 and r=-0.61, P=0.001, respectively), and sperm morphology (r=-0.61, P=0.001, and r=-0.59, P=0.002, respectively).

Conclusions: Infertile men had lower concentrations of omega-3 FAs in spermatozoa than fertile men. These results suggest that research should be performed to assess the potential benefits of omega-3 FA supplementation as a therapeutic approach in infertile men with idiopathic OAT."

-Urology and Nephrology Research Center, Department of Urology, Shahid Modarress Hospital, Shahid Beheshti University (MC), Tehran, Iran.
https://pubmed.ncbi.nlm.nih.gov/19666200/

Inflammatory Bowel Disease (IBD)

"According to the Centers for Disease Control and Prevention, the incidence of inflammatory bowel diseases (IBD) is about 1 in 250 people in the United States. The disease is characterized by chronic or recurring inflammation of the gut. Because of the localization of the endocannabinoid system in the gastrointestinal tract, it may be a potential pharmacologic target for the treatment of IBD and other diseases. Fatty acid amide hydrolase (FAAH) is a potential candidate because it is upregulated in IBD. FAAH hydrolyzes and, as a consequence, inactivates anandamide (AEA), a prominent endocannabinoid. Inhibition of FAAH would lead to increases in the amount of AEA oxidized by cytochrome P450s (P450s). "…

-Department of Pharmacology, University of Michigan, Ann Arbor, Michigan.
https://pubmed.ncbi.nlm.nih.gov/27000802/

…"IBD is classified as a group of chronic systemically natured diseases of unclear pathology which cause inflammation of the digestive tract, including Crohn's disease (CD) and ulcerative colitis (UC) [125]. While environmental factors indeed play a significant role in the etiology of the disease, more recent attention has been placed on various dietary and nutritional factors, specifically the lipid components of the diet as triggers of IBD [125, 126]. It is difficult to suggest that dietary influences or supplementation can reduce the incidence of IBD or impact beneficially (through anti-inflammatory effects) upon the disease progression since, like many chronic diseases, IBD is

multifactorial. Despite this, lower prevalence of IBD has been observed with consumption of diets rich in n-3 LC-PUFA derived from fish oils, such as that seen of the Greenland Eskimos [127, 128]. It has also been reported that patients of IBD who supplement their diets with n-3 PUFA show anti-inflammatory actions, with decreased production of LTB4 by neutrophils and colonic mucosa, resulting from incorporation of the n-3 PUFA into the gut mucosal tissue [129, 130]. A recent study using IL-10 knockout mice (mice that spontaneously develop colitis) demonstrated significantly reduced colonic inflammation when fed n-3 PUFA-rich fish oil as compared with mice that were fed n-6 PUFA-rich corn oil [131]. In Japan, increased reports in the incidence of IBD correlate with the increased dietary intake of n-6 PUFA [132, 133]. Importantly, while n-3 PUFA show decreased production of LTB4 by neutrophils and colonic mucosa [129, 130], metabolism of AA increases the production of LTB4 within the inflamed intestinal mucosa of IBD [134]. A more recent report demonstrated abnormal prevalence of the enzymes that coordinate to generate LTB4 from membrane-derived AA in active IBD biopsies [53]. The recruitment of neutrophils and other leukocytes to the IBD gut mucosa seen with colonic injury may be a direct result of the increased ability to generate LTB4 from AA [53]. It is clear from the literature that n-3 PUFA have a positive effect on reducing the risk of IBD [135–137]. The situation is less clear for n-6 PUFA, although the proinflammatory eicosanoids derived from AA have been shown to play a crucial role in the pathogenesis of all these related inflammatory disorders. As n-3 PUFA have been shown to alleviate the progression of IBD, while n-6 PUFA have been implicated in the origin of IBD, the importance of a balance in the ratio of n-6 : n-3 PUFA in today's dietary regime is highlighted.”…

-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland
-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

Polyunsaturated fatty acids, inflammatory processes and inflammatory bowel diseases

“With regard to inflammatory processes, the main fatty acids of interest are the n-6 PUFA arachidonic acid (AA), which is the precursor of inflammatory eicosanoids like prostaglandin E(2) and leukotriene B(4), and the n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are found in oily fish and fish oils. EPA and DHA inhibit AA metabolism to inflammatory eicosanoids. They also give rise to mediators that are less inflammatory than those produced from AA or that are anti-inflammatory. In addition to modifying the lipid mediator profile, n-3 PUFAs exert effects on other aspects of inflammation like leukocyte chemotaxis and inflammatory cytokine production. Some of these effects are likely due to changes in gene

expression, as a result of altered transcription factor activity. Fish oil has been shown to decrease colonic damage and inflammation, weight loss and mortality in animal models of colitis. Fish oil supplementation in patients with inflammatory bowel diseases results in n-3 PUFA incorporation into gut mucosal tissue and modification of inflammatory mediator profiles. Clinical outcomes have been variably affected by fish oil, although some trials report improved gut histology, decreased disease activity, use of corticosteroids and relapse."

-Philip C Calder
-Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, UK
https://pubmed.ncbi.nlm.nih.gov/18504706/

See also Supplements

Inflammation & The Endocannabinoid System (ECS)

Cannabinoid signalling regulates inflammation and energy balance: the importance of the brain-gut axis.

"Energy balance is controlled by centres of the brain which receive important inputs from the gastrointestinal tract, liver, pancreas, adipose tissue and skeletal muscle, mediated by many different signalling molecules. Obesity occurs when control of energy intake is not matched by the degree of energy expenditure. Obesity is not only a state of disordered energy balance it is also characterized by systemic inflammation. Systemic inflammation is triggered by the leakage of bacterial lipopolysaccharide through changes in intestinal permeability. The endocannabinoid system, consisting of the cannabinoid receptors, endogenous cannabinoid ligands and their biosynthetic and degradative enzymes, plays vital roles in the control of energy balance, the control of intestinal permeability and immunity. In this review we will discuss how the endocannabinoid system, intestinal microbiota and the brain-gut axis are involved in the regulation of energy balance and the development of obesity-associated systemic inflammation. Through direct and indirect actions throughout the body, the endocannabinoid system controls the development of obesity and its inflammatory complications."

Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary
https://www.ncbi.nlm.nih.gov/pubmed/22269477

Inflammation can lead to circadian sleep disorders

“Inflammation, which is the root cause of autoimmune disorders including arthritis, Type 1 diabetes, irritable bowel syndrome and Crohn's disease, has unexpected effects on body clock function and can lead to sleep and shiftwork-type disorders, a new Northwestern Medicine study in mice Found.“

-Northwestern University

https://www.sciencedaily.com/releases/2018/10/181031124858.htm

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“The endocannabinoid anandamide exerts neurobehavioral, cardiovascular, and immune-regulatory effects through cannabinoid receptors (CB). Fatty acid amide hydrolase (FAAH) is an enzyme responsible for the in vivo degradation of anandamide. Recent experimental studies have suggested that targeting the endocannabinergic system by FAAH inhibitors is a promising novel approach for the treatment of anxiety, inflammation, and hypertension. “

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

-The Skaggs Institute for Chemical Biology and Department of Cell Biology, The Scripps Research Institute, La Jolla, California

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225481/

Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation

“This review covers reports published in the last 5 years on the anti-inflammatory activities of all classes of cannabinoids, including phytocannabinoids such as tetrahydrocannabinol and cannabidiol, synthetic analogs such as ajulemic acid and nabilone, the endogenous cannabinoids anandamide and related compounds, namely, the elmiric acids, and finally, noncannabinoid components of Cannabis that show anti-inflammatory action. It is intended to be an update on the topic of the involvement of cannabinoids in the process of inflammation. A possible mechanism for these actions is suggested involving increased production of eicosanoids that promote the resolution of inflammation. This differentiates these cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process.”

-Department of Biochemistry & Molecular Pharmacology, University of Massachusetts Medical School, 364 Plantation St., Worcester, Massachusetts 01605 USA

-Department of Medicine, University of Massachusetts Medical School, 364 Plantation St., Worcester, Massachusetts 01605 USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2664885/

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…"This review has focused on the emerging roles of endocannabinoids on the haematological system. However, it is well established that cannabinoids have significant effects on white blood cells and inflammation, such that endocannabinoids are viewed as important immunomodulators. Indeed, the therapeutic potential of cannabinoid-based drugs in managing inflammation and neuroinflammation is under investigation. This area of cannabinoid pharmacology is now well established and the reader is referred to reviews elsewhere (for example, Maccarrone et al., 2002; Walter and Stella, 2004; Croxford and Yamamura, 2005)."…

-School of Biomedical Sciences, University of Nottingham Medical School, Nottingham, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2190025/

See also Blood Cells

Inflammation in Health & Disease

Implications of CB2 [cannabinoid receptor 2] in Inflammatory Disorders

"The potential for the ECS to have an immunomodulatory role through the targeting of CB2 has gained much interest in several inflammatory conditions. Several in vitro and in vivo studies have provided evidence to support an anti-inflammatory role for CB2 in several inflammatory conditions. Administration of CB2-specific ligands exerts anti-inflammatory effects on various immune cells by downregulating cytokine release [127–129] and reducing production of reactive oxygen species [130]. The beneficial immunomodulatory role for CB2 has been examined in several acute inflammatory conditions, including dinitrofluorobenzene-induced hypersensitivity [131], LPS-induced interstitial cystitis [132], sepsis [133], traumatic brain injury [134], and experimental autoimmune encephalomyelitis [135]. In these studies, mice lacking a functional CB2 receptor developed a worsened inflammatory state, characterized by increased leukocyte infiltration and pro-inflammatory cytokine release [131, 136]. Conversely, activation of CB2 by administration of an exogenous agonist reduced the production of pro-inflammatory cytokines and migration of immune cells in animal models of acute inflammation [132–135].

The potential for CB2 modulation in inflammatory conditions extends beyond acute inflammatory disorders. CB2 also exerts beneficial effects in animal models of chronic inflammatory illnesses, such as rheumatoid arthritis [137, 138], collagen-induced arthritis [139], inflammatory bowel disease [140–145], amyotrophic lateral sclerosis ([146, 147]), and atherosclerosis (as

reviewed here)."

-Department of Biomedical Sciences, Center for Inflammation, Infectious Disease and Immunity, Quillen College of Medicine, East Tennessee State University, Johnson City, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020134/

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.."Inflammation has long been recognized as a major cause of disease. It is estimated that some 15% of human cancers are associated with chronic infection and inflammation [83]. Acute and chronic inflammation-mediated tissue injury is observed in many organ systems, including the heart, pancreas, liver, kidney, lung, brain, intestinal tract, and reproductive system."...

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, Chengdu, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

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"Inflammation is the common link among the leading causes of death. Mechanistic studies have shown how various dietary components can modulate key pathways to inflammation including sympathetic activity, oxidative stress, transcription factor nuclear factor kappa B (NF-κB) activation, and proinflammatory cytokine production. Behavioral studies have demonstrated that stressful events and depression can also influence inflammation through these same processes. If the joint contributions of diet and behavior to inflammation were simply additive, they would certainly be important. However, several far more intriguing interactive possibilities are discussed: stress influences food choices; stress can enhance maladaptive metabolic responses to unhealthy meals; and diet can impact mood as well as proinflammatory responses to stressors. Furthermore, because the vagus nerve innervates tissues involved in the digestion, absorption, and metabolism of nutrients, vagal activation can directly and profoundly influence metabolic responses to food, as well as inflammation; in turn, both depression and stress have well-documented negative effects on vagal activation, contributing to the lively interplay between the brain and the gut. As one example, omega-3 fatty acid intake can boost mood and vagal tone, dampen NF-κB activation and responses to endotoxin, and modulate the magnitude of inflammatory responses to stressors. A better understanding of how stressors, negative emotions, and unhealthy meals work together to enhance inflammation will benefit behavioral and nutritional research, as well as the broader biomedical community..."

-Janice K. Kiecolt-Glaser, Ph.D.

-Department of Psychiatry and The Ohio State Institute for Behavioral Medicine Research, The Ohio State University College of Medicine, Columbus, Ohio;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2868080/

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Novel Lipid Mediators and Resolution Mechanisms in Acute Inflammation

To Resolve or Not?

"Because inflammation is appreciated as a unifying basis of many widely occurring diseases, the mechanisms involved in its natural resolution are of considerable interest. Using contained, self-limited inflammatory exudates and a systems approach, novel lipid-derived mediators and pathways were uncovered in the resolution of inflammatory exudates. These new families of local mediators control both the duration and magnitude of acute inflammation as well as the return of the site to homeostasis in the process of catabasis."…

-Charles N. Serhan

-Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine

- Harvard Institutes of Medicine, Brigham

-Women's Hospital and Harvard Medical School, Boston, Massachusetts

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2947253/pdf/main.pdf

Low-grade inflammation, diet composition and health: current research evidence and its translation

..."An unresolved inflammatory response is likely to be involved from the early stages of disease development. "…

-Department of Nutrition, Norwich Medical School, University of East Anglia, Norwich, UK

-Mondelēz International – R&D, Nutrition Department , Saclay, France

-Rowett Institute of Nutrition and Health, University of Aberdeen, Aberdeen, UK

-Formerly ILSI Europe a.i.s.b.l., Avenue E. Mounier 83, Box 6, B-1200, Brussels, Belgium

-Nutrigenomics Research Group, UCD Institute of Food and Health and UCD Conway Institute, Belfield, University College Dublin, Dublin 4, Republic of Ireland

-Department of Food Quality and Nutrition, Research and Innovation Centre, Fondazione Edmund Mach, San Michele all'Adige, Trento, Italy

-Centre for Biological Sciences, Faculty of Natural and Environmental Sciences, University of Southampton, Southampton, UK

-Department of Human Biology, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands

-Nutrigenomics and Neurodegenerative Disease Prevention, Preventative Health Flagship, CSIRO, Animal, Food and Health Sciences, Adelaide, Australia

-Microbiology and Systems Biology, TNO, Zeist, 3704, HE, The Netherlands

-Newtricious R&D B.V., Oirlo, AL, The Netherlands

-School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK

-Department of Internal Medicine, University of Perugia, Perugia, Italy

-Hugh Sinclair Unit of Human Nutrition, Department of Food and Nutritional Sciences, University of Reading, Reading, UK

Faculty of Medicine, University of Southampton, Southampton, UK

-NIHR Southampton Biomedical Research Centre, Southampton University Hospital NHS Foundation Trust and University of Southampton, Southampton, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4579563/

■■■

"Inflammation is a well-known contributing factor to many age-related chronic diseases. One of the possible strategies to suppress inflammation is the employment of functional foods with anti-inflammatory properties."

University of Western Sydney, School of Medicine, Locked Bag 1797, Penrith, Australia.

https://www.ncbi.nlm.nih.gov/pubmed/24262531/

Understanding migraine: Potential role of neurogenic inflammation.

"These findings provide support for the validity of using animal models to investigate mechanisms of neurogenic inflammation in migraine. These also further strengthen the notion of migraine being a neuroinflammatory disease."

Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA.

https://www.ncbi.nlm.nih.gov/pubmed/27293326/

■■■

…"International organisations and many scientists continue to consider obesity the result of an imbalance between energy intake and expenditure. Citing the law of thermodynamics, scientists and industries articulated the concept of 'a calorie is a calorie', which led to the development of a huge weight loss industry, various diets substituting 'calories for other calories' and books promoting 'eat less and exercise more'. These approaches continue to be espoused today, despite the scientific evidence that 'a calorie is not a calorie', and that the sources of calories are important in influencing human metabolism and appetite control.[4–6] For example, calories from vegetable oils high in linoleic acid (LA), an ω-6 [omega-6] fatty acid, are proinflammatory and thrombogenic, whereas calories from eating fish high in ω-3 [omega-3] fatty acids are anti-inflammatory and antithrombotic. High ω-6 fatty acid intake increases white adipose tissue that is stored and prevents its browning.[7 8] Furthermore, calories from ω-6 fatty acid intake from vegetable oils high in LA (corn oil, sunflower, safflower, cottonseed, soya bean oil) have different

effects on fat tissue development and type than calories from ω-3 fatty acid intake high in α-linolenic acid (ALA) (such as flaxseed oil, canola oil, perilla oil, chia oil). In addition, high ω-6 fatty acid intake leads to an inflammatory state, which is at the basis of obesity and other chronic diseases, whereas calories from ω-3 fatty acids have the opposite effect[9 10 (box 1 and table 1)]. ω-6 and ω-3 fatty acids are essential for health and must be obtained from the diet by all mammals including human beings."…

-The Center for Genetics, Nutrition and Health, Washington, DC, USA
-Saint Luke's Mid America Heart Institute, Kansas, Missouri, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5093368/

Inflammatory responses and inflammation-associated diseases in organs

"Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation [1], and acts by removing injurious stimuli and initiating the healing process [2]. Inflammation is therefore a defense mechanism that is vital to health [3]. Usually, during acute inflammatory responses, cellular and molecular events and interactions efficiently minimize impending injury or infection. This mitigation process contributes to restoration of tissue homeostasis and resolution of the acute inflammation. However, uncontrolled acute inflammation may become chronic, contributing to a variety of chronic inflammatory diseases [4].

At the tissue level, inflammation is characterized by redness, swelling, heat, pain, and loss of tissue function, which result from local immune, vascular and inflammatory cell responses to infection or injury [5]. Important microcirculatory events that occur during the inflammatory process include vascular permeability changes, leukocyte recruitment and accumulation, and inflammatory mediator release [2, 6].

Various pathogenic factors, such as infection, tissue injury, or cardiac infarction, can induce inflammation by causing tissue damage. The etiologies of inflammation can be infectious or non-infectious (Table (Table1).1). In response to tissue injury, the body initiates a chemical signaling cascade that stimulates responses aimed at healing affected tissues. These signals activate leukocyte chemotaxis from the general circulation to sites of damage. These activated leukocytes produce cytokines that induce inflammatory responses [7]."….

"Inflammatory pathways impact the pathogenesis of a number of chronic diseases, and involve common inflammatory mediators and regulatory pathways. Inflammatory stimuli activate intracellular signaling pathways that then activate production of inflammatory mediators."

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China
- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University,

Wenjiang, Chengdu, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

Diet and Chronic Diseases: Is There a Mediating Effect of Inflammation?

"Chronic non-communicable diseases like cardiovascular disease (CVD) and diabetes represent the majority of the current burden of disease worldwide, with higher rates and impacts in developed countries but also with alarming trends in developing countries [1,2]. Among the major risk factors, dietary components have been recently shown to play a crucial role, with a double burden of malnutrition affecting both developed and developing countries [1,3]; the risks associated with malnutrition, intended not only as over-nutrition but also as poor diet quality, have been reported to significantly impact not only cardio-metabolic disorders (far more studied over the last decades), but also cancer and certain aspects related to mental health [4,5]. All these groups of diseases, in spite of the different organs and systems involved, disability and prognosis impacted, have been hypothesized and partially demonstrated to have a common risk factor, or starting point, in general low-grade, clinically silent inflammation [6]. Such inflammatory state is supposed to be assessed through testing for biomarkers, such as pro-inflammatory cytokines, and may be caused by a number of conditions, including, but not limited to, obesity (pro-inflammatory cytokines are produced by an excess of adipose tissue), active smoking, and exercising [7,8,9]. These observations provided the rationale for the hypothesis that diet may modify the risk of major chronic non-communicable diseases by affecting the inflammatory status [10]."…

"Other studies have been conducted lately, including studies summarizing the evidence of the inflammatory potential of diet increasing the risk of depression [25], certain cancer, such as gynecological, urological, and colorectal cancers [26,27,28], and mortality [29,30]. Future studies further elucidating and describing the mechanistic processes involved with a pro-inflammatory diet and the development of chronic non-communicable diseases would provide definitive evidence for the usability of the DII tool and its application in clinical setting for testing current diets and, eventually, for promoting improvements to diet quality."

-South Carolina Statewide Cancer Prevention and Control Program, University of South Carolina, Columbia, SC , USA;
-Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC, USA
-Connecting Health Innovations LLC, Columbia, SC, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6683086/

Terminology to Describe Inflammation of various Body Parts

arthro-	joint	arthritis	inflamed joints
broncho-	bronchial tubes	bronchitis	inflammation of the bronchial tubes
cardiac-	heart	carditis	inflammation of the heart
cerebo-	brain	cerebritis	inflammation of the brain
choleo-	gallbladder	cholecystitis	inflamed gallbladder
conjunctiva-	outer lining of the eye	conjunctivitis	inflammation of the outer lining of the eye
dermis-	skin	dermatitis	inflamed skin
gastric-	stomach	gastritis	inflammation of the stomach lining
hepato-	liver	hepatitis	inflamed liver
myo-	muscle	myositis	inflammed muscle
nephro-	kidney	nephritis	inflamed kidney
neuro-	nerve	neuritis	inflamed nerves
osteo-	bone	osteitis	inflamed bone
periodontal-	gums	periodontitis	inflamed gums
pneumo-	lungs	pneumonitis	inflamed lungs
salpingo-	fallopian tubes	salpingitis	inflamed fallopian tubes
vagina-	vagina	vaginitis	inflammation of the of the vagina
vascular-	blood vessel	vasculitis	inflamed blood vessels

“Inflammation is set off by insult or injury to the body, and it turns out that the body can be pretty sensitive to insults. Inflammation can occur in reaction to infections, physical injuries, exposure to chemicals and allergens, stretching and manipulation of body tissue, burns, lacerations, and contusions. Sometimes substances occurring naturally in one’s own body can trigger inflammation, in what is called autoimmunity. And under the right circumstances, stress or other emotional reactions may trigger inflammation in some people.

Not only can just about any provocation set off inflammation, but virtually any tissue or organ can be inflamed. In medicine, the suffix -itis is added to words to denote inflammation of the organ or tissue represented by that word. So anytime you see a word that ends in -itis, the subject is inflammation. For example, the Greek word rhino refers to nose, so the word rhinitis

refers to inflammation (of the inner lining) of the nose. Arthro- refers to joints, so arthritis refers to inflammation of the joints. A person with arthritis has joints that are painful and swollen, and which can also be red and hot. Table 2-1 lists the medical terms for different body parts, along with the word that describes inflammation of that part. Pain is closely related to inflammation. Even the lightest touch can cause severe pain in inflamed tissue. This is one of the reasons doctors squeeze and poke and prod at various locations of your body when you are sick. They are trying to locate potential sites of inflammation. In medicine, the suffix -algia means "pain." Hence, arthralgia means "pain in a joint." A person with arthritis (inflammation of the joints) has arthralgia (pain in the joints), but there are other causes of arthralgias in addition to inflammation."

- Terminology Table and Quote above are from the book
The Inflammation Cure, Dr. William Joel Meggs, M.D., Ph.D. (Pg. 15-16)

■■■

.."Inflammation is a cellular response to a traumatic injury, irritation from toxic chemicals, or infection caused by microbial pathogens. This complex process involves numerous pathways of cellular and plasma origin with interrelated biological events, often leading to painful conditions, such as in rheumatoid arthritis, asthma, allergy, inflammatory bowel syndrome, atherosclerosis, and neurodegenerative disease [1,2]. The phenomena of inflammations are largely regulated by various mediators like reactive oxygen and nitrogen intermediates, prostacyclins, prostaglandin, leukotrienes, cytokines, and histamine, which could be expressed in macrophages, hepatocytes, and endothelial or smooth muscle cells [3]. One of distinctive mediators is nitric oxide radical, generated from the terminal guanido-nitrogen atom of l-arginine by NADPH-dependent enzymes known as nitric oxide synthase (NOS), of which the Ca2+ independent inducible form (iNOS) has been expressed in inflamed tissues in response to lipopolysaccharide (LPS), interferon-gamma (INF-γ), tumor necrosis factor (TNF), interleukin-1beta (IL-1β), and found to be responsible for the pathophysiology of inflammation [4]. The highly reactive nitric oxide radical could be initiated form another stronger oxidant, viz. peroxynitrite (ONOO−) by combining with superoxide anion radicals, harmful to functional normal tissues [5,6]. This aforementioned statement reflects the role of reactive oxygen and nitrogen species in the pathophysiology of inflammation. In addition scavenging of superoxide radicals and suppression of nitric oxide and iNOS protein could represent a novel therapeutic approach against inflammatory diseases.

In general, steroids and cyclooxygenase inhibitors such as prednisolone, aspirin, and indomethacin have long been used as the main therapeutic anti-inflammatory agents, but they

are frequently associated with significant detrimental effects in patients especially gastrointestinal toxicity [7,8]. Non-steroidal anti-inflammatory drugs (NSAIDs) clearly promote reactive oxygen species (ROS) production. It was proposed that NSAID-mediated gastrointestinal lesions involve the uncoupling of oxidative phosphorylation and inhibition of the electron transport chain causing incomplete reduction of oxygen. Indomethacin, a potent NSAID, was found to bind to a site near complex I and ubiquinone to generate ROS [9,10], and ROS can damage cellular lipids, proteins, and DNA, leading to oxidative stress [11]. Potentially developing natural alternative anti-inflammatory supplements have, thus, increasingly become important [12]. This approach seemingly overcomes the incidences of drug related toxicity and iatrogenic reactions caused by 90% of the non-steroidal anti-inflammatory drugs (NSAIDs) commonly used for treatment of inflammatory conditions [13]. Hence, it would be interesting to explore some of the exotic dietary ingredients customary in ethnic cultures around the world so that the natural product with prospective anti-inflammatory properties could be well-documented and validated scientifically."…

-Department of Physiology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, Thailand;
-Center for Advanced Studies for Agriculture and Food, Kasetsart University, Bangkok, Thailand;
-Department of Biomedical Sciences, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6272999

An update on the role of omega-3 fatty acids on inflammatory and degenerative diseases

"Inflammation is involved in the pathophysiology of many chronic diseases, such as rheumatoid arthritis and neurodegenerative diseases. Several studies have evidenced important anti-inflammatory and immunomodulatory properties of omega-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs). This review illustrates current knowledge about the efficacy of n-3 LC-PUFAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), particularly) in preventing and/or treating several chronic inflammatory conditions (inflammatory bowel diseases and rheumatoid arthritis) as well as their potential benefits on neurodegenerative diseases. It is well established that n-3 LC-PUFAs are substrates for synthesis of novel series of lipid mediators (e.g., resolvins, protectins, and maresins) with potent anti-inflammatory and pro-resolving properties, which have been proposed to partly mediate the protective and beneficial actions of n-3 LC-PUFAs. "…

-Department of Nutrition, Food Science and Physiology and Center for Nutrition Research, University of Navarra, Pamplona, Spain
https://pubmed.ncbi.nlm.nih.gov/25752887/

See also Pro-Inflammation , Omega Ratio

Inflammation & Immune Function

“Several experimental studies showed that a dietary intake of n-3 PUFAs and the improvement in omega-6 and omega-3 ratio could modulate the immune and inflammatory response. After a three-week supplementation with 3.2 g EPA and 2.2 g DHA, an increased content of EPA in neutrophils and monocytes was reported [28]. The anti-inflammatory effects of fish oils are partly mediated by inhibiting the 5-lipoxygenase pathway in neutrophils and monocytes and inhibiting the leukotriene B4 (LTB4)-mediated function of leukotriene B5 (LTB5). In addition, omega-3 decrease interleukins IL-1 and IL-6 inhibits inflammation. For example, rheumatoid arthritis has a strong inflammatory component, which is observed through increased interleukin 1, IL-1 [29]. N-3 PUFAs reduce IL-1 as well as the number of swollen and tender joints. Supplementation with EPA and DHA and the dietary change in the n-6/n-3 ratio appears to be an effective treatment for patients associated with traditional therapies. Similarly, they might be helpful in preventing and contrasting inflammatory joint pain, which can relate to repeated mechanical stress, overuse, and subsequent joint wear, which is typical of sport practice.

Inflammation is characterized by an increase of prostaglandins (PGs), cytokines, and other pro-inflammatory mediators. The ROS produce peroxidation of phospholipid membranes and damage DNA and intracellular proteins. A diet rich of n-3 PUFAs provides photoprotection and contrasts the risk of skin tumors induced by ultraviolet [30]. They compete with arachidonic acid (AA) for the metabolism by cyclooxygenases (COX)/lipoxygenases, which decrease PGs and cytokines [31]. N-3 PUFAs reduce oxidative, inflammatory, and vasogenic processes. In this regard, they were tested in several studies in order to display the reduction of the symptoms of atopic dermatitis, sunburn, aging, and skin infections caused by P. Acnes and S. Aureus because of their anti-microbial and anti-inflammatory action [32]. A higher consumption of n-3 PUFAs improve the response of anti-inflammatory cytokines, LTB3 and PGE3, against the production of AA.

As well as altering eicosanoid production, n-3 PUFAs can also reduce activation of the NF-κB pathway, reducing inflammatory cytokine production contrasting the omega-6 fatty acid AA, which is a known stimulator of NF-κB activity [33]. They also prevent the degradation and subsequent translocation of the NF-κB complex to the nucleus where it induces transcription of inflammatory cytokines. In addiction, a reduction in circulating tumor necrosis factor α (TNF-α)

concentrations, as well as in the expression of inflammatory cytokines and cell surface adhesion molecules has been observed [33]."

-Human and Clinical Nutrition Unit, Department of Medical, Oral and Biotechnological Sciences, University G. D'Annunzio, 66100 Chieti, Italy;

-Cardiology Unit, Cardiology Department, San Camillo De Lellis Hospital, Manfredonia, Foggia, Italy

-Department of Internal and Specialistic Medicine DIBIMIS, University of Palermo, Palermo, Italy;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6357022/

Inflammatory Markers

…"Markers are used in clinical applications to indicate normal versus pathogenic biological processes, and assess responses to therapeutic interventions. Inflammatory markers may be predictive of inflammatory diseases [45–50], and correlate with the causes and consequences of various inflammatory diseases, such as cardiovascular diseases, endothelial dysfunctions, and infection [51, 52]. Stimuli activate inflammatory cells, such as macrophages and adipocytes, and induce production of inflammatory cytokines, such as IL-1β, IL-6, TNF-α, and inflammatory proteins and enzymes. These molecules can potentially serve as biomarkers for diseases diagnosis, prognosis, and therapeutic decision making [53–57].

Inflammatory cytokines

Cytokines (Table (Table2)2) are predominantly released from immune cells, including monocytes, macrophages, and lymphocytes. Pro- and anti-inflammatory cytokines facilitate and inhibit inflammation, respectively. Inflammatory cytokines are classified as ILs, colony stimulating factors (CSF), IFNs, TNFs, TGFs, and chemokines, and are produced by cells primarily to recruit leukocytes to the site of infection or injury [58]. Cytokines modulate the immune response to infection or inflammation and regulate inflammation itself via a complex network of interactions. However, excessive inflammatory cytokine production can lead to tissue damage, hemodynamic changes, organ failure, and ultimately death [59, 60]. A better understanding of how to regulate cytokine pathways would allow for more accurate identification of agent-mediated inflammation and the treatment of inflammatory diseases [58]."…

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, Chengdu, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

See also Cytokine Network , Cytokine Storm , Prostaglandins ,

Inflammaging

"'Inflammaging' refers to the chronic, low-grade inflammation that characterizes aging. Inflammaging is macrophage centered, involves several tissues and organs, including the gut microbiota, and is characterized by a complex balance between pro- and anti-inflammatory responses."

-Institute of Neurological Sciences of Bologna IRCCS, Bologna, Italy
-Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Italy
-Interdepartmental Centre 'L. Galvani' (CIG), University of Bologna, 40126 Bologna, Italy
-Department of Clinical Sciences and Community Health (DISCCO), University of Milan, Milan, Italy
-Laboratory of Endocrine and Metabolic Research, Istituto Auxologico Italiano IRCCS, Cusano Milanino (MI), Italy
https://www.sciencedirect.com/science/article/abs/pii/S1043276016301254

Redefining Chronic Inflammation in Aging and Age-Related Diseases: Proposal of the Senoinflammation Concept

…"The inflammatory process is an essential immunological defense system in living organisms that has evolved to enhance species survival. Short-term, acute inflammation is a first-line defense mechanism that acts against harmful agents, such as pathogens, toxins, or allergens. Under normal conditions, the tightly coordinated actions of various defense components including immune cells, endogenous anti-inflammatory agents, and tissue remodeling processes enable the resolution of acute inflammation by facilitating the elimination of pathogens, infected cells, and repair to damaged tissues to restore body homeostasis [1].

However, when this intricate acute inflammatory response fails to resolve and persists, more defense components are mobilized to create a long-term unresolved immune response known as chronic inflammation. Chronic inflammation, which typically manifests itself in a low-grade manner for a prolonged period, involves macrophage- and lymphocyte-accumulated leukocytes [2], and various other cellular components. It is important to recognize that this chronic inflammation is causally associated with changes in the cellular redox state and cell death signaling pathways [3].

One of the major changes that occur during aging is the dysregulation of the immune response, leading to a chronic systemic inflammatory state. Among the dysregulated proinflammatory mediators, cytokines and chemokines are major culprits in the development of chronic inflammation and the immunosenescence process.

For instance, interleukin (IL)-6, tumor necrosis factor (TNF)-α, and their receptors, are upregulated in aged tissues and cells [4]. Elevated levels of chemokines and C-reactive protein (CRP) have been found to be involved in age-related pathogenesis [5]. We have previously reported that several key intra- or inter-cellular signaling pathways are closely associated with age-related chronic inflammatory changes during aging [3,6-9].

In the aging literature, there are currently two major hypotheses related to age-related inflammation: inflammaging [10,11] and molecular inflammation [3,12-15]. These two are complementary to each other to a large extent but differ in their focus on age-related inflammatory phenomena. However, recent advances in the inflammation field have made it abundantly clear that age-related chronic inflammation needs to be comprehensively defined at the molecular, cellular, and systemic levels. Because chronic inflammation is so widely and deeply involved in many age-related chronic disorders such as atherosclerosis, diabetes, obesity, sarcopenia, and Alzheimer's disease [15], it is necessary to establish a new pathophysiological basis for chronic inflammation in relation to the aging process.

This review summarizes the current knowledge in the field of age-related inflammation. We further discuss the proinflammatory pathways involved in regulating the immunosenescence process and age-related chronic inflammation. We present a new concept with an expanded view of the overall picture of age-related chronic inflammation, which we call senescent inflammation (in short, "senoinflammation"). The salient feature of this concept is to incorporate many proinflammatory mechanisms that have not been previously considered to be important in age-related chronic inflammation."...

-Molecular Inflammation Research Center for Aging Intervention (MRCA), Department of Pharmacy, College of Pharmacy, Pusan National University, Busan 609-735, Korea.

-Pathological and Analytical Center, Korea Institute of Toxicology, Daejeon 34114, Korea.

-Department of Internal Medicine, Pulmonary, Allergy, Critical Care & Sleep Medicine, The Ohio State University, Columbus, OH 43210, USA.

-Korean Medicine (KM)-Application Center, Korea Institute of Oriental Medicine (KIOM), Daegu 41062, Republic of Korea.

-Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, VA 20147, USA.

-Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan 50612, Korea.

-Department of Biopharmaceutical Engineering, Division of Chemistry and Biotechnology, Dongguk University, Gyeongju 38066, Korea.

-Department of Physiology, The University of Texas Health Science Center at San Antonio, TX 78229, USA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6457053/

The beneficial role of anti-inflammatory dietary ingredients in attenuating markers of chronic low-grade inflammation in aging

“Aging in humans is associated with chronic low-grade inflammation (systemic), and this condition is sometimes referred to as "inflammaging". In general, canines also age similarly to humans, and such aging is associated with a decline in mobility, joint problems, weakened muscles and bones, reduced lean body mass, cancer, increased dermatological problems, decline in cognitive ability, reduced energy, decreased immune function, decreased renal function, and urinary incontinence. Each of these conditions is also associated with an increase in pro-inflammatory cytokines. An inflammatory state characterized by an increase in pro-inflammatory markers including but not restricted to tumor necrosis factor-α, interleukin-6, IL-1β, and C-reactive protein (CRP) is believed to contribute to or worsen a general decline in biological mechanisms responsible for physical function with aging. Nutritional management of inflammation in aging dogs is important in maintaining health. In particular, natural botanicals have bioactive components that appear to have robust anti-inflammatory effects and, when included in the diet, may contribute to a reduction in inflammation. While there are scientific data to support the anti-inflammatory effects and the efficacy of such bioactive molecules from botanicals, the clinical data are limited and more studies are needed to validate the efficacy of these ingredients. This review will summarize the role of dietary ingredients in reducing inflammatory molecules as well as review the evidence available to support the role of diet and nutrition in reducing chronic low-grade systemic inflammation in animal and human studies with a special reference to canines, where possible.”

-Kiran S Panickar, Dennis E Jewell
-Hormone Molecular Biology and Clincal Investigation
https://pubmed.ncbi.nlm.nih.gov/26124060/

Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases.

“Human aging is characterized by a chronic, low-grade inflammation, and this phenomenon has been termed as "inflammaging." Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly people, as most if not all age-related diseases share an inflammatory pathogenesis. Nevertheless, the precise etiology of inflammaging and its potential causal role in contributing to adverse health outcomes remain largely unknown. The identification of pathways that control age-related inflammation across multiple systems is therefore important in order to understand whether treatments that modulate inflammaging may be beneficial in old people. The session on inflammation of the Advances in Gerosciences

meeting held at the National Institutes of Health/National Institute on Aging in Bethesda on October 30 and 31, 2013 was aimed at defining these important unanswered questions about inflammaging. This article reports the main outcomes of this session."

-DIMES, Department of Experimental, Diagnostic and Specialty Medicine and CIG, Interdepartmental Center "Luigi Galvani", University of Bologna, Italy. IRCCS Institute of Neurological Sciences, and CNR-ISOF, Bologna, Italy.

-Buck Institute for Research on Aging, Novato, California. Life Sciences Division, Lawrence Berkeley National Laboratory, California.

https://www.ncbi.nlm.nih.gov/pubmed/24833586

Inflammaging: a new immune-metabolic viewpoint for age-related diseases.

"Ageing and age-related diseases share some basic mechanistic pillars that largely converge on inflammation. During ageing, chronic, sterile, low-grade inflammation - called inflammaging - develops, which contributes to the pathogenesis of age-related diseases. From an evolutionary perspective, a variety of stimuli sustain inflammaging, including pathogens (non-self), endogenous cell debris and misplaced molecules (self) and nutrients and gut microbiota (quasi-self). A limited number of receptors, whose degeneracy allows them to recognize many signals and to activate the innate immune responses, sense these stimuli. In this situation, metaflammation (the metabolic inflammation accompanying metabolic diseases) is thought to be the form of chronic inflammation that is driven by nutrient excess or overnutrition; metaflammation is characterized by the same mechanisms underpinning inflammaging. The gut microbiota has a central role in both metaflammation and inflammaging owing to its ability to release inflammatory products, contribute to circadian rhythms and crosstalk with other organs and systems. We argue that chronic diseases are not only the result of ageing and inflammaging; these diseases also accelerate the ageing process and can be considered a manifestation of accelerated ageing. Finally, we propose the use of new biomarkers (DNA methylation, glycomics, metabolomics and lipidomics) that are capable of assessing biological versus chronological age in metabolic diseases."

-IRCCS, Institute of Neurological Sciences of Bologna, Bologna, Italy.

-Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy.

-Clinical Chemistry, Department of Laboratory Medicine, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden.

-Laboratory of Cell Biology, Rizzoli Orthopaedic Institute, Bologna, Italy.

-CNR Institute of Molecular Genetics, Unit of Bologna, Bologna, Italy.

-Laboratory of Molecular Anthropology and Centre for Genome Biology, Department of Biological, Geological and Environmental Sciences (BiGeA), University of Bologna, Bologna, Italy.

-Interdepartmental Centre 'L. Galvani' (CIG), University of Bologna, Bologna, Italy.

https://www.ncbi.nlm.nih.gov/pubmed/30046148

Human Inflammaging

“Human aging is a very complex process that occurs in an intricate biological and physiological setting. Many changes occur with aging and among the most important are changes in immune reactivity associated with cell differentiation stages and the phenomenon of inflammaging, understood as subclinical inflammatory readiness, manifested by elevated levels of proinflammatory factors. It was stated for a long time that this tandem occurs in parallel or eventually sequentially. However, recent evidence points to the fact that, as both originate from chronic antigen stimulation, they mutually drive each other. In this context, inflammaging is considered the basis of most age-related diseases (ARD). In this review concerning human inflammaging, we argue that inflammatory diseases develop during whole life as a diverted (excessive) normal immune reaction to specific stressors. Thus, inflammaging may not be the cause of these diseases; however, it can be the trigger of clinical manifestation of ARD. In this context, the best intervention should aim to regulate the balance between pro- and anti-inflammatory signals and the more appropriate reaction to chronic stimulations to avoid/delay the appearance of associated diseases.”

-Research Center on Aging, Graduate Program in Immunology, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Québec, Canada

-Singapore Immunology Network (SIgN), Agency for Science Technology and Research, Singapore.

-Department of Biology, Faculty of Science, University Tunis El Manar, Tunis, Tunisia.

-Department of Pathophysiology, Medical University of Gdansk, Gdansk, Poland.

https://pubmed.ncbi.nlm.nih.gov/31055573

Inflammaging and 'Garb-aging'

“'Inflammaging' refers to the chronic, low-grade inflammation that characterizes aging. Inflammaging is macrophage centered, involves several tissues and organs, including the gut microbiota, and is characterized by a complex balance between pro- and anti-inflammatory responses. Based on literature data, we argue that the major source of inflammatory stimuli is represented by endogenous/self, misplaced, or altered molecules resulting from damaged and/or dead cells and organelles (cell debris), recognized by receptors of the innate immune system. While their production is physiological and increases with age, their disposal by the proteasome via autophagy and/or mitophagy progressively declines. This 'autoreactive/autoimmune' process fuels the onset or progression of chronic diseases that can accelerate and propagate the aging process locally and systemically. Consequently, inflammaging can be considered a major target for antiaging strategies.”

-Institute of Neurological Sciences of Bologna IRCCS, Italy.
-Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Italy;
-Interdepartmental Centre 'L. Galvani' (CIG), University of Bologna, Bologna, Italy.
-Department of Clinical Sciences and Community Health (DISCCO), University of Milan, Milan, Italy; Laboratory of Endocrine and Metabolic Research, Istituto Auxologico Italiano IRCCS, Italy.
-Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Italy;
-Interdepartmental Centre 'L. Galvani' (CIG), University of Bologna, Bologna, Italy.
https://pubmed.ncbi.nlm.nih.gov/27789101/

Inflammaging: disturbed interplay between autophagy and inflammasomes

In 2000, Franceschi et al. [1] coined the term "inflammaging" in order to refer to a low-grade pro-inflammatory status appearing during the aging process. They emphasized the role of macrophages as well as cellular stress and genetic factors in the generation of the inflammaging condition. In addition, they hypothesized that this inflammatory environment could predispose the organism to the development of several age-related diseases. During recent years, this scenario has been confirmed by a plethora of experimental evidence. However, it seems that concurrently with the chronic, low-level inflammation one encounters several symptoms of immunosenescence, both in the innate and adaptive immune systems [2,3]. The presence of a pro-inflammatory phenotype in aged mammals is evident by (i) increased expression of genes linked to inflammation and immune responses in the tissues of old humans and rodents [4-6], (ii) higher level of cytokines in serum, e.g. IL-6 and TNF-α [7,8], (iii) activation of NF-κB signaling which is the master regulator of inflammatory responses [9-11]. There are tissue specific differences in the production of age-related inflammatory factors as well as in the onset and level of pathological changes [12].

It is known that systemic inflammation linked to inflammaging aggravates e.g. the vascular pathology and provokes atherosclerosis [4]. Moreover, increased systemic cytokine levels activate the hypothalamus-pituitary-adrenal (HPA) axis which augments the sercetion of cortisol [13]. Cortisol is a potent anti-inflammatory agent although it not only induces protein catabolism, e.g. in muscle tissues, but it also promotes bone resorption [See also Osteoporosis]. Chronic inflammation can also enhance the appearance of insulin resistance in muscles and adipose tissues as well as disturb the maintenance of energy homeostasis and subsequently cellular housekeeping functions. Interestingly, the aging process is simultaneously accompanied by both the features accelerating inflammaging and the counteracting, so-called anti-inflammaging characteristics [14]. It seems that the balance between these opposite forces controls the outcome of the aging process, either leading to frailty and degenerative diseases or a healthy old age and longevity."

Inflammasomes: molecular platforms for danger signal recognition

"The aging process jeopardizes the maintenance of cellular homeostasis leading to the activation of a variety of host defence systems. Inflammasomes are intracellular multiprotein sensors which can recognize a large set of danger signals, induced either by pathogens or cellular stress, and once activated, they subsequently stimulate inflammatory responses [15-18]."…

- *Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland*
- *Department of Neurology, Kuopio University Hospital, Kuopio, Finland*
- *Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland*
- *Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3348477/

Inflammasome

Cannabinoids as Key Regulators of Inflammasome Signaling: A Current Perspective

"Inflammasomes are cytoplasmic inflammatory signaling protein complexes that detect microbial materials, sterile inflammatory insults, and certain host-derived elements. Inflammasomes, once activated, promote caspase-1–mediated maturation and secretion of pro-inflammatory cytokines, interleukin (IL)-1β and IL-18, leading to pyroptosis. Current advances in inflammasome research support their involvement in the development of chronic inflammatory disorders in contrast to their role in regulating innate immunity. Cannabis (marijuana) is a natural product obtained from the Cannabis sativa plant, and pharmacologically active ingredients of the plant are referred to as cannabinoids. Cannabinoids and cannabis extracts have recently emerged as promising novel drugs for chronic medical conditions. Growing evidence indicates the potent anti-inflammatory potential of cannabinoids, especially Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), and synthetic cannabinoids; however, the mechanisms remain unclear. Several attempts have been made to decipher the role of cannabinoids in modulating inflammasome signaling in the etiology of chronic inflammatory diseases. In this review, we discuss recently published evidence on the effect of cannabinoids on inflammasome signaling. We also discuss the contribution of various cannabinoids in human diseases concerning inflammasome regulation. Lastly, in the milieu of coronavirus disease-2019 (COVID-19) pandemic, we confer available evidence linking inflammasome activation to the pathophysiology of COVID-19 suggesting overall, the importance of cannabinoids as possible drugs to target inflammasome activation in or to support the treatment of a variety of human disorders including COVID-19."…

Cannabinoids in Inflammation

Cannabinoids and cannabinoid-like compounds have proven potent anti-inflammatory and immunomodulatory properties [19, 21, 35, 51, 52]. In general, cannabinoids work by inducing apoptosis, preventing cell proliferation, reducing cytokine production, and enhancing T-regulatory cells (Tregs) to produce anti-inflammatory effects [19]. Interestingly, cannabinoids may change the balance between the response involving T-helper 1 (Th-1) and Th-2 cells, inhibiting the expression of Th-1–induced cytokines and stimulating the expression of Th-2–induced cytokines [53]. More than 350 patents have been filed on cannabinoids in the treatment of inflammation [54]. Ajulemic acid (anabasum), a novel selective CB2R agonist, is currently undergoing phase II and phase III clinical trials owing to its potent anti-inflammatory effect on neutrophil migration in response to ultraviolet (UV)-killed E. coli-triggered dermal inflammation in humans. Notably, ajulemic acid removed the pathogenic bacteria that caused the inflammation and promoted the biosynthesis of special pro-resolution lipid mediators to boost the body's innate immunity [55, 56].

-Department of Biological Sciences, University of Lethbridge, Lethbridge, AB, Canada

-Edited by: Kuo-Feng Hua, National Ilan University, Taiwan

-Reviewed by: George Kunos, National Institutes of Health (NIH), United States; Antonella Naldini, University of Siena, Italy; Liying Li, Capital Medical University, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7876066/

Inflammatory Breast Cancer (IBC)

"Inflammatory breast cancer (IBC) is rare and accounts for only 1-5% of all breast cancers. Although it is often a type of invasive ductal carcinoma, it differs from other types of breast cancer in its symptoms, outlook, and treatment. IBC has symptoms of inflammation like swelling and redness, but infection or injury do not cause IBC or the symptoms. IBC symptoms are caused by cancer cells blocking lymph vessels in the skin causing the breast to look "inflamed."

Symptoms include breast swelling, purple or red color of the skin, and dimpling or thickening of the skin of the breast so that it may look and feel like an orange peel. Often, you might not feel a lump, even if it is there. If you have any of these symptoms, it does not mean that you have IBC, but you should see a doctor right away."…

-American Cancer Society

https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/types-of-breast-cancer/inflammatory-breast-cancer.html

Insulin Resistance (IR)

…“Chronic inflammation can also enhance the appearance of insulin resistance in muscles and adipose tissues as well as disturb the maintenance of energy homeostasis and subsequently cellular housekeeping functions. “…

- *Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland*
- *Department of Neurology, Kuopio University Hospital, Kuopio, Finland*
- *Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland*
- *Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3348477/

…“Researchers have since shown that TNF-alpha—and, more generally, inflammation—activates and increases the expression of several proteins that suppress insulin-signaling pathways, making the human body less responsive to insulin and increasing the risk for insulin resistance.”…

-By Melinda Wenner

-Scientific American

https://www.scientificamerican.com/article/inflammatory-clues/#

Endocannabinoid signaling and energy metabolism: a target for dietary intervention

“The endocannabinoid (EC) signaling (ECS) system involves the activation of receptors targeted by endogenously produced ligands called endocannabinoids that trigger specific physiologic events in various organs and tissues throughout the body. ECs are lipid mediators that bind to specific receptors and elicit cell signaling. The focus of this review is to discuss the responses that direct pathways of systemic energy metabolism. Recent findings have indicated that an imbalance of the ECS contributes to visceral fat accumulation and disrupts energy homeostasis, which are characteristics of the metabolic syndrome. Constant activation of ECS has been linked to metabolic processes that are associated with the hypothalamus and peripheral tissues of obese patients. In contrast, inhibition of ECS results in weight loss in animal and human subjects. Despite these findings, the mechanism involved in the dysregulation of ECS is unclear. Interestingly, the level of endogenous ligands, derived from arachidonic acid, can be directly manipulated by nutrient intervention, in that a diet rich in long-chain ω-3 polyunsaturated fatty acids will decrease the production of ligands to modulate the activation of target receptors. In contrast, a diet that is high in ω-6 polyunsaturated fatty acids will cause an increase in ECS

activation and stimulate tissue specific activities that decrease insulin sensitivity in muscle and promote fat accumulation in the adipose tissue. The purpose of this review is to explain the components of ECS, its role in adipose and muscle energy metabolism, and how nutritional approaches with dietary ω-3 polyunsaturated fatty acids may reverse the dysregulation of this system to improve insulin sensitivity and control body fat."

-Lipid Chemistry and Molecular Biology Laboratory, Department of Nutritional Sciences, University of Connecticut, Storrs, Connecticut, USA.
https://pubmed.ncbi.nlm.nih.gov/21470818/

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"Our aim was to examine the association between plasma endocannabinoids and markers of **IR** [insulin resistance] in OSA [obstructive sleep apnea] individuals. Results showed that plasma levels of endocannabinoids, especially AEA [anandamide], were significantly increased in patients with OSA and showed a strong correlation with AHI [apnea-hypopnea index] and HOMA-IR [homeostasis model of assessment for insulin resistance index].
IR is the hallmark of type 2 diabetes and can eventually lead to the development of type 2 diabetes. It has been proved that the level of IR is associated with the severity of OSA [19]."

-Department of Respiratory Medicine, The First Hospital of Lanzhou University, Lanzhou, China
-The First Clinical Medical College of Lanzhou University, Lanzhou, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4745295/

Tetrahydrocannabinol-Rich Extracts From Cannabis Sativa L. Improve Glucose Consumption and Modulate Metabolic Complications Linked to Neurodegenerative Diseases in Isolated Rat Brains

"Reduced brain glucose consumption arising from impaired glucose uptake and utilization has been linked to the pathogenesis and complications of neurodegenerative diseases. The ability of Cannabis sativa L. tetrahydrocannabinol (THC)-rich extracts to stimulate brain glucose uptake and utilization as well as its modulatory effect on gluconeogenesis, antioxidative, purinergic and cholinergic activities were investigated in isolated rats' brains. C. sativa leaves were sequentially extracted to yield the hexane and dichloromethane extracts. The extracts were incubated at 37°C with freshly harvested brains in the presence of glucose for 2 h. The control consisted of incubation without the extracts, while brains without the extracts and glucose served as the normal control. Metformin was used as the standard drug. C. sativa extracts caused a significant ($p < 0.05$) increase in brain glucose uptake, with concomitant elevation of glutathione level, superoxide dismutase, catalase, and ecto-nucleoside triphosphate diphosphohydrolase activities

compared to the controls. Incubation with C. sativa extracts also led to depletion in malondialdehyde and nitric oxide levels, acetylcholinesterase, butyrylcholinesterase, glucose 6-phosphatase and fructose-1,6-biphosphatase activities. GC-MS analysis of the extracts revealed the presence of THC. In silico analysis predicted THC to be permeable across the blood-brain-barrier. THC was also predicted to have an oral LD50 and toxicity class values of 482 mg/kg and 4 respectively. These results indicate that C. sativa improves glucose consumption with concomitant suppression of oxidative stress and cholinergic dysfunction, and modulation of purinergic and gluconeogenic activities in brain tissues."…

"The brain's dependence on glucose for energy generation is well documented. Brain glucose homeostasis has also been reported to be important for neuronal generation and maintenance, regulation of neurotransmitter, cognitive function and synaptic plasticity (Neumann et al., 2008). Glucose transporters aid in transporting glucose across the blood brain barrier (BBB) from the blood stream to the brain. Altered glucose homeostasis in the central nervous system (CNS) has been reported in most neurodegenerative diseases such as Alzheimer's and Parkinson diseases (An et al., 2018). This has been attributed to abnormalities in insulin signaling pathways in the brain as well as alteration of the glucose transporters at the BBB (Gejl et al., 2017; An et al., 2018). These abnormalities and alterations often cause deceased brain glucose consumption which can lead to a hypometabolic brain state characterized by glucose dysmetabolism (Zilberter and Zilberter, 2017). Thus, making the brain susceptible to degenerative diseases. This is evident in studies which correlated the risk of Alzheimer's disease with reduced brain glucose metabolism (Duran-Aniotz and Hetz, 2016).

Increased oxidative stress has been linked with decreased brain glucose uptake (Erukainure et al., 2019c). Increased glucose uptake has been shown to improve proteostasis which causes an upregulation of the unfolded protein response that protects against endoplasmic reticulum stress (Scheper and Hoozemans, 2015; Duran-Aniotz and Hetz, 2016). Oxidative stress has been implicated in the etiology and pathogenesis of neurodegenerative diseases (Erukainure et al., 2019b; Salau et al., 2020b). This is evident in the use of antioxidants in treating and managing most neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Gilgun-Sherki et al., 2001; Kim et al., 2015). Antioxidants have been reported for their ability to scavenge free radicals as well as improve the activities of the endogenous antioxidant enzymes (Salau et al., 2020). Oxidative stress has also been implicated in the disturbances of cholinergic and purinergic enzymes activities of the CNS (Erukainure et al., 2019a; Salau et al., 2020). These enzymes have been reported for their respective neurotransmission and bioenergetic roles which are critical for normal functioning of the brain (Ademiluyi et al., 2016; Pepeu and Giovannini, 2017)."

-Department of Pharmacology, School of Clinical Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa,

-Department of Biochemistry, School of Life Sciences, University of KwaZulu-Natal, Durban, South Africa,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7774498

Dietary (n-3) long chain polyunsaturated fatty acids prevent sucrose-induced insulin resistance in rats

…"In diaphragm phospholipids, decreasing the (n-6):(n-3) ratio in the diet increased the concentration of (n-3) LCPUFAs with concomitant decreases in the concentration of (n-6) LCPUFAs. These results suggest that (n-3) LCPUFAs at a level of 2.6 g/kg diet [0.56% energy (n-3) LCPUFAs, (n-6):(n-3) ratio = 10] may prevent sucrose-induced insulin resistance by improving peripheral insulin sensitivity."

-National Institute of Nutrition, Indian Council of Medical Research, Hyderabad-500 007 A.P. India.
https://pubmed.ncbi.nlm.nih.gov/16253960/

See also Obesity , Omega Ratio

Intestinal Motility Disorders

"The phrase intestinal motility disorders applies to abnormal intestinal contractions, such as spasms and intestinal paralysis. This phrase is used to describe a variety of disorders in which the gut has lost its ability to coordinate muscular activity because of endogenous or exogenous causes."
https://emedicine.medscape.com/article/179937-overview

Endocannabinoid-related compounds in gastrointestinal diseases

"In the last years, accumulating lines of evidence have pointed out the homoeostatic role of the ECS in regulating intestinal motility, sensitivity and inflammation. An impairment of ECS signalling has been suggested to play a key role in several gastrointestinal disorders, such as FGIDs [functional gastrointestinal disorders], IBDs [Inflammatory bowel disease] and liver diseases. Even if conflicting results have been produced in vivo, convincing evidence suggests that pharmacological manipulation of this multifaceted system might provide new therapeutic options in treating GI diseases. The complexity and the redundancy of ECS make the manipulation of this complex system an appealing target for therapeutic purposes, although the possibility of central side effects strongly limited the current use of these compounds in clinical settings."

-Department of Clinical Medicine and Surgery, 'Federico II' University of Naples, Naples, Italy,
-Division of Neurogastroenterology & Motility, Great Ormond Street Hospital and University of College (UCL), London
-Department of Physiology and Pharmacology 'Vittorio Erspamer', La Sapienza University of Rome, Rome, Italy,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5783846/

Interleukin-6 (IL-6)

"The cytokine interleukin 6 (IL-6) is known to regulate inflammation [1]. Higher circulating concentrations of IL-6 have also been associated with obesity and visceral adipose tissue (VAT) deposition [2,3,4], lipid metabolism [1] and increased risk for cardiovascular disease (CVD) [5]. In addition, there is a growing body of evidence linking polymorphisms within the IL-6 gene to increased risk of obesity and dyslipidaemia [1,6,7,8,9]."

-UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, University of Cape Town, Cape Town, South Africa
-Department of Statistics, University of Western Cape, Cape Town, South Africa
-Non-communicable Disease Research Unit (NCDRU), South African Medical Research Council, South Africa
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4073161

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…"Reducing the omega-6/3 ratio caused a lower release of the proinflammatory cytokine IL-6 at hours 6 and 8.28 Additionally, Nelson and Hickey performed a study showing that an isocaloric replacement of LA with ALA for just 4 days leads to a reduction in soluble IL-6 receptor.29 These studies suggest that replacing omega-6 with omega-3 reduces inflammation."…

-Saint Luke's Mid America Heart Institute, Kansas, Missouri, USA
-Dr James J DiNicolantonio & James H O'Keefe
https://openheart.bmj.com/content/openhrt/5/2/e000946.full.pdf

Arachidonic acid stimulates interleukin-6 release from rat peritoneal macrophages in vitro: evidence for a prostacyclin-dependent mechanism

"Interleukin-6 (IL-6) is a cytokine involved in the differentiation of B-cells to antibody secreting plasma cells, the activation of T-cells, and the stimulation of hepatocyte production of acute phase proteins. Because of the pro-inflammatory effects of this cytokine, we investigated the ability of the fatty acid arachidonic acid (AA) to regulate the release of IL-6 from rat resident peritoneal macrophages (M phi) in vitro. AA (0.5-16 microM) stimulated IL-6 release during a 4 h incubation period in a biphasic manner, with 4 microM AA generating a peak of IL-6 release (3-5-

fold). AA (0.5-16 microM) also induced an increasing release of the AA metabolite thromboxane B2 (TXB2). The AA-induced release of IL-6 occurred within 1-2 h of incubation, whereas TXB2 concentrations were elevated within 5 min of AA treatment. The TX synthetase inhibitor CGS 12970 (4.0 microM and 40.0 microM) effectively blocked the generation of TXB2, but increased prostacyclin (PGI2) generation and potentiated the release of IL-6. In addition, PGI2, as well as the PGI2 agonists iloprost and cicaprost, stimulated IL-6 release from M phi by greater than 5-fold over vehicle-treated basal levels. These data suggest that PGI2 (but not TXA2) is involved in AA-induced IL-6 release from peritoneal M phi."

-Department of Physiology, Medical University of South Carolina
https://pubmed.ncbi.nlm.nih.gov/7511246

Interleukin-17 (IL-17)

Cannabinoid receptor 2 counteracts interleukin-17-induced immune and fibrogenic responses in mouse liver

"Interleukin (IL)-17 is a proinflammatory and fibrogenic cytokine mainly produced by T-helper (Th)17 lymphocytes, together with the hepatoprotective and antifibrogenic cytokine, IL-22. Cannabinoid receptor 2 (CB2) is predominantly expressed in immune cells and displays anti-inflammatory and antifibrogenic effects."…

"Finally, in vitro studies also demonstrated that CB2 receptor activation in macrophages and hepatic myofibroblasts blunts IL-17-induced proinflammatory gene expression."..

"Conclusion: These data demonstrate that CB2 receptor activation decreases liver fibrosis by selectively reducing IL-17 production by Th17 lymphocytes via a STAT5-dependent pathway, and by blunting the proinflammatory effects of IL-17 on its target cells, while preserving IL-22 production."

-Inserm, U955, Créteil, France; Paris-Est University, Faculty of Medicine, UMR-S955, Créteil, France.
https://pubmed.ncbi.nlm.nih.gov/23813495/

Intermittent explosive disorder (IED)

Anger induced by interferon-alpha is moderated by ratio of arachidonic acid to omega-3 fatty acids

…"Elevated anger has also been associated with lower long-chain omega-3 (LCn-3) fatty acid levels. We examined whether fatty acids could influence vulnerability to anger during IFN-α exposure."…

"LCn-3 [omega-3] fatty acid status may influence anger development during exposure to elevated inflammatory cytokines, and may interact with genetic risk for increased brain TNF-α. LCn-3 supplements may be one strategy for minimizing this adverse side effect of IFN-α."….

-Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine
https://pubmed.ncbi.nlm.nih.gov/24182638/

Interstitial Nephritis

"Interstitial nephritis is a kidney condition characterized by swelling in between the kidney tubules. The main functions of your kidneys are to filter your blood and to get rid of waste from your body. The kidney tubules reabsorb water and important organic substances from the filtered blood and secrete substances you don't need into your urine for removal from your body. Swelling of these tubules can cause a number of kidney symptoms that range from mild to severe. Interstitial nephritis can be acute (sudden) or chronic (long term)."…

-Written by Joan Jovinelly
-Heathline
-Medically reviewed by Carissa Stephens, R.N., CCRN, CPN
https://www.healthline.com/health/interstitial-nephritis

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…"Massive and prolonged consumption of analgesics, particularly the combination of aspirin, caffeine, and acetaminophen, is associated with chronic interstitial nephritis and a predisposition to papillary necrosis (Chapter 124); medullary ischemia is thought to be caused by inhibition of synthesis of vasodilatory prostaglandins by aspirin, and direct toxicity is attributed to metabolites of phenacetin. Similarly, medullary perfusion is thought to be compromised in diabetic nephropathy (Chapter 126) and obstructive pyelonephritis (Chapter 125).

The clinical manifestations of papillary necrosis can include flank pain and hematuria. If the

papilla is sloughed, obstruction may occur at the renal pelvis or ureter of the affected kidney, with referred pain migrating from the flank to the groin. A sloughed papilla may precipitate frank renal failure if the function of the contralateral kidney is impaired or if obstruction occurs at the level of the bladder or urethra (Chapter 125).

Classically, papillary necrosis is diagnosed on an excretory pyelogram as a calyceal defect after sloughing of a papilla, but CT with contrast is as good for advanced lesions. If the necrotic papilla is retained, however, the defect will be more subtle. Transitional cell carcinoma (Chapter 203) can occur in the setting of papillary necrosis or can mimic its appearance. Obstruction, if present, must be relieved, but treatment otherwise is limited to pain control and hydration."...

-Donald W. Landry, Hasan Bazari
-Goldman's Cecil Medicine (Twenty Fourth Edition), 2012
https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/excedrin

Iritis

Turning Down the Thermostat: Modulating the Endocannabinoid System in Ocular Inflammation and Pain

"The endocannabinoid system (ECS) has emerged as an important regulator of both physiological and pathological processes. Notably, this endogenous system plays a key role in the modulation of pain and inflammation in a number of tissues. The components of the ECS, including endocannabinoids, their cognate enzymes and cannabinoid receptors, are localized in the eye, and evidence indicates that ECS modulation plays a role in ocular disease states. Of these diseases, ocular inflammation presents a significant medical problem, given that current clinical treatments can be ineffective or are associated with intolerable side-effects. Furthermore, a prominent comorbidity of ocular inflammation is pain, including neuropathic pain, for which therapeutic options remain limited. Recent evidence supports the use of drugs targeting the ECS for the treatment of ocular inflammation and pain in animal models; however, the potential for therapeutic use of cannabinoid drugs in the eye has not been thoroughly investigated at this time. This review will highlight evidence from experimental studies identifying components of the ocular ECS and discuss the functional role of the ECS during different ocular inflammatory disease states, including uveitis and corneal keratitis. Candidate ECS targeted therapies will be discussed, drawing on experimental results obtained from both ocular and non-ocular tissue(s), together with their potential application for the treatment of ocular inflammation and pain."....

Conclusion

"Evidence to date suggests a role for the ECS in mitigating ocular inflammation and pain. Although research in this area is still relatively limited, the potential for developing novel pharmacological tools exploiting the ECS for ocular inflammation and pain looks promising given that targeting both the CB1R [cannabinoid receptor 1] and CB2R [cannabinoid receptor 2] has proven beneficial in models of intraocular inflammation, including EAU and EIU (Xu et al., 2007; Toguri et al., 2015). Activation of cannabinoid receptors, specifically CB2R, results in decreases in immune cell migration (during both innate and adaptive immune responses), T-cell proliferation, inflammatory mediator release and alterations in local blood flow. Furthermore, there are indications that cannabinoids may have comparable and, in some cases, superior efficacy and less side-effects compared to traditional immunosuppressive therapeutics used in the clinic (Toguri et al., 2014). In addition to an anti-inflammatory role for cannabinoids in uveitis, this class of drugs, particularly cannabinoids that act at CB1R, may have therapeutic relevance for corneal surface damage and pain. However, at this time research on corneal ECS is still in its infancy and further investigation of the corneal ECS and the effects of cannabinoids in models of corneal disease, including CNP, must be conducted in order to better clarify cell and receptor targets and identify how alterations in the ECS affect corneal function (Yang et al., 2010, 2013; Murataeva et al., 2015).

Furthermore, while topical and regional cannabinoid therapies offer several advantages for treating ocular inflammation and pain, it should also be noted that there are challenges in formulation of these very lipophilic compounds for drug delivery and their use may result in dose-dependent ocular toxicity including hyperemia and reduction in tear production, as well as tachyphylaxis with chronic use (Green and Roth, 1982; Jay and Green, 1983). Future research should explore novel cannabinoid drug combinations that maximize efficacy and limit dose including allosteric modulators (Cairns et al., 2016b), as well as appropriate routes of local delivery, novel drug formulations and studies of both acute and chronic dosing in representative models of ocular disease."

-Department of Pharmacology, Dalhousie University, Halifax, NS, Canada
-Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada
-Anesthesia, Pain Management & Perioperative Medicine, Dalhousie University, Halifax, NS, Canada
-Edited by: Allyn C. Howlett, Wake Forest School of Medicine, USA
-Reviewed by: Kyriaki Thermos, University of Crete, Greece; Jean-Francois Bouchard, Université de Montréal, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5024674/
CB1R-/- cannabinoid 1 receptor knockout mice, (lacking these receptors)

Iron Deficiency

…"Correlations between fatty acids and growth suggest that the mechanism whereby iron deficiency affects growth is in some way related to abnormal fatty acid shifts that disturb the

delicate balance of essential fatty acids in membranes. Additional omega 3 and omega 6 fatty acids may be necessary to counteract the effect of iron deficiency in rats. Additional omega 3 and omega 6 fatty acids may be necessary to counteract the effect of iron deficiency in rats."

-National Research Programme for Nutritional Intervention of the Medical Research Council, Tygerberg, South Africa.
https://www.ncbi.nlm.nih.gov/pubmed/9089804

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…"Iron deficiency most commonly occurs through blood loss but may also ensue from inadequate dietary intake, dietary inhibitors [8], states of increased dietary iron requirement such as pregnancy [9] or conditions such as celiac disease with abnormal gastrointestinal tract mucosa leading to iron malabsorption [10]."…

-The Ohio State University, Columbus, Ohio / Davis Heart and Lung Research Institute
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4101028/

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"The anemia of inflammation, commonly observed in patients with chronic infections, malignancy, trauma, and inflammatory disorders, is a well-known clinical entity. Until recently, we understood little about its pathogenesis. It now appears that the inflammatory cytokine IL-6 induces production of hepcidin, an iron-regulatory hormone that may be responsible for most or all of the features of this disorder (see the related article beginning on page 1271)."

-Children's Hospital, Howard Hughes Medical Institute, Harvard Medical School, and Dana-Farber Cancer Institute, Boston, Massachusetts, USA / Nancy C. Andrews
http://content-assets.jci.org/manuscripts/21000/21441/JCI0421441.pdf

"Iron deficiency (ID)5 is the most common micronutrient deficiency worldwide because increased requirements for growth are often not met by dietary sources (1). "…

-Laboratory of Human Nutrition, Institute of Food, Nutrition and Health, Swiss Federal Institute of Technology Zürich, Switzerland.
https://academic.oup.com/ajcn/article/96/6/1327/4571461

Iron Overload

…"Iron excess may occur via augmented dietary or supplemental intake [5], genetic disorders such as certain forms of hemochromatosis that lead to excess intestinal iron absorption [6] or

transfusion-induced iron overload [7].”…

-The Ohio State University, Columbus, Ohio / Davis Heart and Lung Research Institute
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4101028/

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“Iron overload syndromes encompass a wide range of hereditary and acquired conditions. Major developments in the field of genetics and the discovery of hepcidin as a central regulator of iron homeostasis have greatly increased our understanding of the pathophysiology of iron overload syndromes.”….

“Iron overload is associated with significant morbidity and mortality. Sensitive diagnostic tests and effective therapy are widely available and can prevent complications associated with iron accumulation in end- organs. Therapeutic phlebotomy remains the cornerstone of therapy for removal of excess body iron, but novel therapeutic agents including oral iron chelators have been developed for iron overload associated with anaemia.”…

“Iron overload disorders are common. Inexpensive screening tests as well as confirmatory diagnostic tests are widely available. Increased awareness of the causes and importance of early diagnosis and knowledge of the appropriate use of genetic testing are encouraged. The availability of novel treatments should increase therapeutic options for patients with iron overload disorders.”

-Department of Hepatology, Virginia Mason Medical Center, Seattle, WA, USA.
https://pubmed.ncbi.nlm.nih.gov/22385471/

■■■

“Acetaminophen (APAP), a major cause of acute liver injury in the Western world, is mediated by metabolism and oxidative stress. Recent studies have suggested a role for iron in potentiating APAP-induced liver injury although its regulatory mechanism is not completely understood. The current study was designed to unravel the iron-regulating pathways in mice after APAP-induced hepatotoxicity. Mice with severe injury showed a significant increase in liver iron concentration and oxidative stress. Concurrently, the plasma concentration of hepcidin, the key regulator in iron metabolism, and hepatic hepcidin antimicrobial peptide (Hamp) mRNA expression levels were significantly reduced.“…

-Department of Pharmacology and Toxicology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
https://pubmed.ncbi.nlm.nih.gov/22610607

Iron Homeostasis and the Inflammatory Response

..“The rapid evolution of molecular information about iron transport and homeostasis has uncovered a comprehensive understanding of the complex mechanisms involved in this process. It has long been recognized that iron levels must be tightly regulated to provide an essential nutrient that is involved in oxygen delivery, metabolism and redox regulation while guarding against excessive levels of a primary toxicant that can generate reactive oxygen species (ROS) to produce cellular damage and death. Unlike other essential minerals, the delicate balance between iron nutrition and toxicity is maintained by systemic control mechanisms that drive iron conservation and limit uptake until needs are presented – in contrast, homeostasis of many other metals is more simply controlled by eliminating excess. Ultimately, these features of iron and its homeostasis are intimately tied to the response to inflammation and infection and therefore provide major survival mechanisms that are unique in human physiology.

A large body of clinical evidence demonstrates disease susceptibility and the response to infection and inflammation worsen with elevated iron stores. The relationships between iron overload and infectious diseases are particularly well documented.”…

-Marianne Wessling-Resnick, Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, MA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108097/

See also Atherosclerosis , Iron Deficiency

Irritable Bowel Syndrome (IBS)

“Irritable bowel syndrome (IBS) is a common disorder that affects the large intestine. Signs and symptoms include cramping, abdominal pain, bloating, gas, and diarrhea or constipation, or both.“

-Mayo Clinic

https://www.mayoclinic.org/diseases-conditions/irritable-bowel-syndrome/symptoms-causes/syc-20360016

■■■

“Hericium erinaceus (HE), a traditional edible mushroom, is known as a medicine food homology to ameliorate gastrointestinal diseases. To investigate whether HE is clinically effective in alleviating inflammatory bowel disease (IBD), HE extracts (polysaccharide, alcoholic extracts and whole extracts were prepared using solvent extraction methods) were administrated for 2 weeks

in rats with IBD induced by trinitro-benzene-sulfonic acid (TNBS) enema (150 mg/kg). Significant clinical and histological changes in IBD rats were identified, including damage activity, common morphous and tissue damage index scores in colonic mucosa and myeloperoxidase (MPO) activity. The damage activity, common morphous and tissue damage index scores in colonic mucosa ($P < 0.05$) were improved, MPO activities were decreased. Inflammatory factors were also differentially expressed in colonic mucosa in IBD rats, including serum cytokines, Foxp3 and interleukin (IL)-10 were increased while NF-κB p65 and tumor necrosis factor (TNF)-α were decreased ($P < 0.05$), and T cells were activated ($P < 0.05$), especially in the alcohol extracts-treated group. We also found that the structure of gut microbiota of the H. erinaceus extracts-treated groups changed significantly by compared with the model group. Further studies revealed that the polysaccharides in HE extracts may play a prebiotic role, whereas the alcoholic extracts show bactericidin-like and immunomodulatory effects. Taken together, we demonstrated that H. erinaceus extracts could promote the growth of beneficial gut bacteria and improve the host immunity in vivo IBD model, which shows clinical potential in relieving IBD by regulating gut microbiota and immune system."….

- State Key Laboratory of Applied Microbiology Southern China, Guangdong Provincial Key Laboratory of Microbial Culture Collection and Application, Guangdong Open Laboratory of Applied Microbiology, Guangdong Institute of Microbiology, Guangzhou, China

- Department of Pharmacy, The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

- Departerment of Infertility and Sexual Medicine, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

- Guangdong Yuewei Edible Fungi Technology Co. Ltd, Guangzhou 510070, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5689651/

…"Recently, gut microbiota is considered an important factor in the progress of IBD [8–10], although the etiology and pathogenesis of IBD are still unclear and varied. In genetically susceptible individuals, the gut mucosal integrity is damaged and the microbial antigens escape through the epithelial barrier more easily, thereby activating inappropriate immune response or underlying chronic inflammation [11]. The gut microbiota plays an important role in maintaining the intestinal balance by activating the natural Toll-like receptors in the damage and repair process of intestinal mucosal integrity in patients with IBDs [12, 13]. Previous studies indicated that enteric flora disturbance could cause IBDs in mice and reduce the microbial diversity in patients, as when the intestinal bacteria increased, but some of the Bacteroidetes and Firmicutes decreased [8, 14]. How the enteric flora disturbance influences the IBDs is still unclear. It might be related to invasion of some pathogens and reduction in some protective bacteria, resulting in the activation of some abnormal immune cells, destruction of Th1- and Th17-mediated immune

responses, increase in the mucous membrane permeability, loss of immune tolerance function, and so on [8, 14]. Previous studies showed that probiotic bacteria might be useful in preventing and treating acute and chronic conditions including antibiotic-associated diarrhea and IBDs [15]. Variation in host physiology caused by different diet, age, lifestyle, genetics and other factors might have a significant impact on microbiota [16–19]. At present, the outcomes of clinical and animal studies on gut microbiota lack consistency, and to understand the impacted gut microbiota function factors need an improved study design and better control over microbiota-mediated effects."

- State Key Laboratory of Applied Microbiology Southern China, Guangdong Provincial Key Laboratory of Microbial Culture Collection and Application, Guangdong Open Laboratory of Applied Microbiology, Guangdong Institute of Microbiology, Guangzhou, China

- Department of Pharmacy, The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

- Departerment of Infertility and Sexual Medicine, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

- Guangdong Yuewei Edible Fungi Technology Co. Ltd, Guangzhou 510070, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5689651/

IBS and Endocannabinoid Deficiency

"The Endocannabinoid System (ECS) is known to modulate several functions, including mood, anxiety, and memory retrieval of traumatic events and it directly coordinates GI propulsion, secretion, inflammation, and nociception, providing a rationale for agents capable of interacting with the ECS as treatment candidates for IBS (Russo, 2016)."…

"The ECS is ubiquitously expressed in the human body and it actively controls gut homeostasis."…

"Clinical Endocannabinoid Deficiency (CED) has been confirmed as a plausible feature in a series of difficult-to-characterize psychosomatic pathologies, which display hyperalgesia, anxiety, and depression (Russo, 2004, 2016); Migraine, fibromyalgia and IBS fall in this category, often showing comorbidity in the three diagnosis (Nicolodi and Sicuteri, 1996; Sperber et al., 1999; Peres et al., 2001). CED occurs either as a congenital disorder, or as a result of epigenetic changes.

IBS subtypes exhibit distinct variations of the ECS tone. IBS-D patients show genetic alterations affecting endocannabinoid metabolism, variants of the CNR1 and FAAH genes, and lower levels of Oleoylethanolamine (OEA) and PEA compared to healthy subjects (Fichna et al., 2013). Specifically, the CNRI rs806378 CT/TT genotype shows a significant association with colonic transit in IBS-D (Camilleri et al., 2013). Conversely, IBS-C patients show levels of OEA higher than healthy volunteers, and reduced levels of FAAH mRNA in intestinal tissues (Fichna et al., 2013).

Some of these changes may occur as the result of chronic stress, which profoundly impacts the ECS: it silences the Cnr1 gene promoter via an increased methylation by DNA (cytosine-5)-methyltransferase 1, but it also activates the Trpv1 promoter via acetylation (Hong et al., 2015). This results in reduced levels of CB1 and increased levels of TRPV1 in the sensory neurons localized in the pelvic organs, including the colon, which is a feature of visceral pain, as later discussed (Fichna et al., 2013).

Stress in the early-life stage is also an important contributor to IBS development and it is associated with epigenetic changes that lead to visceral hypersensitivity (Moloney et al., 2015). Maternal deprivation increases the expression of the endocannabinoid genes Cnr1, Cnr2a, Cnr2b, and GPR55 in the frontal cortex of male rats, whereas in female rats, increased expression was reported only in the hippocampus, a difference that may underline the prevalence of IBS in the female population (Marco et al., 2014). The relevance of pediatric stress in IBS is supported by the fact that infantile colitis, characterized by visceral sensitivity and dysphoria and resistant to most pharmacotherapies, seem to be offset by the endocannabinoids present in maternal milk, reason for it is hypothesized that this condition may also be a CED (Russo, 2004). Taken these data together, genetic polymorphisms and alterations in gene expression are associated with disturbances in GI motility and sensation, supporting the pathophysiologic significance of alterations in the ECS in the gut (Moloney et al., 2015).”

-Department of Neuroscience, University of Padua, Padua, Italy

-Molecular Biology and Biochemistry Lab, Department of Neurogastroentherology, University of Naples Federico II, Naples, Italy

-Department of Medicine, University of Padua, Padua, Italy

-Edited by: Rajeev K. Singla, Sichuan University, China

-Reviewed by: Vipan K. Parihar, University of California, Irvine, United States; Marcus Scotti, Federal University of Paraíba, Brazil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7186328/

Endocannabinoid system in irritable bowel syndrome and cannabis as a therapy

“Irritable bowel syndrome (IBS) global burden is underestimated despite its high prevalence. It's a gastrointestinal disease having obscure pathophysiology with multiple therapies yet unsatisfactory remedies. The Endocannabinoid system (ECS) of our body plays a key role in maintaining normal physiology of the gastrointestinal tract as well as involves abnormalities including functional diseases like IBS. This review highlights the importance of the Endocannabinoid system, its connections with the normal gastrointestinal functions and abnormalities like IBS. It also discusses the role of cannabis as medical therapy in IBS patients. A

literature search for articles related to endocannabinoids in IBS and medical cannabis in PubMed and Google Scholar was conducted. The studies highlighted the significant participation of ECS in IBS. However, the breach in obtaining the promising therapeutic model for IBS needed further investigation in ECS and uncover other treatments for IBS. This review summarizes ECS, highlights the relationship of ECS with IBS and explores cannabis as a potential therapy to treat IBS."

-California Institute of Behavioural Neurosciences and Psychology, CA, USA.
https://pubmed.ncbi.nlm.nih.gov/31987224/

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..."The authors found that patients with IBS exhibited significantly higher scores for depression, higher proportions of plasma saturated fatty acids and monounsaturated fatty acids, and lower proportions of docosahexaenoic acid and total omega-3 polyunsaturated fatty acids in plasma are associated with IBS in Asian female patients. Further study is indicated to confirm the causality of this association."...

"Siguel and Lerman noted PUFA deficiency in patients with chronic gastrointestinal disorder.[8] Malnutrition with EFA insufficiency was also observed in diseases of the bowel, with poor EFA absorption noted in patients with celiac disease.[9] In research on IBS, Solakivi et al found intestinal PUFA malabsortion to be the main characteristic of IBS.[3] Sun et al showed that DHA (22:6n3) in erythrocytes and plasma provided the strongest correlations with EFAs intake.[10] Erythrocyte fatty acid content represents the long-term intake of EFAs, whereas plasma fatty acid content indicates more recent dietary intake of EFAs.[11]

A meta-analysis by Lovell and Ford showed that the incidence of IBS is moderately higher among women than men. The constipation-predominant type of IBS is also more common in women.[12]"

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5728949/

The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome

"Irritable bowel syndrome (IBS) is a spectrum of disorders characterized by abdominal discomfort and pain, associated with altered bowel habits. Though gut motility, secretion and sensation may be altered in patients with IBS, the pathophysiology of this condition remains to be fully understood. The endocannabinoid system is involved in the regulation of numerous gastrointestinal functions including motility, sensation and secretion under both physiological

and pathophysiological conditions. Activation of cannabinoid (CB)(1) and CB(2) receptors under various circumstances reduces motility, limits secretion and decreases hypersensitivity in the gut. Drugs that alter the levels of endocannabinoids in the gut also reduce motility and attenuate inflammation. In this review, we discuss the role of the endocannabinoid system in gastrointestinal physiology. We go on to consider the involvement of the endocannabinoid system in the context of symptoms associated with IBS and a possible role of this system in the pathophysiology and treatment of IBS."

-Division of Gastroenterology, Department of Medicine, Snyder Institute of Infection, Immunity and Inflammation, University Calgary, Calgary, AB, Canada.

https://pubmed.ncbi.nlm.nih.gov/18710476

J

Jaundice

"Almost all newborns will develop a total bilirubin level above the upper limit of normal for adults and older children bilirubin of 1.5 mg/dl with less than 5% of the total bilirubin conjugated.[2] Up to 60% of term infants[12] and 80% of newborns with a gestational age of 35 weeks or more[13] will develop jaundice, which occurs when serum bilirubin reaches and exceeds 5 mg/dl. Neonatal jaundice appears to be more common in people living at high altitudes and those living around the mediterranean sea, especially Greece."….

"Bilirubin comes from the breakdown in heme, which is produced from the breakdown of hemoglobin. Heme is converted to biliverdin, iron, and carbon monoxide by the enzyme heme oxygenase[14]; biliverdin is then converted to bilirubin by biliverdin reductase. The conversion of heme to bilirubin takes place in the reticuloendothelial system. The unconjugated bilirubin is hydrophobic and is transported to the liver bound to albumin where it is conjugated by the enzyme uridine diphosphate-glucuronosyltransferase (UGT). Conjugated bilirubin, which is water-soluble, is excreted in bile and into the gastrointestinal (GI) tract and mostly excreted in feces after being metabolized by bacterial flora. Some conjugated bilirubin is deconjugated to unconjugated bilirubin and reabsorbed through the enterohepatic circulation.[15]"…

-New York University

-Lincoln Medical & Mental Center

https://www.ncbi.nlm.nih.gov/books/NBK532930/

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"The concentration of bilirubin in the serum in a group of 119 premature and full-term infants was studied after the administration of water-soluble vitamin K and vitamin K1. It appeared that large doses of water-soluble vitamin K produced a higher concentration of bilirubin than was found in the control infants. Vitamin K1 administered intravenously did not have a hyperbilirubinemic effect."

-Pediatrics March 1958, 21 (3) 397-402;
https://pediatrics.aappublications.org/content/21/3/397

■■■

"Recent reports have indicated that administration of large doses of a water-soluble vitamin-K analogue (Synkavit) causes an increase in the bilirubin in the serum and was potentially dangerous as regards the development of kernicterus in premature infants. The present report compares the effects of large and small doses of the water-soluble vitamin-K analogue (Synkavit) on the bilirubin in the plasma of premature babies on the fifth day of life. One group of premature babies received 10 mg of Synkavit daily by intramuscular injection for 3 days. Another group received an injection of 1 mg of Synkavit on the first day of life. The bilirubin attained a concentration of 18 mg/100 ml or higher in the plasma in 21 out of 55 babies in the first group receiving the larger dose, while only 2 premature infants out of 51 who received the smaller dose developed a concentration of bilirubin in the plasma of 18 mg/100 ml or higher. There were two deaths from kernicterus in the group receiving the larger dose and no deaths or signs of kernicterus in the group receiving the smaller dose. It is pointed out that a single dose of 0.5 to 1.0 mg of vitamin-K is as effective as larger doses in preventing postnatal hypoprothrombinemia. It is suggested that the routine use of the smaller dose should be adopted in an effort to reduce the incidence of kernicterus in premature infants."

-Pediatrics September 1956, 18 (3) 377;
https://pediatrics.aappublications.org/content/18/3/377

Juvenile Arthritis

…."The daily requirements of nonsteroidal anti-inflammatory drugs (NSAIDs) obviously

decreased. ω-3 FAs supplements reduce the inflammatory response and improve the clinical manifestation in JIA [juvenile idiopathic arthritis] patient. The daily intake of NSAID dose decreased thus reducing the risk of related side effects. Our results support the use of omega-3 fatty acids as an add-on therapy to conventional treatment of JIA."

-Rheumatology Department, Faculty of Medicine, Cairo University, Giza, Egypt.
https://pubmed.ncbi.nlm.nih.gov/21922187/

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"The use of additional treatment methods in inflammatory joints disease therapy is very important. But the main principles of diet therapy for patients with rheumatoid joint inflammation and reactive arthritis and possibility of focused impact on disease activity by means of alimentary factors have not still been formed out. The aim of the investigation was to study the effect of diet therapy including ω-3 polyunsaturated fatty acids (PUFAs) on joint syndrome evidence and on bone turnover markers of children with inflammatory joint diseases."…

…"No adverse effects of PUFAs have been observed. It was concluded that ω-3 PUFAs increased the action of basic therapy favoring advances in inflammatory process activity control, provided decrease of non-steroidal antiinflammatory drugs (NSAID) intake and proved to be an important supplement in diet therapy of children inflammatory joints diseases."

-I. Horbachevsky Ternopil State Medical University, Ukraine.
https://pubmed.ncbi.nlm.nih.gov/30645882/

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See Supplements for related research quotes.

K

Kawasaki Disease

"Kawasaki disease is an illness that makes the blood vessels in the body swell and become inflamed. The exact cause of Kawasaki disease is unknown. Because it causes a high fever and swelling of the lymph nodes, Kawasaki disease is thought to be related to an infection. It may

occur in children who have a genetic predisposition to the disease. The disease is not contagious."

-Cincinnati Children's Hospital
https://www.cincinnatichildrens.org/health/k/kawasaki

Plasma prostaglandin E2 level in Kawasaki disease

"Plasma levels of prostaglandin E2 and prostaglandin F2 alpha were determined in 15 patients in the acute and recovery stages of Kawasaki disease, 10 patients with anaphylactoid purpura, 16 with bacterial and viral infections and 10 healthy children. Plasma levels of prostaglandin E2 were markedly increased in the acute stage of Kawasaki disease, and these levels were decreased in the recovery stage. The prostaglandin F2 alpha/prostaglandin E2 ratio in the acute stage of Kawasaki disease was markedly decreased. Plasma levels of prostaglandin E2 in patients with anaphylactoid purpura, bacterial and viral infections were within the normal range. In Kawasaki disease which is associated with systemic vasculitis with a severe inflammatory reaction, prostaglandin E2 is considered to be more selectively produced and released than prostaglandin F2 alpha, suggesting that prostaglandin E2 plays an important role in the immunological and inflammatory reaction."

-Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan.
https://pubmed.ncbi.nlm.nih.gov/3162772/

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…"One key finding in standard KD [Kawasaki Disease] is the role played by prostaglandin E2 (PGE2) [8], [9]. All KD patients have increased plasma PGE2 concentrations compared to normal controls. "…

-Trauma Research Department, Swedish Medical Center, CO, United States
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7358144/

Keratin Disease

…"Epidermolytic ichthyosis (EI), pachyonychia congenita (PC) and epidermolysis bullosa (EB) are rare genodermatoses caused by function-impairing mutations in different keratins (EI: K1 or K10; PC: K6, K16 or K17; EB: K5 or K14) [182]. Thus, pharmacologically induced down-regulation of the

mutated, dysfunctional keratins, and ideally, up-regulation of other ones capable of compensating the role of the mutated molecules, is thought to be an innovative, novel approach in these diseases [176,182]. Since irrespective of the above open questions, it seems to be safe to assume that appropriate modulation of the eCB signaling and/or administration of various pCBs may be capable of inducing marked alterations in the keratin expression profile in human epidermis, it is not surprising that such interventions were already suggested to be exploited in these diseases [176,182].

Along these lines, it is important to note that according to a recent observational study reporting 3 cases of self-initiated topical CBD [Cannabidiol] use in patients with EB, CBD may improve quality of life in such patients. Indeed, one patient was weaned completely off oral opioid analgesics, and all 3 patients reported faster wound healing, less blistering, and amelioration of pain. The authors concluded that the effects might have been due to the anti-inflammatory activity of CBD, but in light of the above data, one can speculate that CBD might have beneficially modulated the keratin expression profile as well [183]. Likewise, in another small pilot study, three EB patients, who were prescribed pharmaceutical-grade sublingually administered cannabinoid-based medicine (CBM) comprising THC and CBD, reported improved pain scores, reduced pruritus and decreased overall analgesic drug intake [184]. Further studies are therefore invited to exploit putative therapeutic potential of the (endo)cannabinoid signaling in the clinical management of keratin diseases."…

-Department of Physiology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-Department of Immunology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-HCEMM Nonprofit Ltd., Szeged, Hungary
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429381/

■■■

"A type of protein found on epithelial cells, which line the inside and outside surfaces of the body. Keratins help form the tissues of the hair, nails, and the outer layer of the skin. They are also found on cells in the lining of organs, glands, and other parts of the body. Certain keratins may be found in higher than normal amounts in patients with different types of epithelial cell cancers, including lung, breast, colorectal, bladder, and head and neck cancers. Measuring the amount of specific keratins in the blood may help to plan cancer treatment or find out how well treatment is working or if cancer has come back. A keratin is a type of tumor marker. Also called cytokeratin."

-National Cancer Institute
https://www.cancer.gov/publications/dictionaries/cancer-terms/def/keratin

Kidney Disease

…"Kidney disease secondary to diabetes represents the main cause of long-term, chronic, end-stage kidney disease [1]. When poor kidney function is detected with classical indicators, like urea and creatinine, it implies that the pathophysiological process of kidney disease is in the advanced stages. Therefore, it is desirable to identify other markers, which can be detected before changes in urea and creatinine appear, to indicate the earlier stages of kidney failure [13]. In the present study, we evaluated the molecules that are eliminated by the kidney, which have been shown to play a role in the physiopathology of this chronic disease, secondary to diabetes. These biomarkers reflect glomeruli/podocyte status and tubular damage. In addition, they were postulated to be useful in identifying the earlier steps of diabetic nephropathy."…

-Universidad de Colima, Centro Universitario de Investigaciones Biomédicas, Av. 25 de Julio No. 965, Col. Villas San Sebastián, Colima 28045, Colima, Mexico;

-Universidad de Colima-Cátedras-CONACyT, Centro Universitario de Investigaciones Biomédicas, Av. 25 de Julio No. 965, Col. Villas San Sebastián, Colima 28045, Colima, Mexico

-Universidad de Colima, Facultad de Medicina, Escuela de Nutrición, Av. Universidad No. 333, Col. Las Víboras, Colima 28040, Colima, Mexico;

-Instituto Mexicano del Seguro Social, Centro de Investigaciones Biomédicas de Occidente, Sierra Mojada No. 800, Col. Independencia, Guadalajara 44340, Jalisco, Mexico

-Universidad Michoacana de San Nicolás de Hidalgo, Instituto de Investigaciones Químico-Biológicas; Av. Francisco J Mujica S/N, Morelia 58020, Michoacán, Mexico;

-Universidad de Colima, Facultad de Medicina, Av. Universidad No. 333, Col. Las Víboras, Colima 28040, Colima, Mexico;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6337195/

Obesity and kidney disease: differential effects of obesity on adipose tissue and kidney inflammation and fibrosis

…."Thus, it is becoming increasingly clear that there is an important cross-talk between adipose tissue and the kidney, especially in obesity-related kidney disease, although similar cross-talk is likely important with diabetes and possibly hypertension-associated kidney disease as well. The use of systemic AMPK [AMP-activated protein kinase] activation is likely to have profound effects on adipose tissue which could contribute to the reduced inflammation and fibrosis observed in the kidney. Nevertheless, there are likely kidney specific effects of AMPK activators as well. In addition, use of systemic anti-inflammatory and anti-TGF-b antibodies likely also have profound effects on adipose tissue which are beneficial systemically and for improvement in renal structure and function. In future studies, further understanding and elucidation of key pathways linking adipose tissue to the kidney will suggest improved treatment approaches which

will likely have widespread application and implications for progressive CKD of many etiologies."

-Center for Renal Translational Medicine, University of California San Diego
-Veterans Affairs San Diego Healthcare System
-Institute for Metabolomic Medicine, University of California San Diego
-Laboratory of Experimental Nephrology, Faculty of Medicine, Université Libre de Bruxelles (ULB), Brussels, Belgium
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4847436/

AMPK [AMP-activated protein kinase] is an ubiquitous heterotrimeric enzyme that is considered to be the master energy sensor in all eukaryotic cells. - University of Melbourne, PMID: 19584320

CB1 receptor mediates the effects of glucocorticoids on AMPK activity in the hypothalamus.

"AMP-activated protein kinase (AMPK), a regulator of cellular and systemic energy homeostasis, can be influenced by several hormones. Tissue-specific alteration of AMPK activity by glucocorticoids may explain the increase in appetite, the accumulation of lipids in adipose tissues, and the detrimental cardiac effects of Cushing's syndrome. Endocannabinoids are known to mediate the effects of various hormones and to influence AMPK activity. "

-Centre for Endocrinology, William Harvey Research Institute, Barts and
-London School of Medicine and Dentistry, Queen Mary University of London, London
-UK Department of Endocrine Neurobiology, Institute of Experimental Medicine
-Hungarian Academy of Sciences, Budapest 1083, Hungary Division of Endocrinology,
-Diabetes, Metabolism and Molecular Medicine, Department of Medicine, Tupper Research Institute, Tufts Medical Center, Boston, Massachusetts
-USA Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford
https://www.ncbi.nlm.nih.gov/pubmed/23884964

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"Animal trials show that omega-3 fatty acid treatment decreases blood pressure, has anti-inflammatory effects, slows renal failure and moderates the side effects of hypertension (Imig et al. 2005; Zhao et al. 2004). This has been the basis for the study of the effects of omega-3 fatty acids on kidney disease. A recent literature review found that no definitive conclusions can be made about the effectiveness of omega-3 fatty acids for the prevention or treatment of kidney disease (Fassett et al. 2010).

However, just as in the review of effects on cardiovascular disease, the authors point out that there was substantial variability from study to study in the dosages, proportions of specific omega-3 fatty acids administered (i.e., formulations), duration of supplementation, sample sizes and specific outcomes assessed. This again suggests that further studies are needed to better

understand the specific formulations, dosages and markers of effectiveness for omega-3 fatty acid supplementation."

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

■■■

…"Several reports show that particularly high levels of AEA and the enzymes that metabolize this eCB are found in the kidneys. Likewise, the renin–angiotensin–aldosterone system (RAAS) has been characterized at the renal level as the main prohypertensive hormonal system. On the other hand, the kidney also contains an endocrine antihypertensive system that is responsible for three specific biological properties: vasodilation, inhibition of sympathetic activation and renal excretion of ions and water. The AEA and COX-2 metabolites located in the renal medulla stand for a significant antihypertensive system implicated in the long-range regulation of blood pressure. Thus, the inducible isoform of the enzyme cyclooxygenase (COX-2) is known to be constitutively expressed in the kidney, particularly in the medulla.[6] COX-2 was shown to metabolize AEA to prostaglandin ethanolamide analogs called prostamides.[18] When AEA was administered by infusion into the renal medulla, there was a significant increase in urinary flow with elevation of natriuresis. This finding indicates that an AEA metabolized by COX-2 action would indirectly produce the renal excretory effects of this eCB.[6] The AEA and its metabolites are also involved as modulators and mediators of signaling in the inflammatory process, so they could be involved in chronic kidney disease processes associated with inflammation and cardiovascular disease. Contemporaneous cognizance of the AEA and its derivative roles indicates the growing need for major investigation to determine and study the potential action of ECS in the kidney.[19] In addition, the presence of functional CB1 receptor at the renal level, has also been documented, but there is still disagreement about the expression of CB2 receptors in this organ. Moreover, the renal medulla was shown to have high levels of AEA relative to the cortex, and that AEA intramedullary administration incremented urine volume along with sodium and potassium elimination, with little effect on mean arterial pressure (MAP).[6] A well-known feature of AEA is that, when administered exogenously, it has the ability to stimulate NO release by renal endothelial cells, suggesting a fundamental activity of ECS in the regulation of renal hemodynamics. Other studies have reported that AEA increases renal blood flow and reduces the glomerular filtration rate by activation of CB1 receptors present in afferent and efferent arterioles. These findings are independent of their effects on blood pressure and sodium excretion rate.[20] A recent study showed that AEA regulates sodium transport at the loop of Henle ascending thick limb level. In this segment, AEA stimulates the production of NO, blocks the

apical transporter Na+/H+ and the cotransporter Na+/K+/2Cl−, through the CB1 receptor,[21] suggesting an additional AEA activity as a diuretic agent. Another important sodium transporter that maintains the volume and composition of the extracellular fluid is the Na+/K+-adenosine triphosphatase (ATPase) pump situated in the cells of the proximal tubule, which can also increase diuresis when blocked by NO.[20]"…

-Virna Margarita Martín Giménez, Faculty of Chemical and Technological Sciences, Universidad Católica de Cuyo, San Juan Campus, Argentina;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6009078

Inflammatory responses and inflammation-associated diseases in organs

…"Kidney inflammation contributes to progressive renal injury, which may lead to glomerulonephritis, end-stage renal disease, or acute or chronic kidney disease (CKD) [145–147]. Approximately 10–12% of the population suffers from CKD, and some 50% of elderly patients show signs of kidney dysfunction, which is associated with high morbidity and mortality [52]. Kidney inflammation is most commonly induced by infection, ischemia/reperfusion, in situ immune-complex formation/deposition, or complement pathway dysregulation [145]. CKD and acute kidney injury (AKI) are the most severe types of kidney disease [148]. Interstitial inflammation and tubular injury are commonly observed in acute and chronic kidney injury cases. Renal tubular epithelial cells are likely important promoters of kidney inflammation, secreting a variety of inflammatory cytokines in response to both immune and non-immune factors, and leukocyte infiltration depends on the local presence of these cytokines [146]. Stimuli that can induce kidney injury activate transcription factors (NF-κB or MAPK). These stimuli include cytokines, growth factors, DAMPs, and PAMPs, TLRs, Nod-like receptors (NLRs), and metabolic (high glucose, advanced glycosylation end products) and immune mediators [147]."…

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548

Effect of renal replacement therapy on selected arachidonic acid derivatives concentration

…"Chronic kidney disease (CKD) is one of the most frequently occurring diseases that affects 6–15% of the world's population [1, 2]. Progression of renal failure aggravates ongoing inflammation and increases oxidative stress [3]. Chronic inflammation leads to activation of the endothelium, increased synthesis of adhesion molecules, penetration of monocytes into the intima of the

vessels, as well as stimulation of thrombotic processes [4].

Conservative treatment is used in the initial stages of CKD, and dialysis or renal transplantation is necessary at the end-stage. One of the side effects of dialysis is the synthesis of pro-inflammatory factors and increased oxidative stress as a result of the blood contact with artificial materials of dialyzers and the creation of vascular access, which is necessary for dialysis. Consequences of this include transient leukopenia, activation of platelets and cells of the immune and complement systems, and an increase in interleukin-1 concentration [5].

Platelets also play a crucial role during organ transplantation. Many cell-derived blood-borne factors regulate their activation, and to a large extent, depend on the pro-oxidative-antioxidant balance. Healthy endothelium synthesizes prostacyclin (PGI2) and nitric oxide to prevent adhesion and activation of platelets. During ischemia and reperfusion of organs undergoing transplantation, there is excessive adhesion of platelets and leukocytes, leading to inflammation and tissue damage. As a result, it can strongly stimulate the immune response, as well as cause an increase in organ alloreactivity [6].

Arachidonic acid (AA) derivatives released from activated platelets are involved in many physical processes. Notably, they take part in the development of inflammation, asthma, cancer, diabetes, hypertension, and the pathogenesis of kidney diseases.

Activated platelets mainly synthesize thromboxane A2 (TXA2) in response to platelet aggregation and vasoconstriction. In solutions, unstable TXA2 rapidly degraded to an inactive but more stable form TXB2 [7–9]. Although TXA2 appears to be of minor importance in maintaining renal function under physiological conditions, increased TXA2 biosynthesis in the kidney was observed in various animal models of kidney disease. Unfortunately, one of the inherent and most important aspects of organ transplantation that occur in the transplanted organ is ischemia-reperfusion injury (I/R) [10]. Several authors have already reported that during I/R injury and allograft rejection, there is increased production of thromboxane synthase and consequently increased thromboxane B2 (TXB2) concentration. Inhibition of TXA2 synthesis during reperfusion significantly improves graft function in animal models of kidney transplantation [11, 12].

The 5-, 12-, and 15- hydroxyeicosatetraenoic (HETE) acids are formed from arachidonic acid by the lipoxygenase pathway [13]. 12-HETE activity is found in platelets as a result of platelet activation by agonists such as thrombin or collagen. The role of the 12-HETE isoform in platelets is not entirely clear, and the role in the direct regulation of platelet function is undocumented. The relationship between HETE acids, chronic kidney disease, platelet activation, and the type of renal replacement therapy used is not yet fully understood. Studies show that lipoxygenases are involved in kidney damage in the course of diabetic nephropathy, and it has been demonstrated that the urine concentration of 12-HETE significantly increases in this group of patients [14, 15].

Besides, 12-HETE, together with 15-HETE, induces the synthesis of TGF-β1 (transforming growth factor β1) in mesangial cells, where its action stimulates the synthesis of extracellular matrix proteins that lead to kidney fibrosis.

Knowledge of the relationship between the type of renal replacement therapy used and the level of circulating arachidonic acid derivatives can be extremely important. It has been shown that during peritoneal dialysis, increased eicosanoids are synthesized by macrophages and peritoneal mesenchymal cells due to the properties of dialysis fluids, which are generally not biocompatible [16]. Understanding the relationship between the level of arachidonic acid derivatives and the type of renal replacement therapy used may inform us on the chances of patient survival post-kidney transplantation, whether dialysis is still providing effective treatment for a patient, or which type of renal replacement therapy is appropriate for a given patient."…

-Department of Laboratory Medicine, Pomeranian Medical University in Szczecin, Poland
-Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University in Szczecin, Poland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7488457

Role of Arachidonic Acid and Its Metabolites in the Biological and Clinical Manifestations of Idiopathic Nephrotic Syndrome

"Studies concerning the role of arachidonic acid (AA) and its metabolites in kidney disease are scarce, and this applies in particular to idiopathic nephrotic syndrome (INS). INS is one of the most frequent glomerular diseases in childhood; it is characterized by T-lymphocyte dysfunction, alterations of pro- and anti-coagulant factor levels, and increased platelet count and aggregation, leading to thrombophilia. AA and its metabolites are involved in several biological processes. Herein, we describe the main fields where they may play a significant role, particularly as it pertains to their effects on the kidney and the mechanisms underlying INS. AA and its metabolites influence cell membrane fluidity and permeability, modulate platelet activity and coagulation, regulate lymphocyte activity and inflammation, preserve the permeability of the glomerular barrier, influence podocyte physiology, and play a role in renal fibrosis. We also provide suggestions regarding dietary measures that are able to prevent an imbalance between arachidonic acid and its parental compound linoleic acid, in order to counteract the inflammatory state which characterizes numerous kidney diseases. On this basis, studies of AA in kidney disease appear as an important field to explore, with possible relevant results at the biological, dietary, and pharmacological level, in the final perspective for AA to modulate INS clinical manifestations."

-Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Pediatric Nephrology, Dialysis and Transplant Unit, Via

della Commenda 9, 20122 Milan, Italy;
-Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy;
-Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Intermediate Care Unit, 20122 Milan, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8196840/

■■■

…"Animal trials show that omega-3 fatty acid treatment decreases blood pressure, has anti-inflammatory effects, slows renal failure and moderates the side effects of hypertension (Imig et al. 2005; Zhao et al. 2004). This has been the basis for the study of the effects of omega-3 fatty acids on kidney disease. A recent literature review found that no definitive conclusions can be made about the effectiveness of omega-3 fatty acids for the prevention or treatment of kidney disease (Fassett et al. 2010).

However, just as in the review of effects on cardiovascular disease, the authors point out that there was substantial variability from study to study in the dosages, proportions of specific omega-3 fatty acids administered (i.e., formulations), duration of supplementation, sample sizes and specific outcomes assessed. This again suggests that further studies are needed to better understand the specific formulations, dosages and markers of effectiveness for omega-3 fatty acid supplementation."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See Supplements for related research quotes.

See also Supplements

Kidney Failure (Renal Failure)

…"The results show that the use of combination therapy with DHA and EPA in SHRcp rats improved or prevented renal failure associate with metabolic syndrome with decreasing triglyceride levels and increasing ω-3 PUFA lipid mediators."…

-Department of Environmental Physiology, Shimane University Faculty of Medicine, Japan;
-Department of Developmental Biology, Shimane University Faculty of Medicine, Japan
-Department of Health Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Bunkyo-ku, Tokyo, Japan;
-Disease Model Cooperative Research Association, Hamamatsu, Shizuoka, Japan;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6271130

It is recommenced to get DHA & EPA omega-3s from diet. Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider algae based DHA from a quality source. See Supplements for related research quotes.

■■■

"Triacylglycerols are formed by linking fatty acids with an ester linkage to three alcohol groups in glycerol. Triacylglycerols are the form in which fat energy is stored in adipose tissue. Triacylglycerols are sometimes referred to as triglycerides."

-Omega Fatty Acids in Brain and Neurological Health (Second Edition), 2019
https://www.sciencedirect.com/topics/neuroscience/triacylglycerol

"The hallmark of obesity and one of the key contributing factors to insulin resistance, type 2 diabetes and cardiovascular disease is excess triacylglycerol (TG) storage."....

-Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada
https://pubmed.ncbi.nlm.nih.gov/21963564/

Kidney Inflammation

Arachidonic Acid Metabolism and Kidney Inflammation

"As a major component of cell membrane lipids, Arachidonic acid (AA), being a major component of the cell membrane lipid content, is mainly metabolized by three kinds of enzymes: cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450) enzymes. Based on these three metabolic pathways, AA could be converted into various metabolites that trigger

different inflammatory responses. In the kidney, prostaglandins (PG), thromboxane (Tx), leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs) are the major metabolites generated from AA. An increased level of prostaglandins (PGs), TxA2 and leukotriene B4 (LTB4) results in inflammatory damage to the kidney. Moreover, the LTB4-leukotriene B4 receptor 1 (BLT1) axis participates in the acute kidney injury via mediating the recruitment of renal neutrophils. In addition, AA can regulate renal ion transport through 19-hydroxystilbenetetraenoic acid (19-HETE) and 20-HETE, both of which are produced by cytochrome P450 monooxygenase. Epoxyeicosatrienoic acids (EETs) generated by the CYP450 enzyme also plays a paramount role in the kidney damage during the inflammation process. For example, 14 and 15-EET mitigated ischemia/reperfusion-caused renal tubular epithelial cell damage. Many drug candidates that target the AA metabolism pathways are being developed to treat kidney inflammation. These observations support an extraordinary interest in a wide range of studies on drug interventions aiming to control AA metabolism and kidney inflammation."…

-Traditional Chinese Medicine History and Literature, Institute for Literature and Culture of Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, China

-Institute for Literature and Culture of Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, China

-Key Laboratory of Traditional Chinese Medicine for Classical Theory, Ministry of Education, Shandong University of Traditional Chinese Medicine, Jinan 250355, China

-The Institute for Tissue Engineering and Regenerative Medicine, The Liaocheng University, Liaocheng 252000, China

-Research Institute of Biotechnology & Medical Converged Science, Dongguk University-Seoul, Goyangsi 10326, Korea

-Institute of Clinical Chemistry, University Hospital Zurich, University of Zurich, Wagistrasse 14, 8952 Schlieren, Switzerland

-Guizhou University of Traditional Chinese Medicine, Fei Shan Jie 32, Guiyang 550003, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6695795/

Kidney Stones

The Efficacy of Polyunsaturated Fatty Acids as Protectors against Calcium Oxalate Renal Stone Formation: A Review

"In the pathogenesis of hypercalciuria and hyperoxaluria, n-6 polyunsaturated fatty acids (PUFAs) have been implicated by virtue of their metabolic links with arachidonic acid (AA) and prostaglandin PGE2. Studies have also shown that n-3 PUFAs, particularly those in fish oil—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—can serve as competitive substrates for AA in the n-6 series and can be incorporated into cell membrane phospholipids in the latter's place, thereby reducing urinary excretions of calcium and oxalate. The present review

interrogates several different types of study which address the question of the potential roles played by dietary PUFAs in modulating stone formation. Included among these are human trials that have investigated the effects of dietary PUFA interventions. We identified 16 such trials. Besides fish oil (EPA+DHA), other supplements such as evening primrose oil containing n-6 FAs linoleic acid (LA) and γ-linolenic acid (GLA) were tested. Urinary excretion of calcium or oxalate or both decreased in most trials. However, these decreases were most prominent in the fish oil trials. We recommend the administration of fish oil containing EPA and DHA in the management of calcium oxalate urolithiasis."…

"During the past 30 years, studies have claimed that the dietary intake of n-3 polyunsaturated fatty acids, particularly those occurring in marine fish and fish oils, reduces the risk of urinary stone formation [1,2,3,4,5,6,7]. Other studies have shown an increased risk associated with diets rich in the n-6 fatty acid arachidonic acid (AA) [1,3].

Studies that have suggested a protective effect for n-3 fatty acids have demonstrated reductions in important stone risk factors such as hypercalciuria [2,4,8,9,10], hyperoxaluria [6], or both [1,7,11]. On the other hand, other studies have questioned the veracity of this association [8,12,13,14,15]. For example, the study by Taylor and co-workers involving over 230,000 subjects in 3 three large national US cohorts showed that an increased intake of dietary n-3 PUFAs is highly unlikely to reduce the risk for kidney stone formation [13]. Studies suggesting a lithogenic role for n-6 PUFAs have based their claims on AA being a precursor of the pro-inflammatory and pro-aggregatory dienoic metabolite prostaglandin PGE2 [1], which is thought to affect calcium excretion by influencing renal tubular function and possibly by increasing intestinal calcium absorption [1,3,11]. Also, increased AA may induce hyperoxaluria by activating anion carriers and, consequently, the intestinal and renal transport of oxalate [11]. The process of renal parenchymal calcification is then triggered, which itself is likely to be etiologically significant in the pathogenesis of calcium oxalate stone formation.

In view of these contradictory findings, an assessment of the potential protective role of polyunsaturated fatty acids in stone formation and the mechanisms by which these fatty acids achieve these effects is warranted. The present review interrogates reports and studies published since the early 1950s on the various approaches employed by researchers for testing this notion and offers convincing evidence that studies involving dietary PUFA intervention are the most effective of these. Our review shows that the ingestion of fish oil, a rich source of n-3 fatty acids, reduces important physicochemical risk factors for calcium oxalate kidney stones."…

-Department of Chemistry, University of Cape Town, Cape Town 7701, South Africa
-University Stone Centre, Department of Urology, University Hospital of Bonn, 53127 Bonn, Germany;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7230958

Knee Pain

…"In adults with knee pain, a high n-6:n-3 ratio is associated with greater clinical pain/functional limitations, experimental pain sensitivity, and psychosocial distress compared to a low ratio group. Findings support consideration of the n-6:n-3 PUFA ratio and additional clinical endpoints in future research efforts."

-Department of Aging & Geriatric Research, University of Florida, Gainesville, FL, USA
-Pain Research & Intervention Center of Excellence, University of Florida
-Department of Anesthesia, Cincinnati Children's Hospital, Cincinnati, OH, USA
-Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL, USA
-Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, FL, USA
-Department of Biostatistics, University of Florida, Gainesville, Florida, USA
-Department of Psychology, University of Alabama at Birmingham, AL, USA
-Department of Medicine/ Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, AL, USA
-College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, USA
-Center of Excellence for Stress and Mental Health (CESAMH)
-VA San Diego Healthcare System
-University of California, San Diego, CA, USA
-Department of Medicine, University of Florida, Gainesville, FL, USA
-Biostatistics Department, School of Public Health University of Alabama at Birmingham, AL, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5701880/

See also Osteoarthritis

L

Leaky Gut

Also referred to as gut/intestinal permeability

Pharmacological effects of cannabinoids on the Caco-2 cell culture model of intestinal permeability

"Activation of cannabinoid receptors decreases emesis, inflammation, gastric acid secretion, and

intestinal motility. However, the effects of cannabinoids on intestinal permeability have not yet been established. The aim of the present study is to examine the effects of cannabinoids on intestinal permeability in an in vitro model. Caco-2 cells were grown until fully confluent on inserts in 12-well plates. Transepithelial electrical resistance (TEER) measurements were made as a measure of permeability. EDTA (50 μM) was applied to reversibly increase permeability (reduce TEER). The effects of cannabinoids on permeability in combination with EDTA, or alone, were assessed. Potential target sites of action were investigated using antagonists of the cannabinoid (CB)(1) receptor, CB(2) receptor, transient receptor potential vanilloid subtype 1 (TRPV1), peroxisome proliferator-activated receptor (PPAR)γ, PPARα, and a proposed cannabinoid receptor. When applied to the apical or basolateral membrane of Caco-2 cells, Δ(9)-tetrahydrocannabinol (THC) and cannabidiol (CBD) enhanced the speed of recovery of EDTA-induced increased permeability. This effect was sensitive to cannabinoid CB(1) receptor antagonism only. Apical application of endocannabinoids caused increased permeability, sensitive to cannabinoid CB(1) receptor antagonism. By contrast, when endocannabinoids were applied basolaterally, they enhanced the recovery of EDTA-induced increased permeability, and this involved additional activation of TRPV1. All cannabinoids tested increased the mRNA of the tight junction protein zona occludens-1, but only endocannabinoids also decreased the mRNA of claudin-1. These findings suggest that endocannabinoids may play a role in modulating intestinal permeability and that plant-derived cannabinoids, such as THC and CBD, may have therapeutic potential in conditions associated with abnormally permeable intestinal epithelium."

-School of Graduate Entry Medicine and Health, Royal Derby Hospital, University of Nottingham, Nottingham, United Kingdom.

https://pubmed.ncbi.nlm.nih.gov/20592049/

When the endocannabinoid system (ECS) is over-activate in an inflammatory manner it becomes destructive.

The endocannabinoid system links gut microbiota to adipogenesis

"Obesity is characterised by altered gut microbiota, low-grade inflammation and increased endocannabinoid (eCB) system tone; however, a clear connection between gut microbiota and eCB signalling has yet to be confirmed. Here, we report that gut microbiota modulate the intestinal eCB system tone, which in turn regulates gut permeability and plasma lipopolysaccharide (LPS) levels. The impact of the increased plasma LPS levels and eCB system tone found in obesity on adipose tissue metabolism (e.g. differentiation and lipogenesis) remains unknown. By interfering with the eCB system using CB(1) agonist and antagonist in lean and

obese mouse models, we found that the eCB system controls gut permeability and adipogenesis. We also show that LPS acts as a master switch to control adipose tissue metabolism both in vivo and ex vivo by blocking cannabinoid-driven adipogenesis. These data indicate that gut microbiota determine adipose tissue physiology through LPS-eCB system regulatory loops and may have critical functions in adipose tissue plasticity during obesity."…

"Taken together, these in vivo and in vitro experiments support the hypothesis that the eCB system has an important function in the regulation of gut permeability through a CB1 receptor-dependent mechanism."…

"Recent studies have proposed that obesity and its associated inflammation dysregulate adipose tissue metabolism by impairing adipogenesis (Gustafson et al, 2009; Isakson et al, 2009; McLaughlin et al, 2009). This phenomenon is associated with increased eCB system tone. Understanding the molecular mechanisms responsible for altered adipogenesis is essential to avoid the associated metabolic complications. Here, we show that selective changes in gut microbiota or CB1 receptor antagonist reduce the inflammatory tone in obese mice by impacting the strength of the gut barrier and plasma LPS levels. This process may participate in the restoration of adipogenesis after reducing eCB system tone (e.g. with prebiotics or CB1 receptor antagonists) in pathological situations such as obesity."…

"Obesity is characterised by a massive expansion of adipose tissues, in addition to metabolic and inflammatory complications (Hotamisligil and Erbay, 2008). Here, we characterise the crosstalk between gut microbiota and the regulation of adipogenesis by the eCB system and provide evidence that gut microbiota physiologically regulate the activity of the peripheral eCB system in intestinal and adipose tissue. The peripheral eCB system, in turn, controls gut barrier function and adipogenesis.

Obesity is characterised by dysregulated eCB system tone (Figure 5) (Engeli et al, 2005; Bluher et al, 2006; Matias et al, 2006; Cote et al, 2007; D'Eon et al, 2008; Starowicz et al, 2008; Di Marzo et al, 2009; Izzo et al, 2009), altered gut permeability and increased plasma LPS levels (Cani et al, 2008, 2009). Pharmacological blockade of the CB1 receptor has been shown to reduce obesity associated with inflammation by an unresolved mechanism (Gary-Bobo et al, 2007; Caraceni et al, 2009). In this study, we evaluated the function of intestinal eCB system activation in the development of gut permeability, a major source of metabolic inflammation."

-Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2925525/

Targeting the endocannabinoid system for gastrointestinal diseases: future therapeutic strategies

"Cannabinoids extracted from the marijuana plant (Cannabis sativa) and synthetic cannabinoids have numerous effects on gastrointestinal (GI) functions. Recent experimental data support an important role for cannabinoids in GI diseases. Genetic studies in humans have proven that defects in endocannabinoid metabolism underlie functional GI disorders. **Mammalian cells have machinery, the so-called endocannabinoid system (ECS), to produce and metabolize their own cannabinoids in order to control homeostasis of the gut in a rapidly adapting manner.** Pharmacological manipulation of the ECS by cannabinoids, or by drugs that raise the levels of endogenous cannabinoids, have shown beneficial effects on GI pathophysiology. This review gives an introduction into the functions of the ECS in the GI tract, highlights the role of the ECS in GI diseases and addresses its potential pharmacological exploitation."

-Division of Gastroenterology, Department of Medicine, University of Calgary
http://www.ncbi.nlm.nih.gov/pubmed/22111567

Learning Disability

…"A higher level of education was also associated with a greater number of servings of total fish and fish high in n-3 LCPUFA consumed over the course of 30 days"…

-Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE 68198, USA; (M.T.)
-College of Public Health, University of Nebraska Medical Center, Omaha, NE 68198, USA;
-Department of Nutritional Sciences, University of Arizona, Tucson, AZ 85721, USA;
-Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA 16802, USA;
-Division of Biomedical Sciences, School of Medicine, University of California Riverside, Riverside, CA 92521, USA
-College of Allied Health Professions, University of Nebraska Medical Center, Omaha, NE 68198, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7400855/

■■■

…"Brain membranes have a very high content in essential polyunsatured fatty acids [PUFAs] for which they depend on alimentation. Any dietary lack of essential polyunsatured fatty acids has consequences on cerebral development, modifying the activity of enzymes of the cerebral membranes and decreasing efficiency in learning tasks."

- University of Liège, CUP La Clairière, Bertrix.
https://pubmed.ncbi.nlm.nih.gov/12640327/

Limonene

Antitumorigenic effects of limonene and perillyl alcohol against pancreatic and breast cancer.

“Perillyl alcohol is a natural product from cherries and other edible plants. Perillyl alcohol and d-limonene, a closely related dietary monoterpene, have chemotherapeutic activity against pancreatic, mammary, and prostatic tumors. In addition, perillyl alcohol, limonene, and other dietary monoterpenes have chemopreventive activity. Several mechanisms may account for the antitumorigenic effects of monoterpenes. For example, many monoterpenes inhibit the post-translational isoprenylation of cell growth-regulatory proteins such as Ras. Perillyl alcohol induces apoptosis without affecting the rate of DNA synthesis in both liver and pancreatic tumor cells. In addition, monoterpene-treated, regressing rat mammary tumors exhibit increased expression of transforming growth factor beta concomitant with tumor remodeling/redifferentiation to a more benign phenotype. Monoterpenes are effective, nontoxic dietary antitumor agents which act through a variety of mechanisms of action and hold promise as a novel class of antitumor drugs for human cancer.”

Department of Biology, Indiana University-Purdue University at Indianapolis 46202, USA.
https://www.ncbi.nlm.nih.gov/pubmed/8886131

Lion’s Mane (Hericium erinaceus)

Neurohealth Properties of Hericium erinaceus Mycelia Enriched with Erinacines

“Hericium erinaceus, an ideal culinary-medicinal mushroom, has become a well-established candidate in promoting positive brain and nerve health-related activities by inducing the nerve growth factor from its bioactive ingredient. Among its active compounds, only erinacine A has confirmed pharmacological actions in the central nervous system in rats. Hence, this review has summarized the available information on the neurohealth properties of H. erinaceus mycelia enriched with erinacines, which may contribute to further research on the therapeutic roles of these mycelia. The safety of this mushroom has also been discussed. Although it has been difficult to extrapolate the in vivo studies to clinical situations, preclinical studies have shown that there can be improvements in ischemic stroke, Parkinson's disease, Alzheimer's disease, and

depression if H. erinaceus mycelia enriched with erinacines are included in daily meals."

-Grape King Bio Ltd, Zhong-Li Dist., Taoyuan City, Taiwan
-Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei City, Taiwan
-Institute of Food Science and Technology, National Taiwan University, Taipei City, Taiwan
-Department of Food Science, Nutrition and Nutraceutical Biotechnology, Shih Chien University, Taipei City, Taiwan
-Institute of Biotechnology, National Changhua University of Education, Changhua, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987239/

Hericium erinaceus (Lion's Mane) mushroom extracts inhibit metastasis of cancer cells to the lung in CT-26 colon cancer-tansplanted mice

"This study investigated the antimetastatic activity of four Hericium erinaceus edible mushroom extracts using CT-26 murine colon carcinoma cells as an indicator of inhibition of cell migration to the lung. Hot water (HWE) and microwaved 50% ethanol (MWE) extracts of H. erinaceus strongly elicited cancer cell death through apoptosis and inhibited metastasis of cancer cells to the lungs by 66% and 69%, respectively. HWE and MWE reduced the expression of matrix metalloproteinases MMP-2 and MMP-9 in cells and their activities in culture media. Urokinase-type plasminogen activator (u-PA), another extracellular matrix (ECM)-degrading proteinase, also showed decreased protein expression. In CT-26 cells, HWE and MWE down-regulated extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) phosphorylations. The reduced phosphorylations seem to cause reduction of activity of the MMPs, thereby blocking migration and invasion of cells. Dietary administration of HWE and MWE reduced the formation of tumor nodules in the lung by about 50% and 55%, respectively, and prevented increases in lung weight caused by cancer cell metastasis. These results demonstrate the effectiveness of HWE and MWE as beneficial antimetastatic agents, targeting their upstream signaling molecules for mediating the expression of the ECM-degrading proteinases. Acidic and alkaline extracts were not bioactive. Bioactivity seems to be related to composition. H. erinaceus edible mushrooms have the potential to serve as a health-promoting functional food."

-Department of Biological Science, Ajou University, Suwon, Republic of Korea.
https://pubmed.ncbi.nlm.nih.gov/23668749

Composition and mechanism of antitumor effects of Hericium erinaceus mushroom extracts in tumor-bearing mice

"We investigated antitumor effects of the following four extracts of freeze-dried Hericium

erinaceus mushrooms in Balb/c mice intracutaneously transplanted on the backs with CT-26 colon cancer cells: HWE, hot water extraction by boiling in water for 3 h; MWE, microwaving in 50% ethanol/water at 60 W for 3 min; and ACE and AKE, boiling in 1% HCl or 3% NaOH for 2 h. HWE and MWE with a higher content of β-glucans, determined by an assay kit, than ACE and MKE were active in all bioassays. Gas chromatography/mass spectrometry analyses showed the presence of 40, 27, 16, and 13 compounds, respectively, in the four extracts. Daily intraperitoneal (ip) injections of HWE and MWE for 2 weeks significantly reduced tumor weights by 38 and 41%. Tumor regressions were associated with changes in the following cancer biomarkers as compared to phosphate buffer (PBS)-treated control mice: 2.7- and 2.4-fold increases in cytolytic activity of splenic natural killer (NK) cells; restored nitric oxide production and phagocytosis in peritoneal macrophages to 95-98% of normal levels; ~ 2-fold increase in released pro-inflammatory cytokines tumor necrosis factor-α, interleukin-1β, and interleukin-6 from macrophages; and ~ 56 and ~ 60% reductions in the number of blood vessels inside the tumor. The pro-angiogenic factors vascular endothelial growth factor (VEGF), cyclooxygenase 2 (COX-2), and 5-lipoxygenase (5-LOX) were also significantly reduced in mRNA and protein expression by tumor genes. Enzyme-linked immunosorbent assay of tumor cells confirmed reduced expression of COX-2 and 5-LOX (32 and 31%). Reduced COX-2 and 5-LOX expression down-regulated VEGF expression, resulting in inhibition of neo-angiogenesis inside the tumors. The results indicate that induction of NK activity, activation of macrophages, and inhibition of angiogenesis all contribute to the mechanism of reduction of tumor size."

-Department of Molecular Science and Technology, Ajou University, Suwon, 443-749, Republic of Korea.
https://pubmed.ncbi.nlm.nih.gov/21846141

Chemistry, Nutrition, and Health-Promoting Properties of Hericium erinaceus (Lion's Mane) Mushroom Fruiting Bodies and Mycelia and Their Bioactive Compounds

"The culinary and medicinal mushroom Hericium erinaceus is widely consumed in Asian countries, but apparently not in the United States, for its nutritional and health benefits. To stimulate broader interest in the reported beneficial properties, this overview surveys and consolidates the widely scattered literature on the chemistry (isolation and structural characterization) of polysaccharides and secondary metabolites such as erinacines, hericerins, hericenones, resorcinols, steroids, mono- and diterpenes, and volatile aroma compounds, nutritional composition, food and industrial uses, and exceptional nutritional and health-promoting aspects of H. erinaceus. The reported health-promoting properties of the mushroom fruit bodies, mycelia, and bioactive pure compounds include antibiotic, anticarcinogenic,

antidiabetic, antifatigue, antihypertensive, antihyperlipodemic, antisenescence, cardioprotective, hepatoprotective, nephroprotective, and neuroprotective properties and improvement of anxiety, cognitive function, and depression. The described anti-inflammatory, antioxidative, and immunostimulating properties in cells, animals, and humans seem to be responsible for the multiple health-promoting properties. A wide range of research advances and techniques are described and evaluated. The collated information and suggestion for further research might facilitate and guide further studies to optimize the use of the whole mushrooms and about 70 characterized actual and potential bioactive secondary metabolites to help prevent or treat human chronic, cognitive, and neurological diseases."

-Western Regional Research Center, Agricultural Research Service, U.S. Department of Agriculture, 800 Buchanan Street, Albany, California, United States.
https://pubmed.ncbi.nlm.nih.gov/26244378

Redox modulation of cellular stress response and lipoxin A4 expression by Hericium Erinaceus in rat brain: relevance to Alzheimer's disease pathogenesis

"**Background:** There has been a recent upsurge of interest in complementary medicine, especially dietary supplements and foods functional in delaying the onset of age-associated neurodegenerative diseases. Mushrooms have long been used in traditional medicine for thousands of years, being now increasingly recognized as antitumor, antioxidant, antiviral, antibacterial and hepatoprotective agent also capable to stimulate host immune responses.

Results

Here we provide evidence of neuroprotective action of Hericium Herinaceus when administered orally to rat. Expression of Lipoxin A4 (LXA4) was measured in different brain regions after oral administration of a biomass Hericium preparation, given for 3 month. LXA4 up-regulation was associated with an increased content of redox sensitive proteins involved in cellular stress response, such as Hsp72, Heme oxygenase −1 and Thioredoxin. In the brain of rats receiving Hericium, maximum induction of LXA4 was observed in cortex, and hippocampus followed by substantia Nigra, striatum and cerebellum. Increasing evidence supports the notion that oxidative stress-driven neuroinflammation is a fundamental cause in neurodegenerative diseases. As prominent intracellular redox system involved in neuroprotection, the vitagene system is emerging as a neurohormetic potential target for novel cytoprotective interventions. Vitagenes encode for cytoprotective heat shock proteins 70, heme oxygenase-1, thioredoxin and Lipoxin A4. Emerging interest is now focussing on molecules capable of activating the vitagene system as novel therapeutic target to minimize deleterious consequences associated with free radical-

induced cell damage, such as in neurodegeneration. LXA4 is an emerging endogenous eicosanoid able to promote resolution of inflammation, acting as an endogenous "braking signal" in the inflammatory process. In addition, Hsp system is emerging as key pathway for modulation to prevent neuronal dysfunction, caused by protein misfolding."

Conclusions

Conceivably, activation of LXA4 signaling and modulation of stress responsive vitagene proteins could serve as a potential therapeutic target for AD-related inflammation and neurodegenerative damage."

-Department of Biomedical and Biotechnological Sciences, School of Medicine, University of Catania, Viale Andrea Doria 6, 95125 Catania, Italy

-Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4938991

Lipoxin A4 is an allosteric endocannabinoid that strengthens anandamide-induced CB1 receptor activation

"A major advance in the field of cannabinoid research was the discovery of the endocannabinoid system, which is currently thought to consist of two G protein-coupled receptors (cannabinoid CB1 and CB2 receptors) and endogenous compounds such as arachidonoylethanolamide (i.e., anandamide; AEA; Fig. 1) and 2-arachidonoyl glycerol (2-AG) that can activate these receptors and are known as endocannabinoids [1]. This system of receptors and endogenous agonists, which is also made up of enzymes that catalyze endocannabinoid biosynthesis or metabolic degradation, and of processes responsible for the cellular uptake of endocannabinoids, is thought to have numerous roles in both health and disease [2, 3]. Some of these are "autoprotective" in nature and hence beneficial, with examples including the amelioration of inflammatory pain, multiple sclerosis, and Parkinson disease; whereas a few of its other roles, for example, in obesity, are "autoimpairing," and therefore unwanted. AEA, 2-AG, and other "direct" cannabinoid receptor agonists are thought to trigger G protein-mediated signaling of CB1 and CB2 receptors by targeting orthosteric sites on these receptors [1]. There is evidence, however, that the CB1 receptor also contains one or more "allosteric" sites that can be targeted by allosteric modulators in a manner that can enhance or reduce the efficacy with which direct agonists activate this receptor orthosterically [4–7]. Just as the discovery of the CB1 receptor prompted a search for endogenous ligands for this receptor [8], so too the discovery that CB1 receptors contain allosteric sites has prompted a need to look for an endogenous CB1 allosteric modulator.

This need has now been met by Pamplona et al. [9], who, in PNAS, present evidence that the endogenous anti-inflammatory ligand lipoxin A4 [LXA4; Fig. 1] can allosterically enhance AEA-induced activation of CB1 receptors within the brain when it is administered exogenously and when it is produced endogenously. This is a ligand that is already known to target the FPR2/ALX receptor as an agonist, mainly outside the brain, and, like AEA and 2-AG, to be an eicosanoid that is formed from arachidonic acid [10–12].“

-School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, Scotland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529042

Lipids

“Lipids are important cellular and extracellular molecules. They are critical for cell structure, function, and energy, as well as organs and body insulation and protection. In addition, lipids metabolites are extremely essential for a wide range of cellular communication and metabolism. However, defective lipids metabolism is well known to modulate a wide range of chronic diseases such as cardiovascular diseases and cancer and several other genetically defective lipids pathways with severe health implications.

Major lipids in human health and diseases may broadly be classified as saturated and unsaturated fatty acids, sterols, phospholipids, sphingosine derivatives, and various other lipids metabolites such as eicosanoids.

The Genome Wide Association Studies (GWAS) helped identify several genetically defective lipids pathways and linked them to causes of morbidity and mortality around the globe. This GWAS emerging technology has unraveled many metabolic defects associated with dietary lipids and causes of many health conditions such as obesity, cardiovascular neurodegenerative defects, and cancer. GWAS studies have demonstrated that many of the lipids disorders mechanisms are associated primarily with oxidative stress and inflammation. It is unclear how the environmental modulators and lifestyle are linked to these disorders, which prompt further investigations to determine the initial causes and possible intervention approaches.”

-Department of Chemistry, Biochemistry, College of Science, Imam Abdulrahman Bin Faisal University, Saudi Arabia

-Department of Biology, College of Science, Imam Abdulrahman Bin Faisal University, Saudi Arabia

-Department of Biochemistry, Beni Suef University, Beni Suef, Egypt

-Department of Biomedical and Nutritional Sciences, University of Massachusetts, Lowell, MA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6632456

…“Lipids play a crucial role in cell membrane integrity, cell signaling, and metabolism. A major class of lipids is polyunsaturated fatty acids (PUFAs), which are characterized by more than one double bond in their carbon backbone. PUFAs are divided into two major classes: omega-3 (n-3) or omega-6 (n-6) fatty acids, depending on whether the first double bond is on the third or sixth carbon from the terminal methyl group. PUFAs can synthesized from the essential fatty acids, linoleic acid and alpha-linoleic acid, through a biosynthesis pathway involving fatty acid desaturases and elongases to result in long-chain PUFAs (LC-PUFAs, defined as 18–22 carbons) such as docosahexaenoic acid (DHA) as well as very long-chain PUFAs (VLC-PUFAs; defined as greater than 22 carbons) (Fig. 7.1).”

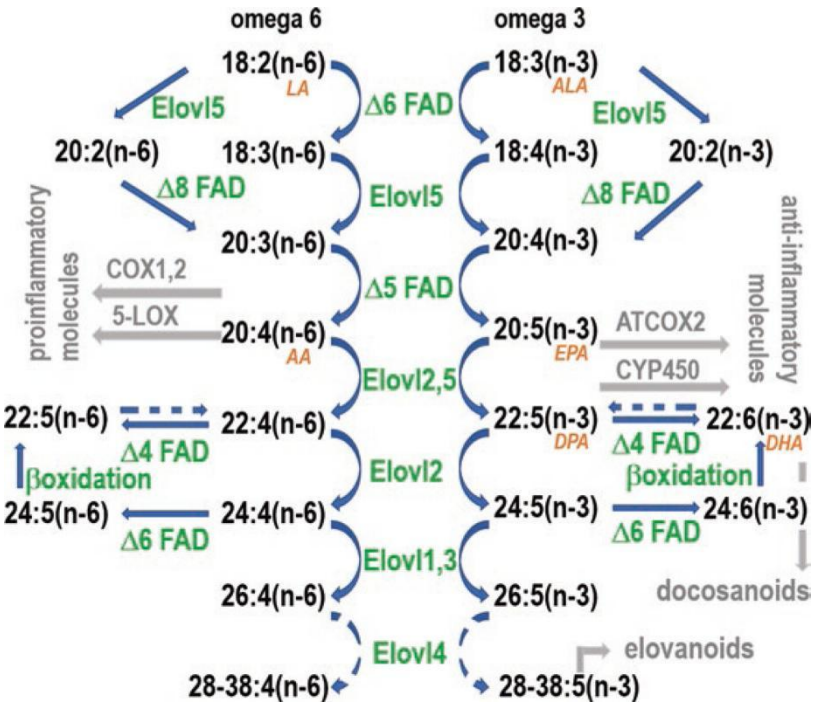

Fig. 7.1

“Omega-3 and omega-6 long-chain fatty acids synthesis pathways compete for the same enzymatic machinery in the cell. Several secondary products of the pathway play an important role in modulating cell homeostasis“

-Viterbi Family Department of Ophthalmology, Shiley Eye Institute, University of California, San Diego, La Jolla, CA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7526619

Lipids and Alzheimer's Disease

"Lipids, as the basic component of cell membranes, play an important role in human health as well as brain function. The brain is highly enriched in lipids, and disruption of lipid homeostasis is related to neurologic disorders as well as neurodegenerative diseases such as Alzheimer's disease (AD). Aging is associated with changes in lipid composition. Alterations of fatty acids at the level of lipid rafts and cerebral lipid peroxidation were found in the early stage of AD. Genetic and environmental factors such as apolipoprotein and lipid transporter carrying status and dietary lipid content are associated with AD. Insight into the connection between lipids and AD is crucial to unraveling the metabolic aspects of this puzzling disease. Recent advances in lipid analytical methodology have led us to gain an in-depth understanding on lipids. As a result, lipidomics have becoming a hot topic of investigation in AD, in order to find biomarkers for disease prediction, diagnosis, and prevention, with the ultimate goal of discovering novel therapeutics."….

-Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Taiwan
-Department of Pediatrics, E-DA Hospital, Taiwan
-Department of Orthopedics, E-DA Hospital, Taiwan
-Research Center of Clinical Medicine, National Cheng Kung University Hospital, College of Medicine,
-National Cheng Kung University, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7073164

■■■

…"In addition to their role as structural components of the cell membrane, phospholipids serve as precursors for various second messengers such as arachidonic acid (ArAc), docosahexaenoic acid (DHA), ceramide, 1,2-diacylglycerol, phosphatidic acid, and lyso-phosphatidic acid. Lipids comprise a large number of chemically distinct molecules arising from combinations of fatty acids with various backbone structures. Overall, mammalian cells may contain 1,000–2,000 lipid species. Lipid metabolism may be of particular importance for the CNS, as this organ has the highest concentration of lipids next to adipose tissue."…

- Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- Cardiovascular Research Center, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- Neuroscience Training Program, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- William S. Middleton Veterans Affairs Hospital, Madison, WI.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2293298/

Aging and Lipids

…"During the first two decades of human life, amounts of cerebral lipids increase and then begin to gradually decrease after the age of 50 [13]. Aging causes alterations of adipose tissue distribution with an elevation of systemic free fatty acids (FFA) levels, a common feature of metabolic syndromes [14]. There are age-related alterations of lipid compositions in different brain areas. The saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and PUFA are significantly greater in mid-life males compared to younger males, whereas PUFAs including DHA, AA decrease and MUFAs increase in the grey matter of orbitofrontal cortex with aging [15]. Likewise, aging is related to increased inflammation. Lipids are the mediators that orchestrate many immune responses. Some specialized pro-resolving lipid mediators (SPMs) are particularly associated with aging [16]."…

-Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Taiwan
-Department of Pediatrics, E-DA Hospital, Taiwan
-Department of Orthopedics, E-DA Hospital, Taiwan
-Research Center of Clinical Medicine, National Cheng Kung University Hospital, College of Medicine,
-National Cheng Kung University, Taiwan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7073164

The endocannabinoid system and its role in regulation of metabolism in peripheral tissues

"The endocannabinoid system (ECS) comprises cannabinoid receptors (CB1R and CB2R), endogenous lipid ligands (endocannabinoids) and enzymes that synthesize and degrade these compounds. ECS is involved in the regulation of lipogenesis and fatty acids utilization in liver, skeletal muscle and adipose tissue. Activation of CB1 receptor leads to: (i) increase in the activity of transcription factors which regulate gene expression involved in lipid synthesis (SREBP-1c, PPARgamma), (ii) inhibition of AMP-activated protein kinase and (iii) decrease in fatty acid oxidation. Furthermore, increased level of endocannabinoids is associated with reduced insulin sensitivity in skeletal muscle. ECS is also involved in regulation of adipocyte differentiation. This review summarizes the current knowledge on the regulatory function of endocannabinoids and addresses the role of ECS in the pathogenesis of metabolic disorders."

-Laboratory of Cell Signals and Metabolic Disorders, Institute of Experimental Biology Marcelego Nencki PAN, Warsaw.
https://pubmed.ncbi.nlm.nih.gov/23214136

Fats and Other Lipids

"Lipids are compounds that are insoluble in water but are soluble in organic solvents such as ether and chloroform. Lipids that are important to our discussion include fats and oils (triglycerides or triacyglycerols), fatty acids, phospholipids, and cholesterol.

Fats and oils are esters of glycerol and three fatty acids. They are important in the diet as energy sources and as sources of essential fatty acids and fat-soluble vitamins, which tend to associate with fats. They also contribute satiety, flavor, and palatability to the diet.

Fatty acids generally consist of a straight alkyl chain, terminating with a carboxyl group. The number of carbons in the chain varies, and the compound may be saturated (containing no double bonds) or unsaturated (containing one or more double bonds). Short- and medium-chain saturated fatty acids (SFAs) (4 to 12 carbons in length) are found in milk fat, palm oil, and coconut oil. Other animal and vegetable fats contain predominantly longer-chain SFAs (more than 14 carbons in length) and are found chiefly in meats, butterfat, and some vegetable oils. Monounsaturated fatty acids (MUFAs), such as oleic acid, contain one double bond per molecule, whereas polyunsaturated fatty acids (PUFAs), such as linoleic acid, contain more than one. Linoleic acid is classified as an essential nutrient, since the body requires it but cannot synthesize it. Arachidonic acid is also required by the body but can be synthesized from linoleic acid, which is abundant in oils from corn, soybeans, and safflower seeds.

Linoleic acid (18 carbons with 2 double bonds) and arachidonic acid (20 carbons with 4 double bonds) belong to the omega(ω)-6 group of fatty acids, since the first double bond, counting from the methyl end of the molecule, occurs at carbon number 6. Since linoleic acid has 18 carbon atoms and 2 double bonds, it is usually represented in shorthand as C18:2, ω-6. Under this classification system, oleic acid (C18:1, ω-9) belongs to the ω-9 group, and the PUFAs in fish oils currently receiving much attention belong to the ω-3 group. Chief among these ω-3 fatty acids are eicosapentaenoic acid (EPA), which has 20 carbons and 5 double bonds (C20:5, ω-3), and docosahexaenoic acid (DHA), which has 22 carbons and 6 double bonds (C22:6, ω-3).

A growing body of evidence from studies in animals, including nonhuman primates, indicates that α-linolenic acid, or its longer-chain derivates EPA and DHA, are essential in the diet. These fatty acids appear to play distinctive roles in the structure and function of biologic membranes in the retina and central nervous system (Neuringer and Connor, 1986).

Unsaturated fatty acids form geometric isomers, i.e., the carbon chains are on the same side of the double bond in a cis isomer and on opposite sides of the bond in a trans isomer. Naturally occurring geometric isomers in food are mainly cis isomers, but hydrogenation of oils in the manufacture of margarine and shortening results in formation of some trans isomers. This latter process occurs naturally in the rumen of ruminants.

Phospholipids contain glycerol, fatty acids, phosphate, and, with such exceptions as phosphatidylglycerol and phosphatidylinositol, a nitrogenous component. Lecithin, for example, is made up of glycerol, two fatty acids (one saturated, usually), phosphate, and choline. Phospholipids are important structural components of brain and nervous tissue, of membranes throughout body tissues, and of lipoproteins—the carriers of cholesterol and fats in the blood.

Cholesterol and plant sterols, such as sitosterol, are high-molecular-weight alcohols with a characteristic cyclic nucleus and are unrelated to the structure of fats or phospholipids. Cholesterol frequently exists in foods and body tissues esterified to one fatty acid per molecule. It is a component of membranes in body cells and is required for normal development of the brain and nervous tissue. Furthermore, it is the precursor to bile acids, steroid hormones, and 7-dehydrocholesterol in the skin, which in turn is the precursor to vitamin D.

Cholesterol occurs naturally only in foods of animal origin. The highest concentrations are found in liver and egg yolk, but red meats, poultry (especially the skin), whole milk, and cheese make significant contributions to the diet."….

"Of greatest interest concerning effects of dietary fats and other lipids on hemostasis and eicosanoid metabolism are the ω-3 PUFAs of marine origin (von Schacky et al., 1985b). Some investigators have reported that Eskimo populations in Greenland appear to have reduced mortality from occlusive vascular disease, putatively related to consumption of fish and fish oils containing ω-3 fatty acids (Bang and Dyerberg, 1980). However, the epidemiologic evidence on this assertion is quite incomplete. Furthermore, there is no evidence that dietary supplementation with ω-3 fish oils will reduce the risk of cardiovascular disease (Carroll, 1986a)."

-National Research Council (US) Committee on Diet and Health.
Washington (DC): National Academies Press (US); 1989.
https://www.ncbi.nlm.nih.gov/books/NBK218759/

Lipopolysaccharide (LPS)

"Lipopolysaccharide (LPS) induces host inflammatory responses and tissue injury and has been implicated in the pathogenesis of various age-related diseases"….

…"Lipopolysaccharide (LPS), a highly conserved cell wall component of gram-negative bacteria, is known to initiate signaling cascade for inflammatory mediator expression including cytokines such as tumor necrosis factor α (TNF-α) and interleukin (IL)-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2), and nuclear factor-kappaB (NF-κB) [1]. It is accepted that dysregulated inflammatory responses result in various age-related diseases including acute

respiratory distress syndrome (ARDS), neurodegenerative and vascular diseases [2] and also periodontal disease [3,4]. Oxidative stress mediated by reactive oxygen/nitrogen species (ROS/RNS) has been implicated in the pathogenesis induced by LPS which accelerates the formation of nitric oxide (NO) [5] and prostaglandin E2 (PGE2) [6].”…

“Consequently, the effects of antioxidants against LPS-induced oxidative stress have been studied extensively. Notably, the role of vitamin E against deleterious effects of LPS has been the subject of many in vitro and in vivo studies. In general, it has been observed that vitamin E suppresses inflammatory responses and oxidative damage induced by LPS in both cell culture systems and animal experiments [7–11]. “…

-Health Research Institute, National Institute of Advanced Industrial Science & Technology (AIST),Japan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3757666/

Impact of the omega-3 to omega-6 polyunsaturated fatty acid ratio on cytokine release in human alveolar cells

“**Background**: ω-3 polyunsaturated fatty acids (PUFAs) and ω-6 PUFAs have opposing influences on inflammation. The objective was to determine whether lipopolysaccharide (LPS)-induced cytokine release by human alveolar cells was affected by changes in the ω-3/ω-6 ratio of cell membranes induced by different supplies of PUFAs.”…

“**Results**: The supply of 1:1 and 1:2 DHA/AA ratios reversed the baseline predominance of ω-6 over ω-3 in the ω-3/ω-6 PUFA ratio of cell membranes. The release of proinflammatory cytokines (tumor necrosis factor α, interleukin-6, and interleukin-8) was reduced by 1:1 and 1:2 DHA/AA ratios ($P < .01$ to $P < .001$) but increased by 1:4 and 1:7 DHA/AA ratios ($P < .01$ to $P < .001$) vs control. The 1:1 and 1:2 ratios increased the release of anti-inflammatory interleukin-10 ($P < .001$). The balance between proinflammatory and anti-inflammatory cytokines showed an anti-inflammatory response with 1:1 and 1:2 ratios and a proinflammatory response with 1:4 and 1:7 ratios ($P < .001$).

Conclusions: This study showed that proinflammatory cytokine release was dependent on the proportion of ω-3 in the ω-3/ω-6 ratio of alveolar cell membranes, being reduced with the supply of a high proportion of DHA and increased with a high proportion of AA, respectively. These results support the biochemical basis for current recommendations to shift the PUFA supply from ω-6 to ω-3 in nutrition support of patients with acute lung injury.”

-Department of Anesthesiology and Intensive Care, S. Giovanni Battista Hospital, University of Turin, Turin, Italy.
https://pubmed.ncbi.nlm.nih.gov/21224438/

…"Two key n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), can substantially decrease LPS-induced TNF-α expression by blocking NF-κB activation [32-33]. Moreover, EPA can also decrease LPS-induced TNF-α mRNA in vitro, with the modulation of TNF-α expression occurring at the transcriptional level [32]. Furthermore, as described earlier, oxidants and oxidized cell components can activate the NF-κB pathway, promoting inflammation [4]; the n-3 PUFAs also decrease oxidative stress [34-35]. Thus n-3 PUFA's inhibition of NF-κB transcriptional activity could influence expression of proinflammatory genes."…

-Janice K. Kiecolt-Glaser, Ph.D.

-Department of Psychiatry and The Ohio State Institute for Behavioral Medicine Research, The Ohio State University College of Medicine, Columbus, Ohio;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2868080

…"Brain cells membranes are particularly enriched in DHA and AA (Bourre et al., 1993; Salem and Niebylski, 1995). Because chronic dietary imbalance of n-3/n-6 PUFA leads to brain DHA decrease (Pifferi et al., 2005), such a diet could impair the expression and action of cytokines in the brain. Thus, we postulated that lower n-3 PUFA status in the brain, resulting from n-3 PUFA dietary deficiency from gestation to adulthood, may alter LPS behavioural effects by disturbing cerebral innate immune activation and action. Our attention was focused on IL-6 expression and signalling pathways as potential candidates for regulation by n-3 PUFA."…

-Psychoneuroimmunologie, Nutrition et Genetique, PsyNuGen, INRA 1286, CNRS 5226, Université Bordeaux 2, 146 rue Leo Saignat, France

-Integrative Immunology and Behavior program, University of Illinois at Urbana-Champaign, Illinois 61801, USA

-Unité de Nutrition et Régulation Lipidique des Fonctions Cérébrales NuReLiCe, France

-Corresponding author: Sophie Layé, PhD, PsyNuGen, Université Bordeaux 2

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769572/

"Macrophage-derived endocannabinoids have been implicated in endotoxin (lipopolysaccharide (LPS))-induced hypotension, but the endocannabinoid involved and the mechanism of its regulation by LPS are unknown. In RAW264.7 mouse macrophages, LPS (10 ng/ml) increases anandamide (AEA) levels >10-fold via CD14-, NF-kappaB-, and p44/42-dependent, platelet-activating factor-independent activation of the AEA biosynthetic enzymes, N-acyltransferase and phospholipase D. LPS also induces the AEA-degrading enzyme fatty acid amidohydrolase (FAAH),

and inhibition of FAAH activity potentiates, whereas actinomycin D or cycloheximide blocks the LPS-induced increase in AEA levels and N-acyltransferase and phospholipase D activities. In contrast, cellular levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) are unaffected by LPS but increased by platelet-activating factor. LPS similarly induces AEA, but not 2-AG, in mouse peritoneal macrophages where basal AEA levels are higher, and the LPS-stimulated increase in AEA is potentiated in cells from FAAH-/- as compared with FAAH+/+ mice. Intravenous administration of 107 LPS-treated mouse macrophages to anesthetized rats elicits hypotension, which is much greater in response to FAAH-/- than FAAH+/+ cells and is susceptible to inhibition by SR141716, a cannabinoid CB1 receptor antagonist. We conclude that AEA and 2-AG synthesis are differentially regulated in macrophages, and AEA rather than 2-AG is a major contributor to LPS-induced hypotension."

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland 20892, USA.

https://pubmed.ncbi.nlm.nih.gov/12949078/

Lipoxin A4

Anti-inflammatory lipoxin A4 is an endogenous allosteric enhancer of CB1 cannabinoid receptor

"Allosteric modulation of G-protein–coupled receptors represents a key goal of current pharmacology. In particular, endogenous allosteric modulators might represent important targets of interventions aimed at maximizing therapeutic efficacy and reducing side effects of drugs. Here we show that the anti-inflammatory lipid lipoxin A4 is an endogenous allosteric enhancer of the CB1 cannabinoid receptor. Lipoxin A4 was detected in brain tissues, did not compete for the orthosteric binding site of the CB1 receptor (vs. 3H-SR141716A), and did not alter endocannabinoid metabolism (as opposed to URB597 and MAFP), but it enhanced affinity of anandamide at the CB1 receptor, thereby potentiating the effects of this endocannabinoid both in vitro and in vivo. In addition, lipoxin A4 displayed a CB1 receptor-dependent protective effect against β-amyloid (1–40)-induced spatial memory impairment in mice. The discovery of lipoxins as a class of endogenous allosteric modulators of CB1 receptors may foster the therapeutic exploitation of the endocannabinoid system, in particular for the treatment of neurodegenerative disorders."

-Laboratory of Psychopharmacology, Department of Pharmacology, Universidade Federal de Santa Catarina, 88049-900, Florianópolis, Brazil;

-D'Or Institute for Research and Education, 22281-100, Rio de Janeiro, Brazil;

-Department of Chemistry, Universidade Federal de Santa Maria, 97105-900, Santa Maria, Brazil;

-Institut National de la Santé et de la Recherche Médicale U862, NeuroCentre Magendie, Endocannabinoids and

Neuroadaptation, 33077 Bordeaux, France;

-U862 NeuroCentre Magendie, Group Endocannabinoids and Neuroadaptation, 33077 Bordeaux, France;

-Laboratory of Neuroplasticity, Max Planck Institute of Psychiatry, D-80804 Munich, Germany;

-Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg-University, D-55099 Mainz, Germany;

-Instituto de Biofisica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, 21941-902, Rio de Janeiro, Brazil; and

-Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, 21941-599, Rio de Janeiro, Brazil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529012

Roles of lipoxin A4 in preventing paracetamol-induced acute hepatic injury in a rabbit mode

…"Lipoxin A4 significantly mitigates paracetamol-induced hepatic injury, in which anti-inflammation effect may play an important role, leading to hepatic apoptosis and necrosis."

-Emergency Center, Zhongnan Hospital, Wuhan University, 169 Donghu Road, Wuchang, Wuhan, Hubei, China

https://pubmed.ncbi.nlm.nih.gov/23851615

Lipoxin A4 exerts protective effects against experimental acute liver failure by inhibiting the NF-κB pathway

"Although rare, acute liver failure (ALF) is associated with high levels of mortality, warranting the development of novel therapies."….

"These results indicated that LXA4 inhibited NF-κB activation, reduced the secretion of pro-inflammatory cytokines, and inhibited apoptosis of liver cells, thereby exerting protective effects against ALF."

-Department of Infection, Dongfeng Hospital Affiliated to Hubei Medical University, Shiyan, Hubei 442008, P.R. China.

-Department of Pharmacy, Dongfeng General Hospital Affiliated to Hubei Medical University, Shiyan, Hubei 442008, P.R. China.

-Center of Reproductive Medicine, People's Hospital Affiliated to Hubei Medical University, Shiyan, Hubei 442000, P.R. China.

-Shennong Wudang Institute of Traditional Chinese Medicine, Shiyan Hospital of TCM Affiliated to Hubei University of Chinese Medicine, Shiyan, Hubei 442012, P.R. China.

-Department of Emergency, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China.

-Department of Infection, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China.

https://pubmed.ncbi.nlm.nih.gov/26865215/

See also Lion's Mane (Hericium erinaceus)

Liver Cancer

Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy

"Hepatocellular carcinoma (HCC) is the third cause of cancer-related death worldwide. When these tumors are in advanced stages, few therapeutic options are available. Therefore, it is essential to search for new treatments to fight this disease. In this study, we investigated the effects of cannabinoids – a novel family of potential anticancer agents – on the growth of HCC. We found that Δ9-tetrahydrocannabinol (Δ9-THC, the main active component of Cannabis sativa) and JWH-015 (a cannabinoid receptor 2 (CB2) cannabinoid receptor-selective agonist) reduced the viability of the human HCC cell lines HepG2 (human hepatocellular liver carcinoma cell line) and HuH-7 (hepatocellular carcinoma cells), an effect that relied on the stimulation of CB2 receptor. We also found that Δ9-THC- and JWH-015-induced autophagy relies on tribbles homolog 3 (TRB3) upregulation, and subsequent inhibition of the serine–threonine kinase Akt/mammalian target of rapamycin C1 axis and adenosine monophosphate-activated kinase (AMPK) stimulation. Pharmacological and genetic inhibition of AMPK upstream kinases supported that calmodulin-activated kinase kinase β was responsible for cannabinoid-induced AMPK activation and autophagy. In vivo studies revealed that Δ9-THC and JWH-015 reduced the growth of HCC subcutaneous xenografts, an effect that was not evident when autophagy was genetically of pharmacologically inhibited in those tumors. Moreover, cannabinoids were also able to inhibit tumor growth and ascites in an orthotopic model of HCC xenograft. Our findings may contribute to the design of new therapeutic strategies for the management of HCC."…

-Department of Biochemistry and Molecular Biology, School of Medicine, Alcalá University, Madrid, Spain

-Department of Biochemistry and Molecular Biology, School of Biology, Complutense University, and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131949/

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"Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Hepatocellular carcinoma occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection."…

-Mayo Clinic

https://www.mayoclinic.org/diseases-conditions/hepatocellular-carcinoma/cdc-20354552

Dietary fatty acids and risk of hepatocellular carcinoma in the Singapore Chinese Health Study

"In this large cohort study of Chinese men and women, intake of omega-6 PUFA was associated with increased risk of HCC. Although dietary omega-3 PUFA was not associated with overall risk of HCC, higher ratio of omega-6 to omega-3 PUFA conferred an increased risk of HCC. These results provided the first epidemiologic evidence for the role of dietary omega-6 PUFA in the development of HCC that was presumably due to underlying non-alcoholic steatohepatitis (NASH).

Metabolic derivatives from omega-6 PUFA are thought to be pro-inflammatory while those from omega-3 PUFA have anti-inflammatory properties [17]. Studies suggest that omega-3 PUFA improves insulin sensitivity and reduce inflammation in NASH via their action on circulating triglyceride levels and regulating gene transcription factors involved in hepatic lipid metabolism, fatty acid oxidation and inflammatory pathways [18, 19]. Conversely, metabolism of omega-6 PUFA leads to increased levels of pro-inflammatory products, such as prostaglandin E2, thromboxane and indirectly C-reative protein, plasminogen activator inhibitor (PAI)-1, TNF- α and IL-6 [20, 21], which have been implicated in causing advanced fibrosis in NASH, and subsequently to cirrhosis and ultimately to HCC [22, 23]. NASH patients, compared to controls, were reported to have a significant increase of omega-6 PUFA levels within hepatic lipid content, while omega-3 PUFA levels were comparable [24]. Similarly, when dietary patterns were assessed, dietary intake of omega-3 PUFA was comparable between NASH patients and controls, while dietary intake of omega-6 PUFA was significantly higher in NASH patients relative to controls [25]. Lipidomic studies in phosphatase and tensin homolog (Pten) null mouse models with NASH demonstrated a positive correlation between omega-6 PUFA and HCC tumour burden, but a negative correlation between omega-3 PUFA and tumour burden [11]."

-Duke-NUS Graduate Medical School, National University of Singapore, Singapore

-Saw Swee Hock School of Public Health, National University of Singapore, Singapore

-University Medicine Cluster, Division of Gastroenterology, National University Health System, Singapore

-Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore

-Department of Gastroenterology & Hepatology, Singapore General Hospital, Singapore

-National Registry of Diseases Office, Health Promotion Board, Singapore

-Division of Cancer Control and Population Sciences, University of Pittsburgh Cancer Institute, Pennsylvania, PA USA

-Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, PA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4824657/

Liver Diseases & Liver Failure

Omega 3 - Omega 6: What is right for the liver?

“Linoleic and alpha-linolenic acids are the fatty acids designated as "essential" since they are not synthesized by mammalian cells and must be provided in the diet. The recent dietary shift towards the consumption of n-6 (omega-6) at the expense of n-3 (omega-3) polyunsaturated fatty acids (PUFAs) is thought to be a primary cause of many diseases related to the Western diet. The body converts linoleic acid to arachidonic acid and derives eicosapentaenoic acid from alpha-linolenic acid. Ideally the effects of these fatty acids and their eicosanoid derivatives are tailored to the specific biological needs of the body. The balance between n-3 and n-6 PUFAs is essential for metabolism and maintenance of the functions of both classes. The availability of n-3 long chain PUFAs plays a major role in regulating both fat accumulation and its elimination by the liver. Derangement of hepatic n-6:n-3 PUFA ratio impacts on the histological pattern of fatty liver through modulation of the amount of intrahepatic lipids. Moreover, the influence of PUFAs and their eicosanoid products on hepatic microcirculation and ischemia/reperfusion injury has been demonstrated in many studies. This concise review article will focus on the role of PUFAs and eicosanoids in hepatic steatosis, microcirculation and ischemia/reperfusion injury.”

-Swiss HPB (Hepato-Pancreatico-Biliary) Centre, Department of Visceral and Transplant Surgery, University Hospital Zurich, Ramistrasse 100, Zurich, Switzerland.

https://pubmed.ncbi.nlm.nih.gov/17869370

The concept of "the inflamed brain" in acute liver failure: mechanisms and new therapeutic opportunities

“The presence and severity of a systemic inflammatory response is a major predictor of brain edema and encephalopathy in acute liver failure (ALF) and polymorphisms of the gene coding for the proinflammatory cytokine TNF-alpha are known to influence the clinical outcome in ALF. Recent reports provide robust evidence for a role of neuroinflammation(inflammation of the brain per se) in ALF with the cardinal features of neuroinflammation including activation of microglial cells and increased production in situ of pro-inflammatory cytokines such as TNF-alpha

and interleukins IL-1beta and IL-6. Multiple liver-brain signalling pathways have been proposed to explain the phenomenon of neuroinflammation in liver failure and these include direct effects of systemically-derived cytokines, recruitment of monocytes relating to microglial activation as well as effects of liver failure-derived toxins and altered permeability of the blood-brain barrier. Synergistic mechanisms involving ammonia and cytokines have been proposed. Currently-available strategies aimed at lowering of blood ammonia such as lactulose, probiotics and rifaximin have the potential to dampen systemic inflammation as does the anti-oxidant N-acetyl cysteine, mild hypothermia and albumin dialysis. Experimental studies demonstrate that deletion of genes coding for TNF-alpha or IL-1 leads to attenuation of the CNS consequences of ALF and administration of the TNF-alpha receptor antagonist etanercept has comparable beneficial effects in experimental ALF. Together, these findings confirm a major role for central neuroinflammatory mechanisms in general and mechanisms involving TNF-alpha in particular in the pathogenesis of the cerebral consequences of ALF and open the door to novel therapeutic interventions in this often fatal disorder."

-Department of Medicine, University of Montreal, Montreal, QC, Canada.
https://pubmed.ncbi.nlm.nih.gov/26481639

Endocannabinoids signaling: Molecular mechanisms of liver regulation and diseases

"The endocannabinoid system (ECS) includes endocannabinoids (eCBs), cannabinoid (CB) receptors and the enzymes that are responsible for endocannabinoid production and metabolism. The ECS has been reported to be present in both brain and peripheral tissues. Recent studies have indicated that eCBs and their receptors are involved in the development of various liver diseases. They were found to be altered in response to many danger factors. It is generally accepted that eCB may exert a protective action via CB2 receptors in different liver diseases. However, eCBs have also been demonstrated to have pathogenic role via their CB1 receptors. Although the therapeutic potential of CB1 receptor blockade in liver diseases is limited by its neuropsychiatric side effects, many studies have been conducted to search for novel, peripherally restricted CB1 antagonists or CB2 agonists, which may minimize their neuropsychiatric side effects in clinical use. This review summarizes the current understanding of the ECS in liver diseases and provides evidence for the potential to develop new therapeutic strategies for the treatment of these liver diseases."

-Institute of Liver Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.
https://pubmed.ncbi.nlm.nih.gov/27100518/

Hepatic steatosis in n-3 [omega-3] fatty acid depleted mice: focus on metabolic alterations related to tissue fatty acid composition

…"n-3 [omega-3] PUFA depletion leads to important metabolic alterations in murine liver. Steatosis occurs through a mechanism independent of the shift between beta-oxidation and lipogenesis. Moreover, long term n-3 PUFA depletion decreases the expression of factors involved in the unfolded protein response, suggesting a lower protection against endoplasmic reticulum stress in hepatocytes upon n-3 PUFA deficiency."

-Unit of Pharmacokinetics, Metabolism, Nutrition and Toxicology, Université catholique de Louvain, Brussels, Belgium.
https://pubmed.ncbi.nlm.nih.gov/19046413/

The endocannabinoid system in chronic liver disease

"Despite the public concern about the controversial use and abuse of marijuana, the scientific community has focused on the therapeutic potentials of cannabinoid compounds and had highlighted the importance of endocannabinoids and their receptors in physiology and disease. Endocannabinoids have been shown to be important mediators in neuroendocrine and psychiatric processes such as food intake, drug reward and energy metabolism. Cannabinoid receptors are expressed by several cell lines in the liver, such as hepatocytes, myofibroblastic cells, endothelial cells and probably cholangiocytes. A perpetuating role in liver damage for the endocannabinoid system has been proposed in several steps of chronic liver disease progression. Being a major cause of death worldwide, chronic liver disease is an important problem. New therapies are needed in order to stop or slow damage progression. This review summarizes the results of experimental studies involving the endocannabinoid system in liver disease and their clinical and therapeutical implications in hepatology."

-Department of Biomedical Research and Liver Unit, Medica Sur Clinic & Foundation, Mexico City, Mexico.
-Faculty of Medicine, National Autonomous University of Mexico (UNAM)
https://www.sciencedirect.com/science/article/pii/S1665268119320472

Inflammatory responses and inflammation-associated diseases in organs

…"Inflammation in the liver protects this organ from infection and injury, but excessive inflammation may lead to extensive loss of hepatocytes, ischemia-reperfusion injury, metabolic alterations, and eventually permanent hepatic damage [128]. Inflammation can destroy hepatic parenchymal cells, increasing the risk of chronic liver diseases, such as non-alcoholic fatty liver

disease (NAFLD) or viral hepatitis. Chronic liver diseases are a leading cause of morbidity and mortality in the US [129].

The liver is the largest solid organ in the body [130], and is a target of both infectious and non-infectious inflammatory pathologies. Infectious inflammation of the liver is mainly caused by microorganisms, such as bacterial products, hepatitis B virus (HBV), or hepatitis C virus (HCV) [131, 132]. Sterile inflammation (SI) is also important in the pathology of many liver diseases, such as alcoholic or nonalcoholic steatohepatitis, drug-induced liver injury, and ischemia/reperfusion [133–135]. In SI, endogenous DAMPs are released to injured tissues and activate immune cells [136]. While pathogen-driven inflammation and SI differ, they share several functional characteristics. Many receptors and pathways can be activated by both PAMPs and DAMPs [137]. TLR4, for example, can be activated by bacterial LPS and cellular HMGB1. Because of the liver's unique vascular supply, PAMPs of intestinal origin and DAMPs from hepatocytes both contribute to inflammation in a variety of diseases. For example, PRR activation by DAMPs and PAMPs can induce production of pro-inflammatory cytokines and immune cell localization to sites of injury. Recognition of DAMPs and PAMPs results in assembly of the inflammasome, a cytosolic protein complex that activates the serine protease caspase-1, followed by activation and secretion of IL-1β and other cytokines. At the same time, Kupffer cell activation and inflammatory cell recruitment leads to production of cytokines and chemokines that promote long-term inflammation, hepatocyte damage, and/or cholestasis [138].”…

- *College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China*
- *Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, Chengdu, China*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

See Endocannabinoid System, Prostaglandins

Liver Transplant

Effects of Fish Oil Supplementation on Kidney Transplantation: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials

“Several studies in renal transplantation have suggested that supplementation with omega-3 fatty acids (mostly fish oil) may lead to important clinical benefits, such as decreasing cyclosporine (CsA) nephrotoxicity, rejection episodes, and hypertension, while improving hyperlipidemia [5–7].”

-Athina Tatsioni, Mei Chung, Yannan Sun, Bruce Kupelnick, Alice H. Lichtenstein, Ronald Perrone, Priscilla Chew, Joseph Lau and Peter A. Bonis

Journal of the American Society of Nephrology Vol. 16, Issue 8 - 1 Aug 2005
https://jasn.asnjournals.org/content/16/8/2462

Long-Term Synaptic Depression (LTP)

"If synapses simply continued to increase in strength as a result of LTP, eventually they would reach some level of maximum efficacy, making it difficult to encode new information. Thus, to make synaptic strengthening useful, other processes must selectively weaken specific sets of synapses. Long-term depression (LTD) is such a process. "…

-Neuroscience. 2nd edition.
-Purves D, Augustine GJ, Fitzpatrick D, et al., editors.
Sunderland (MA): Sinauer Associates; 2001.
https://www.ncbi.nlm.nih.gov/books/NBK10899

Presynaptic modulation by endocannabinoids

"Modulation of neurotransmitter release by G-protein-coupled receptors (GPCRs) is a prominent presynaptic mechanism for regulation of synaptic transmission. Activation of GPCRs located at the presynaptic terminal can decrease the probability of neurotransmitter release. This presynaptic depression involves activation of Gi/o-type G-proteins that mediate different inhibitory mechanisms, including inhibition of voltage-gated calcium channels, activation of potassium channels, and direct inhibition of the vesicle fusion process. A variety of neurotransmitters and modulatory agents can activate GPCRs that produce presynaptic depression. Among these are lipid metabolites that serve as agonists for GPCRs. The discovery of endocannabinoids and their cognate receptors, including the CB1 receptor, has stimulated intense investigation into the neurophysiological roles of these lipid metabolites. It is now clear that presynaptic depression is the major physiological role for the CB1 receptor. Endocannabinoids activate this receptor mainly via a retrograde signaling process in which these compounds are synthesized in and released from postsynaptic neuronal elements, and travel back to the presynaptic terminal to act on the CB1 receptor. This retrograde endocannabinoid modulation has been implicated in short-term synaptic depression, including suppression of excitatory or inhibitory transmission induced by postsynaptic depolarization and transient

synaptic depression induced by activation of postsynaptic GPCRs during agonist treatment or synaptic activation. Endocannabinoids and the CB1 receptor also play a key role in one form of long-term synaptic depression (LTD) that involves a longlasting decrease in neurotransmitter release."

-Laboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 5625 Fishers Lane, Bethesda, MD
https://pubmed.ncbi.nlm.nih.gov/18064422

Lungs

…"Given the anti-inflammatory mechanism by which omega-3 fatty acids are thought to act in the lungs, it is reasonable to postulate that distinct subgroups of individuals, with unique inflammatory responses or distinct exposures linked to inflammation, may respond differently to omega-3 intake. In support of this, we noted that beneficial associations between ALA and respiratory symptoms were only present among those with low omega-6 (LA) intake. This is a reasonable contingency, given: (1) conversion of ALA to EPA+DHA may be inhibited by increased concentrations of LA [40], and (2) LA and its metabolite arachidonic acid are known substrates for production of pro-inflammatory eicosanoids [41], which may counteract the anti-inflammatory properties of ALA."…

-Johns Hopkins University School of Medicine, Baltimore, MD USA
-University of Nebraska Medical Center, Omaha, NE USA
-Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6533751

Inflammatory responses and inflammation-associated diseases in organs

…"Lung inflammatory diseases involve complex interactions among and between structural and immune cells [139]. Lung inflammation results predominantly from tissue exposure to bacterial and viral pathogens, and/or environmental pollutants. Excessive acute inflammation and subsequent lung injury can cause pulmonary fibrosis and impair gas exchange. Unresolved lung injury and chronic inflammation are frequently observed in acute respiratory distress syndrome, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma [140–142]. Approximately 90% of COPD cases are associated with cigarette smoking-induced inflammation in small airways and lung parenchyma [143]. Cigarette smoking is a major risk factor for COPD, which involves both systemic and pulmonary inflammation. Long-term smoking can cause macrophage, neutrophil,

and activated T lymphocyte infiltration into airways, and promote production of chemokines, oxygen radicals, proteases, and cytokines, including that of TNF-α, IL-6 and IL-8, in the lung [144]."...

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548

Lung Cancer

The oncogenic role of CB2 in the progression of non-small-cell lung cancer.

"Several studies have verified the important role of cannabinoid and cannabinoid receptor agonists in tumor progression. However, little is known about the precise role of CB2 expression level in the progression of non-small-cell lung cancer (NSCLC)."

..."The expression of CB2 in NSCLC tissues and corresponding paracancerous tissues was examined using immunohistochemical staining assay. The expression of CB2 was silenced by siRNA interference and loss-of-function assays were performed to investigate the biological function of CB2 in the proliferation, migration, invasion, and apoptosis of NSCLC cells. The expression of related proteins was detected using western blot analysis."

..."In this study, we observed that CB2 was up-regulated in NSCLC tissues and the up-regulation was correlated with tumor size and advanced NSCLC pathological grading. Moreover, compared with the control group, silencing of CB2 decreased the proliferation, migration and invasion abilities of A549 and H1299 cells, and induced apoptosis by regulation of Bcl-2/Bax axis and active Caspase3. Furthermore, CB2 knockdown inactivated the Akt/mTOR/P70S6K pathway by decreasing the level of p-Akt, p-mTOR and expression of P70S6K in A549 and H1299 cells."

..."Our data suggested that targeting CB2 may inhibit the growth and survival of NSCLC cells, which the Akt/mTOR/P70S6K pathway may be involved in. These results confer the pro-oncogenic role of CB2 in the progression of NSCLC, thus improving our understanding of CB2 in tumor progression."

-Department of Respiratory, The Second Hospital of Shandong University, Jinan, Shandong Province, China.

-Weihai Municipal Hospital, Weihai 264200, Shandong Province, China.

-Department of Emergency Medicine, The Second Hospital of Shandong University, No. 247 Beiyuan Street, Jinan, Shandong Province, China.

https://www.ncbi.nlm.nih.gov/pubmed/31176172

FAAH inhibition enhances anandamide mediated anti-tumorigenic effects in non-small cell lung cancer by downregulating the EGF/EGFR pathway

"The endocannabinoid anandamide (AEA), a neurotransmitter was shown to have anti-cancer effects. Fatty acid amide hydrolase (FAAH) metabolizes AEA and decreases its anti-tumorigenic activity. In this study, we have analyzed the role of FAAH inhibition in non-small cell lung cancer (NSCLC). We have shown that FAAH and CB1 receptor which is activated by AEA are expressed in lung adenocarcinoma patient samples and NSCLC cell lines A549 and H460. Since the synthetic analogue of anandamide (Met-F-AEA) did not possess significant anti-tumorigenic effects, we used Met-F-AEA in combination with FAAH inhibitor URB597 which significantly reduced EGF (epidermal growth factor)-induced proliferative and chemotactic activities in vitro when compared to anti-tumorigenic activity of Met-F-AEA alone. Further analysis of signaling mechanisms revealed that Met-F-AEA in combination with URB597 inhibits activation of EGFR and its downstream signaling ERK, AKT and NF-kB. In addition, it inhibited MMP2 secretion and stress fiber formation. We have also shown that the Met-F-AEA in combination with URB597 induces G0/G1 cell cycle arrest by downregulating cyclin D1 and CDK4 expressions, ultimately leading to apoptosis via activation of caspase-9 and PARP. Furthermore, the combination treatment inhibited tumor growth in a xenograft nude mouse model system. Tumors derived from Met-F-AEA and URB597 combination treated mice showed reduced EGFR, AKT and ERK activation and MMP2/MMP9 expressions when compared to Met-F-AEA or URB597 alone. Taken together, these data suggest in EGFR overexpressing NSCLC that the combination of Met-F-AEA with FAAH inhibitor resulted in superior therapeutic response compared to individual compound activity alone."

- *Department of Pathology, The Ohio State University, Ohio, USA.*
https://pubmed.ncbi.nlm.nih.gov/24811863

■■■

"Given the known impact of IL-17 and inflammation on lung cancer, we were interested in determining if the enrichment of oral commensals in the lungs could drive an IL-17-type inflammation and influence lung cancer progression and prognosis."

-Dr. Leopoldo Segal, MD, Director of the Lung Microbiome Program and Associate Professor of Medicine, New York University Grossman School of Medicine
https://www.aacr.org/about-the-aacr/newsroom/news-releases/the-lung-microbiome-may-affect-lung-cancer-pathogenesis-and-prognosis/

■■■

"Cannabinoids have been shown to promote the expression of the intercellular adhesion

molecule 1 (ICAM-1) on lung cancer cells as part of their anti-invasive and antimetastatic action."…

"Altogether, our data demonstrate cannabinoid-induced upregulation of ICAM-1 on lung cancer cells to be responsible for increased cancer cell lysis by LAK cells. These findings provide proof for a novel antitumorigenic mechanism of cannabinoids."

-Institute of Toxicology and Pharmacology, University of Rostock, Rostock, Germany.

-Section of Molecular Oncology and Immunotherapy, Department of General Surgery, University of Rostock, Rostock, Germany.

-Department of Radiotherapy and Radiation Oncology, University of Rostock, Rostock, Germany.

-Institute of Toxicology and Pharmacology, University of Rostock, Rostock, Germany.

https://pubmed.ncbi.nlm.nih.gov/25069049/

Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1

"Cannabinoids inhibit cancer cell invasion via increasing tissue inhibitor of matrix metalloproteinases-1 (TIMP-1)."…

"ICAM-1-dependent anti-invasive cannabinoid effects were confirmed in primary tumor cells from a lung cancer patient. In athymic nude mice, CBD elicited a 2.6- and 3.0-fold increase of ICAM-1 and TIMP-1 protein in A549 xenografts, as compared to vehicle-treated animals, and an antimetastatic effect that was fully reversed by a neutralizing antibody against ICAM-1 [% metastatic lung nodules vs. isotype control (100%): 47.7% for CBD + isotype antibody and 106.6% for CBD + ICAM-1 antibody]. Overall, our data indicate that cannabinoids induce ICAM-1, thereby conferring TIMP-1 induction and subsequent decreased cancer cell invasiveness."

-Institute of Toxicology and Pharmacology, Department of General Surgery, University of Rostock, Germany.

https://pubmed.ncbi.nlm.nih.gov/22198381/

Cannabinoid receptors, CB1 and CB2, as novel targets for inhibition of non-small cell lung cancer growth and metastasis

"Non-small cell lung cancer (NSCLC) is the leading cause of cancer deaths worldwide; however, only limited therapeutic treatments are available. Hence, we investigated the role of cannabinoid receptors, CB1 and CB2, as novel therapeutic targets against NSCLC. We observed expression of CB1 (24%) and CB2 (55%) in NSCLC patients. Furthermore, we have shown that the treatment of NSCLC cell lines (A549 and SW-1573) with CB1/CB2- and CB2-specific agonists Win55,212-2 and JWH-015, respectively, significantly attenuated random as well as growth factor-directed in vitro

chemotaxis and chemoinvasion in these cells. We also observed significant reduction in focal adhesion complex, which plays an important role in migration, upon treatment with both JWH-015 and Win55,212-2. In addition, pretreatment with CB1/CB2 selective antagonists, AM251 and AM630, prior to JWH-015 and Win55,212-2 treatments, attenuated the agonist-mediated inhibition of in vitro chemotaxis and chemoinvasion. In addition, both CB1 and CB2 agonists Win55,212-2 and JWH-133, respectively, significantly inhibited in vivo tumor growth and lung metastasis (~ 50%). These effects were receptor mediated, as pretreatment with CB1/CB2 antagonists abrogated CB1/CB2 agonist-mediated effects on tumor growth and metastasis. Reduced proliferation and vascularization, along with increased apoptosis, were observed in tumors obtained from animals treated with JWH-133 and Win55,212-2. Upon further elucidation into the molecular mechanism, we observed that both CB1 and CB2 agonists inhibited phosphorylation of AKT, a key signaling molecule controlling cell survival, migration, and apoptosis, and reduced matrix metalloproteinase 9 expression and activity. These results suggest that CB1 and CB2 could be used as novel therapeutic targets against NSCLC."

-Division of Experimental Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

https://pubmed.ncbi.nlm.nih.gov/21097714/

Lupus

Omega-3 fatty acid stops known trigger of lupus

"A team of Michigan State University researchers has found that consuming an omega-3 fatty acid called DHA, or docosahexaenoic acid, can stop a known trigger of lupus and potentially other autoimmune disorders."…

- ScienceDaily.com / Michigan State University

https://www.sciencedaily.com/releases/2016/09/160929133613.htm

Systemic lupus erythematosus (SLE)

"Systemic lupus erythematosus (SLE), is the most common type of lupus. SLE is an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels. There is no cure for lupus, but medical interventions and lifestyle changes can help control it."…

-Centers for Disease Control and Prevention (CDC)

https://www.cdc.gov/lupus/facts/detailed.html

Omega-3 fatty acid dietary supplementation in systemic lupus erythematosus.

"The effect of dietary fish oil (Omega-3 fatty acids--eicosapentenoic acid [EPA] and docosahexaenoic acid [DHA] on several mechanisms involved in immune, inflammatory and atherosclerotic vascular disease was determined in 12 subjects with systemic lupus erythematosus (SLE) and nephritis. These out-patients supplemented their usual diet for five weeks with daily doses of 6 g of fish oil, followed by a five-week washout period, then five weeks of 18 g of fish oil daily. The platelet EPA content rose six-fold with the lower and 15-fold with the higher dose of fish oil, and similar changes occurred to the platelet DHA content. The platelet arachidonic acid incorporation was reduced by 16 and 20%, respectively. These changes were associated with a reduction in collagen-induced platelet aggregation and an increase in red cell flexibility and a decrease in whole blood viscosity."

…"We conclude that in patients with lupus nephritis, dietary supplementation with fish oil affects the mechanisms involved in inflammatory and atherosclerotic vascular disease."

-Department of Medicine, University of Western Ontario, London, Canada.

https://www.ncbi.nlm.nih.gov/pubmed/2811063

Dietary Omega Polyunsaturated Fatty Acid Intake and Patient-Reported Outcomes in Systemic Lupus Erythematosus: The Michigan Lupus Epidemiology and Surveillance Program

Objective

"To examine associations between dietary intake of omega-3 (n-3; generally antiinflammatory) and omega-6 (n-6; generally proinflammatory) fatty acids and patient-reported outcomes in systemic lupus erythematosus (SLE)."…

Conclusion

"This population-based study suggests that higher dietary intake of n-3 fatty acids and lower n-6:n-3 ratios are favorably associated with patient-reported outcomes in SLE, particularly self-reported lupus activity and sleep quality."

- University of Michigan, Ann Arbor

- University of Birmingham, Birmingham UK,

- Centers for Disease Control and Prevention, Atlanta Georgia,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6842394/

Significance and impact of dietary factors on systemic lupus erythematosus pathogenesis

“Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology, although its mechanisms involve genetic, epigenetic and environmental risk factors. Considering that SLE pathogenesis is yet to be explored, recent studies aimed to investigate the impact of diet, in terms of triggering or altering the course of the disease. To study the impact of diet on SLE pathogenesis, we conducted a search on Pubmed using the keywords ‘diet and autoimmune diseases’, ‘diet and lupus’, ‘caloric restriction and lupus’, ‘polyunsaturated fatty acids and lupus’, ‘vitamin D and lupus’, ‘vitamin C and lupus’ ‘vitamin E and lupus’ ‘vitamin A and lupus’ ‘vitamin B and lupus’, ‘polyphenols and lupus’, ‘isoflavones and lupus’, ‘minerals and lupus’, ‘aminoacids and lupus’, ‘curcumin and lupus’ and found 10,215 papers, from which we selected 47 relevant articles. The paper clearly emphasizes the beneficial role of personalized diet in patients with SLE, and the information presented could be used in daily practice. Proper diet in SLE can help preserve the body's homeostasis, increase the period of remission, prevent adverse effects of medication and improve the patient's physical and mental well-being.”

…”In patients with stable disease a diet rich in polyunsaturated fatty acids may have a positive impact on overall clinical status (15). Omega-3 fatty acids, such as eicosapentanoic acid and docosahexanoic acid, elicit an anti-inflammatory effect by decreasing the level of C reactive protein (CRP) and other inflammatory mediators (17,18). Caloric restriction and well-established diet supplementation with omega-3 PUFA, eicosapentanoic acid and docosahexanoic acid (at a ratio of 3:1), regulates levels of total cholesterol, LDL-C and TG. Apart from the anti-inflammatory effect, adding omega-3 PUFA in SLE patients diet protects against free radicals and helps defend cardiovascular alteration by reducing the level of antibodies (anti-dsDNA), interleukins (IL-1α, IL-1β, IL-2) and TNF-α, and regulating proteinuria and blood pressure (6,18). Other omega-3 acids like α-linolenic acid and Y-linolenic acid also have beneficial effects by limiting TNF-α and IL-2 secretion. No downsides of introducing omega-3 PUFA to SLE patients' diet were found, as opposed to omega-6 PUFA supplementation, which may exacerbate SLE activity (6).”…

-University of Medicine and Pharmacy ‘Carol Davila’, Bucharest, Romania
-The Second Department of Dermatology, Colentina Clinical Hospital, Bucharest, Romania
-Dr. Anca Răducan Anti-Aging Dermatology Clinic, Constanta, Romania
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6327661/

Polyunsaturated omega-3 fatty acids and systemic lupus erythematosus: what do we know?

“Various studies have demonstrated the impact of omega-3 fatty acids on the concentration of C reactive protein (CRP), pro-inflammatory eicosanoids, cytokines, chemokines and other inflammatory mediators. Therefore, the supplementation of these types of lipids may represent additional option treatment for chronic systemic diseases, such as Systemic Lupus Erythematous and other rheumatic diseases. The role of these lipids has not been well established, yet. However, it seems there is a direct relationship between its intake and the decrease of the disease clinical manifestations as well as of the inflammatory status of the patients. ”....

-Program for Sciences Applied to Adult Health, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil.

-Department of Clinical Medicine, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil.

-Department of Surgery, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil.

-Department of the Locomotor Apparatus, Faculty of Medicine of the Federal University of Minas Gerais, Belo Horizonte, MG, Brazil.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6842394/

N-3 [omega-3] Polyunsaturated Fatty Acids and Autoimmune-Mediated Glomerulonephritis

‘Consumption of n-3 polyunsaturated fatty acids (PUFAs) found in fish oil suppresses inflammatory processes making these fatty acids attractive candidates for both the prevention and amelioration of several organ-specific and systemic autoimmune diseases. Both pre-clinical and clinical studies have been conducted to determine whether fish oils containing the n-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) can be used in the prevention and treatment of immunoglobulin A nephropathy (IgAN) and lupus nephritis. In a toxin-induced mouse model that mimics the early stages of IgAN, n-3 PUFA consumption suppresses aberrant interleukin (IL)-6-driven IgA production and mesangial IgA immune complex deposition by impairing phosphorylation of upstream kinases and activation of transcription factors essential for IL-6 gene transcription. n-3 PUFAs can also suppress production of anti-double-stranded DNA IgG antibodies and the resultant development of lupus nephritis in the NZBW F1 mouse and related models. These effects have been linked in part to impaired expression of proinflammatory cytokines and adhesion molecules as well as increases in antioxidant enzymes in kidney and immune organs. Several recent clinical trials have provided compelling evidence that n-3 PUFA supplementation could be useful in treatment of human IgAN and lupus nephritis, although some other studies suggest such supplementation might be without benefit. Future investigations employing genomics/proteomics and novel genetically

altered mice should provide further insight into how n-3 PUFAs modulate these diseases as well help to identify clinically relevant biomarkers. The latter could be employed in future well-designed, long-term clinical studies that will resolve current controversies on n-3 PUFA efficacy in autoimmune-mediated glomerulonephritis."

Lupus Contagious (Is Lupus Contagious)

Lycopene

"a red carotenoid pigment present in tomatoes and many berries and fruits."

- Oxford Language / Google

Antioxidant activity of topically applied lycopene

"**Background**: Ultraviolet (UV) rays cause depletion of the antioxidant substances contained in the epidermis. This is the rationale for the use of topical antioxidant substances.

Methods: We studied the protective activity against UV radiation of a product based on lycopene and a product containing a mixture of vitamins E and C. Photostimulation was applied with a solar simulator and the cutaneous response was evaluated instrumentally.

Results: The lycopene-based product had a much greater protective ability than the product containing the mixture of vitamins.

Conclusions: Lycopene has suitable characteristics to be used successfully in the prevention of cutaneous damage by free radicals. Its antioxidant ability is probably due to its high reductive power."

-Dipartimento Farmaco Chimico Tecnologico, Istituto di Scienze Dermatologiche, Università degli Studi di Siena, Siena, Italy

https://pubmed.ncbi.nlm.nih.gov/14678532

Discovering the link between nutrition and skin aging

…"Carotenoids are vitamin A derivates like β-carotene, astaxanthin, lycopene and retinol, which are all highly effective antioxidants and have been documented to possess photoprotective properties. Findings of Scarmo et al. suggest that human skin, is relatively enriched in lycopene and β-carotene, compared with lutein and zeaxanthin, possibly reflecting a specific function of hydrocarbon carotenoids in human skin photoprotection.[24]"…

"Lycopene is a bright red carotene and carotenoid pigment and phytochemical found in

tomatoes and other red fruits and vegetables, such as red carrots, watermelons and papayas (but not strawberries or cherries). Although lycopene is chemically a carotene, it has no vitamin A activity.

β-carotene and lycopene are usually the dominating carotenoids in human blood and tissues and are known to modulate skin properties when ingested as supplements or as dietary products. While they cannot be compared with sunscreen, there is evidence that they protect the skin against sunburn (solar erythema) by increasing the basal defense against UV light-mediated damage.[45]

A study confirmed that the amounts of lycopene in plasma and skin are comparable to or even greater than those of β-carotene. When skin is exposed to UV light stress, more skin lycopene is destroyed compared with β-carotene, suggesting a role of lycopene in mitigating oxidative damage in tissues.[46] Lycopene and tomato products are also mentioned for preventing cancer.[47,48]"

-Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center; Dessau, Germany
-Laboratory for Biogerontology, Dermato-Pharmacology and Dermato-Endocrinology; Institute of Clinical Pharmacology and Toxicology; Charité Universitaetsmedizin Berlin; Berlin, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3583891

M

Macrophages

Interaction between Cannabinoid System and Toll-Like Receptors Controls Inflammation

…."The endocannabinoid system consists not only of cannabinoid receptors, but also of endogenous cannabinoids and their biosynthetic and metabolizing enzymes. **Macrophages are major producers of endogenous cannabinoids** [23], which may not be a coincidence. Both exogenous and endogenous cannabinoids inhibit proinflammatory cytokine production by macrophages stimulated through Toll-like receptors (TLRs). TLRs play a crucial role in macrophages sensing danger to trigger inflammatory responses. Conversely, activation of macrophages via TLRs alters their expression of cannabinoid receptors and levels of endogenous cannabinoids. This review discusses the endocannabinoid system and TLR family and evaluates the interaction between them with emphasis on the innate immune system."…

-Department of Microbiology and Immunology, Virginia Commonwealth University, Richmond, VA , USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4997072/

Endocannabinoid system acts as a regulator of immune homeostasis in the gut

"Exogenous cannabinoids such as marijuana exert their influence through cannabinoid receptors. Endogenous cannabinoids such as anandamide (AEA) function through the same receptors, and their physiological roles are a subject of intense study. Here, we show that AEA plays a pivotal role in maintaining immunological health in the gut. The immune system in the gut actively tolerates the foreign antigens present in the gut through mechanisms that are only partially understood. We show that AEA contributes to this critical process by promoting the presence of CX3CR1hi macrophages, which are immunosuppressive. These results uncover a major conversation between the immune and nervous systems. In addition, with the increasing prevalence of ingestion of exogenous marijuana, our study has significant implications for public health."….

-Department of Immunology and Carole and Ray Neag Comprehensive Cancer Center, University of Connecticut School of Medicine, Farmington, CT, USA;
-Division of Diabetes and Endocrinology, Connecticut Children's Medical Center, Farmington, CT, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5441729/

Treatment of macrophage-related disorders (US PATENT US20150037320A1)

..."Macrophages are white blood cells produced by the division of monocytes. Monocytes and macrophages are phagocytes, and play a role in innate immunity (non-specific immune defenses) as well as helping to initiate adaptive immunity (specific defense mechanisms). These cells phagocytose (engulf and then digest) cellular debris and pathogens either as stationary or as mobile cells. When activated by pathogens or by other mechanisms, macrophages stimulate and recruit lymphocytes and other immune cells to respond to the insult."…

"Although macrophages play a vital role in host immune defenses, activated macrophages are also involved in the progression of a number of diseases and disorders. Activated macrophages elicit massive leukocyte infiltration and flood the surrounding tissue with inflammatory mediators, pro-apoptotic factors, and matrix degrading proteases. These actions can result in inflammation that can dismantle tissues to the point of inflicting serious injury. Tissue destruction perpetrated by macrophage-induced inflammation has been associated with the development of tumors, autoimmune disorders, and other conditions."..

"Oxidative agents such as chlorite can return macrophages to their inactivated state. Immunosuppressant agents can mitigate macrophage activation. The present invention provides methods for the treatment of macrophage-related diseases and related conditions with oxidative agents or immunosuppressant agents."

Summary of Invention

In one aspect, the present invention provides a method of treating a macrophage related disease comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising an oxidative agent."…

-University of California,
-Neuraltus Pharmaceuticals Inc
-US PATENT US20150037320A1
https://patents.google.com/patent/US20150037320A1

Macrophages are mentioned in many categories throughout this book

See also Lipopolysaccharide (LPS)

Macular Degeneration

The relationship of dietary lipid intake and age-related macular degeneration

…"Dietary arachidonic acid [omega-6] was directly associated with NV AMD [neovascular age-related macular degeneration] prevalence (OR, 1.54; 95% CI, 1.04-2.29)."…
"Higher intake of omega-3 LCPUFAs and fish was associated with decreased likelihood of having NV AMD."

-AREDS Coordinating Center, The EMMES Corporation, 401 N. Washington Street, Rockville, MD
https://pubmed.ncbi.nlm.nih.gov/17502507

■■■

…"Omega-6/omega-3 ratio is connected with development of neovascular ARMD. Decreased ratio protects against neovascular ARMD."..

-Department of Ophtalmology, Rijeka University Hospital Center, Rijeka, Croatia.
https://pubmed.ncbi.nlm.nih.gov/22220460

See also Uveitis & Uveoretinitis

Malondialdehyde (MDA)

Malondialdehyde (MDA) as a lipid peroxidation marker

"Free radicals generate the lipid peroxidation process in an organism. Malondialdehyde (MDA) is one of the final products of polyunsaturated fatty acids peroxidation in the cells. An increase in free radicals causes overproduction of MDA. Malondialdehyde level is commonly known as a marker of oxidative stress and the antioxidant status in cancerous patients."

-Department of Respiratory Disorders Hospital No., Sosnowiec, Poland
https://pubmed.ncbi.nlm.nih.gov/15765761/

Association between the Ratio of Omega-6/Omega-3 FattyAcids Intake to Plasma Malondialdehyde Level in Patients with Knee Osteoarthritis

" One of several factors in the pathogenesis of osteoarthritis (OA) is the generation of oxidative stress, inducing lipid peroxidation, and producing malondialdehyde (MDA). Omega3 fatty acids have role in inhibiting the oxidative stress, but their levels are determined by the omega-6/omega-3 ratio."….

"The results of the linear regression analysis after controlling the confounding factors (age, BMI, and physical activity score) on MDA levels showed that there was a correlation between the ratio of omega-6/omega-3 fatty acids intake to plasma MDA levels in knee OA patients. An increase in the intake ratio of omega-6/omega-3 fatty acids by 1 unit will increase plasma MDA levels by 0.023 (with the range between 0.004-0.04) units and this is statistically significant (p <0,05)."…

"Based on the research result, it is concluded that high ratio of omega-6/omega-3 fatty acids intake can increase plasma MDA levels in patients with knee OA. Subsequent education is required on the importance of increasing the consumption of dietary sources of omega-3 fatty acids, in order to achieve an optimal ratio between the intake of omega-6 and omega-3 fatty acids.

-Department of Nutrition, Faculty of Medicine, University of Indonesia,
-Department of Nutrition, Cipto Mangunkusumo National General Hospital, Faculty of Medicine,University of Indonesia, Jakarta

-Department of Orthopedic Surgery, Cipto Mangunkusumo National General Hospital,
-Department of Orthopedic Surgery, Bhayangkara RS Sukanto Hospital, Jl. RS Polri,
-Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Indonesia
https://iopscience.iop.org/article/10.1088/1755-1315/217/1/012055/pdf

Maltodextrin (MDX)

…"In previous work, we determined that the polysaccharide dietary additive, maltodextrin (MDX), impairs cellular anti-bacterial responses and suppresses intestinal anti-microbial defense mechanisms. In this addendum, we review potential mechanisms for dietary deregulation of intestinal homeostasis, postulate how dietary and genetic risk factors may combine to result in disease pathogenesis, and discuss these ideas in the context of recent findings related to dietary interventions for IBD."…

-Mucosal Immunology and Biology Research Center; Division of Pediatric Gastroenterology and Nutrition; Massachusetts General Hospital; Boston, MA USA
-Department of Pediatrics; Harvard Medical School; Boston, MA USA
-Department of Pathobiology; Lerner Research Institute; Cleveland Clinic; Cleveland, OH USA
-Department of Molecular Medicine; Cleveland Clinic Lerner College of Medicine at Case Western Reserve University; Cleveland, OH USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4615306/

The dietary polysaccharide maltodextrin promotes Salmonella survival and mucosal colonization in mice.

"In the latter half of the 20th century, societal and technological changes led to a shift in the composition of the American diet to include a greater proportion of processed, pre-packaged foods high in fat and carbohydrates, and low in dietary fiber (a "Western diet"). Over the same time period, there have been parallel increases in Salmonella gastroenteritis cases and a broad range of chronic inflammatory diseases associated with intestinal dysbiosis. Several polysaccharide food additives are linked to bacterially-driven intestinal inflammation and may contribute to the pathogenic effects of a Western diet. Therefore, we examined the effect of a ubiquitous polysaccharide food additive, maltodextrin (MDX), on clearance of the enteric pathogen Salmonella using both in vitro and in vivo infection models. When examined in vitro, murine bone marrow-derived macrophages exposed to MDX had altered vesicular trafficking, suppressed NAPDH oxidase expression, and reduced recruitment of NADPH oxidase to Salmonella-containing vesicles, which resulted in persistence of Salmonella in enlarged Rab7+

late endosomal vesicles. In vivo, mice consuming MDX-supplemented water had a breakdown of the anti-microbial mucous layer separating gut bacteria from the intestinal epithelium surface. Additionally, oral infection of these mice with Salmonella resulted in increased cecal bacterial loads and enrichment of lamina propria cells harboring large Rab7+ vesicles. These findings indicate that consumption of processed foods containing the polysaccharide MDX contributes to suppression of intestinal anti-microbial defense mechanisms and may be an environmental priming factor for the development of chronic inflammatory disease."

-Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA;
- Department of Molecular Medicine, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, Ohio, USA.
-Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA.
-Department of Anatomic Pathology, Robert J. Tomsich Pathology & Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, USA.
-Department of Biology, John Carroll University, University Heights, Ohio, USA.
https://www.ncbi.nlm.nih.gov/pubmed/25000398

See also Gut Health

Major Depression

Endocannabinoid Signaling in the Etiology and Treatment of Major Depressive Illness

…"Depression is accompanied by increased inflammation [104], leading to the hypothesis that suppressed 2-AG could contribute to an increased inflammatory state seen in depression. Another possible role for the eCBs is as a mediator of the coincidence between cardiovascular morbidity and major depression [105]. In a study of depressed women, we found that both diastolic and mean arterial blood pressures were positively correlated with serum contents of AEA and 2-AG, an association that did not occur in controls [106]. Whether or not the deficit in circulating 2-AG could contribute to the emotional and behavioral symptoms associated with depression is unknown at this time.

These data suggest that measurement of circulating eCBs could provide a useful biomarker for depression in general, but more importantly, could be used in a personalized medicine approach to diagnose "low eCB" depression as a subtype that might be more amenable to an ECS-mediated therapies."….

- Cecilia J. Hillard, Ph.D., Neuroscience Research Center, Medical College of Wisconsin
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4002665/

"There is now evidence that major depression is accompanied by decreased levels of omega3 poly-unsaturated fatty acids (PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). There is a strong comorbidity between major depression and chronic fatigue syndrome (CFS). The present study has been carried out in order to examine PUFA levels in CFS. In twenty-two CFS patients and 12 normal controls we measured serum PUFA levels using gas chromatography and mass spectrometry. We found that CFS was accompanied by increased levels of omega6 PUFAs, i.e. linoleic acid and arachidonic acid (AA), and mono-unsaturated fatty acids (MUFAs), i.e. oleic acid. The EPA/AA and total omega3/omega6 ratios were significantly lower in CFS patients than in normal controls. The omega3/omega6 ratio was significantly and negatively correlated to the severity of illness and some items of the FibroFatigue scale, i.e. aches and pain, fatigue and failing memory. The severity of illness was significantly and positively correlated to linoleic and arachidonic acid, oleic acid, omega9 fatty acids and one of the saturated fatty acids, i.e. palmitic acid. In CFS subjects, we found significant positive correlations between the omega3/omega6 ratio and lowered serum zinc levels and the lowered mitogen-stimulated CD69 expression on CD3+, CD3+ CD4+, and CD3+ CD8+ T cells, which indicate defects in early T cell activation. **The results of this study show that a decreased availability of omega3 PUFAs plays a role in the pathophysiology of CFS and is related to the immune pathophysiology of CFS. The results suggest that patients with CFS should respond favourably to treatment with--amongst other things--omega3 PUFAs, such as EPA and DHA. The results of this study show that a decreased availability of omega3 PUFAs plays a role in the pathophysiology of CFS and is related to the immune pathophysiology of CFS. The results suggest that patients with CFS should respond favourably to treatment with--amongst other things--omega3 PUFAs, such as EPA and DHA.**"

-M-Care4U Outpatient Clinics, and the Clinical Research Center for Mental Health, Antwerp, Belgium.
https://www.ncbi.nlm.nih.gov/pubmed/16380690

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"Data from ecologic studies across different countries suggested an inverse association between seafood consumption and national rates of major depression [185] and bipolar disorder [186].

Several small studies have found omega-3 fatty acid concentrations to be lower in plasma [187-189] and adipose tissue [190] of individuals suffering from depression compared to controls. Although it is not known how omega-3 fatty acid intake affects the incidence of depression, modulation of neuronal signaling pathways and eicosanoid production have been proposed as possible mechanisms [191]. There may be some benefit of omega-3 PUFA supplementation on depressive

disorders, but it is difficult to compare studies and draw conclusions due to great heterogeneity among the trials [192, 193]. Small sample sizes, lack of standardization of therapeutic doses, type of omega-3 PUFA administered, co-treatment with pharmacological agents, and diagnostic criteria vary among the trials. A 2012 systematic review of all published randomized controlled trials investigated the effect of omega-3 PUFA supplementation on the prevention and treatment of several types of depression and other neuropsychiatric disorders [192]. With respect to major depression, most studies reported a positive effect of omega-3 supplements on depressive symptoms, though efficacy is still considered inconclusive given the great variability among trials. A few themes emerged from this review: more trials reported positive effect for omega-3 PUFA supplements as an adjunct to pharmacological treatment; in monotherapy trials, EPA alone was more effective than DHA alone; and in combination trials, positive effects were more likely if an EPA:DHA ratio of >1.5–2.0 was administered.

A 2014 meta-analysis grouped trials by type of diagnosis of depression [194]. A positive effect of omega-3 supplementation was found in 11 trials in participants with a diagnosis of major depressive disorder (according to the Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria). Omega-3 supplementation also appeared to be effective in the pooled analysis of eight trials in participants not formally diagnosed with major depressive disorder, i.e., adults with depressive symptoms despite ongoing treatment, untreated patients with mild-to-severe depressed mood, patients with a history of at least one major depressive episode, women with borderline personality disorder, patients with recurrent self-harm, and postmenopausal women with psychological distress and depressive symptoms. There was no mood improvement with omega-3 supplements in generally healthy adults experiencing depressive symptoms, as suggested by the pooled analysis of six trials [194]."

- Oregon State University
https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids#neuropsychiatric-disorders-treatment

Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress

.."Basal serum concentrations of AEA [Anandamide] and 2-AG, but not PEA or OEA, were significantly reduced in women with major depression relative to matched controls, indicating a deficit in peripheral endocannabinoid activity. "...

-Department of Psychology, University of British Columbia, Vancouver, B.C., Canada.
https://pubmed.ncbi.nlm.nih.gov/19394765/

Polyunsaturated fatty acid and depression:

"In major depression, all studies revealed a significant decrease of the polyunsaturated omega 3 fatty acids and/or an increase of the omega 6/omega 3 ratio in plasma and/or in the membranes of the red cells. In addition, two studies found a higher severity of depression when the level of polyunsaturated omega 3 fatty acids or the ratio omega 3/omega 6 was low. Parallel to these modifications, other biochemical perturbations have been reported in major depression, particularly an activation of the inflammatory response system, resulting in an increase of the pro-inflammatory cytokines (interleukins: IL-1b, IL-6 and interferon g) and eicosanoids (among others, prostaglandin E2) in the blood and the CSF of depressed patients. These substances cause a peroxidation and, consequently a catabolism of membrane phospholipids, among others those containing polyunsaturated fatty acids. The cytokines and eicosanoids derive from polyunsaturated fatty acids and have opposite physiological functions according to their omega 3 or omega 6 precursor. Arachidonic acid (omega 6) is, among others, precursor of pro-inflammatory prostaglandin E2 (PGE2), whereas polyunsaturated omega 3 fatty acids inhibit the formation of PGE2. It has been shown that a dietary increase of polyunsaturated omega 3 fatty acids reduced strongly the production of IL-1 beta, IL-2, IL-6 and TNF-alpha (tumor necrosis factor-alpha). In contrast, diets with a higher supply of linoleic acid (omega 6) increased significantly the production of pro-inflammatory cytokines, like TNF-alpha. Therefore, polyunsaturated omega 3 fatty acids could be associated at different levels in the pathophysiology of major depression, on the one hand through their role in the membrane fluidity which influences diverse steps of neurotransmission and, on the other hand, through their function as precursor of pro-inflammatory cytokines and eicosanoids disturbing neurotransmission. In addition, antidepressants could exhibit an immunoregulating effect by reducing the release of pro-inflammatory cytokines, by increasing the release of endogenous antagonists of pro-inflammatory cytokines like IL-10 and, finally, by acting like inhibitors of cyclo-oxygenase."

-Université de Liège, CUP La Clairière, Bertrix.
https://pubmed.ncbi.nlm.nih.gov/12640327/

Omega-3 Polyunsaturated Fatty Acids in Prevention of Mood and Anxiety Disorders

…"The PUFAs hypothesis is enlightening a promising path to discover, at least partially, the unsolved of depression. Firstly, it has been observed that countries with a high consumption of fish diet appear to have a lower prevalence of major depressive disorder (MDD) 25,26) and bipolar disorders (BD),27) implying a preventive effect of omega-3 PUFA on mood disorders.

Secondly, patients with MDD have lower levels of n-3 PUFAs in tissues of blood14) and brain.28–30) In our recent meta-analytic review including 3,318 subjects,14) the results further support omega-3 fatty acid deficits in MDD by showing a significant decrease in the levels of EPA (effect size [ES]=−0.18, p=0.004), DHA (ES=−0.35, p=0.0002) and total n-3 PUFA (ES=−0.51, p<0.0001).”…

-Department of Psychiatry and Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan

-Graduate Institute of Neural and Cognitive Sciences, China Medical University, Taichung, Taiwan

-Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry, Tokyo, Japan

-Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, Korea

-Address for correspondence: Kuan-Pin Su, MD, PhD, Department of Psychiatry, China Medical University Hospital

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4540034

Serum Endocannabinoid and Mood Changes after Exercise in Major Depressive Disorder

“The endocannabinoid (eCB) system is implicated in the pathophysiology of depression and is responsive to acute exercise in healthy adults.

Purpose: We aimed to describe acute changes in serum eCB across a prescribed moderate (MOD) and a self-selected/preferred (PREF) intensity exercise session in women with major depressive disorder (MDD) and determine relationships between changes in eCB and mood states.

Methods: Women with MDD (n = 17) exercised in separate sessions for 20 min on a cycle ergometer at both MOD or PREF in a within-subjects design. Blood was drawn before and within 10 min after exercise. Serum concentrations of eCB (anandamide [AEA], 2-arachidonoylglycerol) and related lipids (palmitoylethanolamine, oleoylethanolamine, 2-oleoylglycerol) were quantified using stable isotope-dilution, liquid chromatography/mass spectrometry/mass spectrometry. The profile of mood states and state-trait anxiety inventory (state only) were completed before, 10 min and 30 min postexercise.

Results: Significant elevations in AEA (P = 0.013) and oleoylethanolamine (P = 0.024) occurred for MOD (moderate effect sizes: Cohen's d = 0.58 and 0.41, respectively). Significant (P < 0.05) moderate negative associations existed between changes in AEA and mood states for MOD at 10 min (depression, confusion, fatigue, total mood disturbance [TMD] and state anxiety) and 30 min postexercise (confusion, TMD and state anxiety). Significant (P < 0.05) moderate negative associations existed between 2-arachidonoylglycerol and mood states at 10 min (depression and confusion) and 30 min postexercise (confusion and TMD). Changes in eCB or related lipids or

eCB-mood relationships were not found for PREF.

Conclusion: Given the broad, moderate-strength relationships between improvements in mood states and eCB increases after MOD, it is plausible that the eCB system contributes to the mood-enhancing effects of prescribed acute exercise in MDD. Alternative mechanisms are likely involved in the positive mood state effects of preferred exercise."

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6727944

See also Depression , Social Functioning , Mental Health

Marfan Syndrome

"Marfan syndrome (MFS) is a pleiotropic genetic disease involving the cardiovascular system where a fibrillin-1 mutation is present. This mutation is associated with accelerated activation of transforming growth factor β (TGFβ1) which contributes to the formation of aneurysms in the root of the aorta. There is an imbalance in the synthesis of thromboxane A2 (TXA2) and prostacyclin, that is a consequence of a differential protein expression of the isoforms of cyclooxygenases (COXs), suggesting an alteration of arachidonic acid (AA) metabolism. ".."

"Histological examination of the aortas showed an increase of cystic necrosis, elastic fibers and collagen in MFS. The results suggest that there are inflammatory factors coupled to genetic factors that predispose to aortic endothelial dysfunction in the aortic tissue of patients with MFS. There is a decrease in the percentage of AA, associated with an increase of PLA2, COX2/TXA2R, CYP450 4A, and 5-LOX which leads to a greater synthesis of PGE2 than of 6-keto-PGF1α, thus contributing to the formation of the aortic aneurysm. The evident loss of the homeostasis in these mechanisms confirms that there is a participation of the AA pathway in the aneurysm progression in MFS."…

-Department of Immunology, Instituto Nacional de Cardiología "Ignacio Chávez", Mexico City, Mexico
-Department of Physiology, Instituto Nacional de Cardiología "Ignacio Chávez", Mexico City, Mexico
-Cardiothoracic Surgery, Instituto Nacional de Cardiología "Ignacio Chávez", Mexico City, Mexico
-Department of Pathology, Instituto Nacional de Cardiología "Ignacio Chávez", Mexico City, Mexico
-Edited by: John D. Imig, Medical College of Wisconsin, United States
-Reviewed by: Marius Catalin Staiculescu, Washington University in St. Louis, United States; Bysani Chandrasekar, University of Missouri, United States; Luis A. Martinez-Lemus, University of Missouri, United States

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5816394/

Memory

Role of cannabinoid receptors in memory storage.

..."A possible role for cannabinoid receptors and endogenous cannabinoids may thus be to regulate the storage (i.e., encoding) of information, as well as the means by which that information is retrieved."

- Department of Physiology & Pharmacology of Wake Forest University of Medicine
http://www.ncbi.nlm.nih.gov/pubmed/9974179

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"These findings suggest eCB [endocannabinoid system] involvement in encoding of pictorial information."..."These results further emphasize the eCB system as a potential novel target for treatment of memory disorders and a promising target for development of new therapies to reduce memory deficits in humans."

- University Medical Center Utrecht, the Netherlands.
http://www.ncbi.nlm.nih.gov/pubmed/22066583

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"The cannabinoid CB1 receptor system is functionally involved in the processing and encoding of emotionally salient sensory information, learning and memory. " ...

- Department of Anatomy and Cell Biology, The Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada.
http://www.ncbi.nlm.nih.gov/pubmed/19880592

Fatty-Acid Binding Proteins Modulate Sleep and Enhance Long-Term Memory Consolidation in Drosophila

..."Diurnal fluctuations in other lipid species have also been identified in the CNS. Time-of-day cycling has been observed broadly in mammalian brain for the major endocannabinoids anandamide and 2-arachidonoyl-glycerol (2-AG) [53]. Within the rat hippocampus, higher levels of anandamide have been observed during the dark period [53], [54], while higher levels of 2-AG were

observed during the light period [53]. Further, fatty acid amide hydrolase (FAAH), the enzyme which catabolizes anandamide, has levels that also vary based on time-of-day within various regions of the brain [53], [55], suggesting that lipid-metabolism likely also varies over the light/dark cycle. Inhibition of FAAH has recently been shown to promote memory processing [56], implicating anandamide-metabolism in the regulation of memory formation. Oleoylethanolamide (OEA), a monounsaturated analogue of anandamide and an endogenous peroxisome proliferator activated receptor (PPAR)-α agonist, failed to show any diurnal fluctuations within the hippocampus [54]. However, post-training administration of OEA, or exogenous PPAR-α agonists, have recently been shown to enhance memory for inhibitory avoidance and Morris water maze tasks [57]. These data suggest that an increase in specific lipid-signaling pathways are able to enhance memory formation during the consolidation period, and together indicate that increased levels of anandamide or its derivatives are able to enhance memory formation."..

- Department of Genetics, University of Wisconsin-Madison, Madison, Wisconsin, USA,
- Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri, USA,
- Scarab Genomics, LLC, Madison, Wisconsin, USA,
- Department of Neurology, University of Wisconsin-Madison, Madison, Wisconsin, USA,
- Waisman Center, University of Wisconsin-Madison, Madison, Wisconsin, USA,
- Université de Bordeaux and Centre National de la Recherche Scientifique, France
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3029266

Meniere's Disease

Omega-3 fatty acids: a promising possible treatment for Meniere's disease and other inner ear disorders of unknown origin?

"A consolidated therapy for "idiopathic" acute disorders of the inner ear, including Meniere's Disease (MD), does not exist despite the long-lasting and widespread attempts: this lack is strictly linked to pathogenic uncertainties. According to the theoretical model that our group developed and tested over the years, a possible cause of labyrinthine damage could be identified in systemic hemodynamic changes followed by an abnormal peripheral vasoconstriction: the latter could be responsible for a more or less prolonged ischemia able to threaten a highly energy-requiring and complicated organ as the inner ear. A possible way to treat MD attacks - as well as other inner ear disorders that possibly share the same origin - according to our model should be addressed to modulate the peripheral circulation and to maintain the balance of ion exchange, acting both on systemic hemodynamics and on cell and organelle membranes. Despite

the absence of such a proposal in the English literature, a reliable solution could derive from the supplementation of the intake of a nutritional principle as Omega-3 (omega-3) polyunsaturated fatty acids (PUFAs) that seem to theoretically fulfil all the requirements necessary to achieve a homeostasis of the inner ear."

-Department of Internal Medicine and Ageing, University of Bologna, Italy.
https://pubmed.ncbi.nlm.nih.gov/22800802/

Menopause

How is the Endocannabinoid System (ECS) Disrupted in Menopause?

"Reduction in endocannbinoids signaling may be responsible for some of the negative symptoms we associate with menopause. This is not surprising as estrogen levels are linked to endocannabinoid levels, and both peak at ovulation, something that does not occur in menopausal and postmenopausal women. Fatty acid amide hydrolase (FAAH), the enzyme that breaks down the endocannabinoid anandamide and controls it levels, is regulated by estrogen. In fact, activation of estrogen receptors and cannabinoid receptors on the same cells often synergize to produce greater effects than the combination of both by themselves.

All parts of the endocannabinoid system are present in the human ovary, including the endocannabinoid anandamide, and its receptors, CB1 and CB2. Anandamide has role in egg maturity and release during the menstrual cycle. Endocannabinoid deficiency, a state in which levels of anandamide are too low, may spur early menopause. Interestingly underweight women or women with anorexia, who enter menopause early, also have low endocannabinoid levels. Boosting levels of endocannabinoids or stimulating cannabinoid receptors with cannabis may help delay menopause.

Estrogen recruits the endocannabinoid system to regulate emotional response and relieves anxiety and depression through its actions on the brain. Lowered levels of estrogen during and after menopause means less activation of the endocannabinoid system, and poor ability to respond to stress and elevate mood accordingly.

The endocannabinoid system regulates the bone loss seen after menopause. Cannabinoid receptor type 2 (CB2) are found on bone cells, called osteoblasts. A common mutation in the gene that codes CB2 in humans, resulting in fewer CB2 receptors, is associated with osteoperosis after menopause.

Women are more responsive to the pain relieving effects of cannabis and THC when their estrogen levels are at their highest. Because menopausal and postmenopausal women have low

levels of estrogen, this means they will be less responsive to THC and require higher doses than premenopausal women to achieve the same amount of pain relief, and are likely to be closer to men in their response to cannabis. Premenopausal women develop tolerance to THC quickly, and may be more vulnerable to negative side effects of cannabis such as paranoia, anxiety, or dependence. Postmenopausal women may be able to stay on a stable dosage of THC or cannabis for the long-term, and may be less likely to feel anxious or paranoid from cannabis.

The endocannabinoid system's role in menopause and postmenopausal health is an area of medicine lacking in research. One day genetic studies will see if mutations in endocannabinoid system genes are correlated with early or premature menopause. Because the reproductive system contains cannabinoid receptors that interact with estrogen, endocannabinoids directly influence the menstrual cycle and menopause."

-Dr. Michele Ross, PhD, MBA
https://www.linkedin.com/pulse/can-cannabis-replace-ert-menopause-michele-noonan-ross-phd

Menstruation

Painful menstruation and low intake of n-3 [omega-3] fatty acids

"Menstrual pain, dysmenorrhea, which is known to be prostaglandin mediated, can possibly be influenced by the dietary ratio of omega-3 and omega-6 polyunsaturated fatty acids. The prostaglandins derived from marine omega-3 fatty acids are normally less aggressive and therefore expected to be associated with milder menstrual symptoms. This hypothesis was surveyed in an epidemiological study in Danish women based upon self administered questionnaires concerning menstrual history, present symptoms, general health, socio-economic factors, and general dietary habits. Two prospective four-day dietary records were used to estimate average daily nutrient intake. The subjects were recruited by advertising, they were 20-45 years of age, not pregnant, and did not use oral contraceptives. No correlations were found between socioeconomic or anthropometric data and menstrual problems. However, certain dietary habits e.g. low intakes of animal and fish products, and low intakes of specific nutrients (omega-3 PUFA, B12 and omega-3/omega-6 ratio) were correlated with menstrual pain. The other nutrients in the diet were not significantly related to menstrual pain. The results were highly significant and mutually consistent and supported the hypothesis that a higher intake of marine, omega-3 fatty acids correlate with milder menstrual symptoms."

-Ugeskrift Læger / Danish medical journal, B Deutch
https://pubmed.ncbi.nlm.nih.gov/8701537/

The effect of omega-3 supplementation on androgen profile and menstrual status in women with polycystic ovary syndrome: A randomized clinical trial

…"Omega-3 supplementation could reduce serum concentrations of testosterone and regulate menstrual cycle without significant effect on SHBG [sex hormone-binding protein] and FAI [free androgen index]. Future studies with longer period of supplementation are warranted."

-Department of Nutrition, Faculty of Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

-Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

-International Campus of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

-Department of Biostatistics and Epidemiology, Faculty of Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3941370/

Mental Health

Endocannabinoids and Mental Disorders

"Preclinical and clinical data fully support the involvement of the endocannabinoid system in the etiopathogenesis of several mental diseases. In this review we will briefly summarize the most common alterations in the endocannabinoid system, in terms of cannabinoid receptors and endocannabinoid levels, present in mood disorders (anxiety, posttraumatic stress disorder, depression, bipolar disorder, and suicidality) as well as psychosis (schizophrenia) and autism. The arising picture for each pathology is not always straightforward; however, both animal and human studies seem to suggest that pharmacological modulation of this system might represent a novel approach for treatment."

-Department of Theoretical and Applied Sciences and Neuroscience Centre, University of Insubria, Via Manara 7, 21052, Busto Arsizio, VA, Italy.

-Fondazione Zardi Gori, Milan, Italy.

-Department of Theoretical and Applied Sciences and Neuroscience Centre, University of Insubria, Via Manara 7, 21052, Busto Arsizio, VA, Italy

-Fondazione Zardi Gori, Milan, Italy

https://pubmed.ncbi.nlm.nih.gov/26408164/

Omega-3 Polyunsaturated Fatty Acids in Prevention of Mood and Anxiety Disorders

"Psychiatric disorders in general, and major depression and anxiety disorders in particular, account for a large burden of disability, morbidity and premature mortality worldwide. Omega-3 polyunsaturated fatty acids (PUFAs) have a range of neurobiological activities in modulation of neurotransmitters, anti-inflammation, anti-oxidation and neuroplasticity, which could contribute to psychotropic effects. Here we reviewed recent research on the benefits of omega-3 PUFA supplements in prevention against major depression, bipolar disorders, interferon-α-induced depression patients with chronic hepatitis C viral infection, and posttraumatic stress disorder. The biological mechanisms underlying omega-3 PUFAs' psychotropic effects are proposed and reviewed. Nutrition is a modifiable environmental factor that might be important in prevention medicine, which have been applied for many years in the secondary prevention of heart disease with omega-3 PUFAs. This review extends the notion that nutrition in psychiatry is a modifiable environmental factor and calls for more researches on prospective clinical studies to justify the preventive application of omega-3 PUFAs in daily practice."

…"Nutrition is a modifiable environmental factor that might be important in prevention medicine. Omega-3 PUFAs are well tolerated and accepted, and have been applied for many years as the secondary prevention in various chronic medical diseases and mental disorders. In this review, we found that the clinical evidence about omega-3 PUFAs' preventive benefits on mood and anxiety disorders is supported by their regulatory effects on immunomodulation, anti-inflammation, signal transduction, neurotransmission and neuroprotection. "…

-Department of Psychiatry and Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan

-Graduate Institute of Neural and Cognitive Sciences, China Medical University, Taichung, Taiwan

-Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry, Tokyo, Japan

-Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, Korea

-Address for correspondence: Kuan-Pin Su, MD, PhD, Department of Psychiatry, China Medical University Hospital

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4540034/

Oiling the Brain: A Review of Randomized Controlled Trials of Omega-3 Fatty Acids in Psychopathology across the Lifespan

"Around one in four people suffer from mental illness at some stage in their lifetime. There is increasing awareness of the importance of nutrition, particularly omega-3 polyunsaturated fatty acids (n-3 PUFA), for optimal brain development and function. Hence in recent decades, researchers have explored effects of n-3 PUFA on mental health problems over the lifespan,

from developmental disorders in childhood, to depression, aggression, and schizophrenia in adulthood, and cognitive decline, dementia and Alzheimer's disease in late adulthood. This review provides an updated overview of the published and the registered clinical trials that investigate effects of n-3 PUFA supplementation on mental health and behavior, highlighting methodological differences and issues."…

"Mental health is described as "a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community" [1]. About 450 million people worldwide do not enjoy this state of wellbeing, and it is estimated that one in four people will suffer from mental illness at some stage in their lifetime, causing enormous suffering, personal, social and financial burden, as well as associated physical illness [2]. Identification of preventable risk factors and effective treatments therefore constitutes an international priority.

Nutrition has an important role in mental health as the brain relies on both macro- and micronutrients for development and functioning [3,4,5,6]. In particular, suboptimal levels of omega-3 polyunsaturated fatty acids (n-3 PUFA) are emerging as a potentially modifiable risk factor for mental illness. Since their discovery in the 1970s as key components of brain tissue [7], long-chain n-3 PUFA have been postulated to serve critical roles in brain development, and function and a lack of these fatty acids has been implicated in a number of mental health conditions over the lifespan, from developmental disorders and mental retardation in childhood, to depression, bipolar disorder, schizophrenia and borderline personality disorder, stress, hostility and aggression in adulthood, and cognitive decline, dementia and Alzheimer's disease in late adulthood [8].

Although the etiology of these disorders is clearly multifactorial and subject to individual variation, the number of clinical trials addressing suboptimal n-3 PUFA levels as a possible underlying biological contributor to associated symptoms, and importantly symptoms that often co-occur and overlap between these disorders, is steadily growing. Following an overview of n-3 PUFA, we will provide a review of randomized controlled trials [8], and an update of recent trials located via the World Health Organization's International Clinical Trials Registry Platform Search Portal [9], including preliminary results from our own recent studies, focusing on the role of n-3 PUFA in alleviating symptoms of psychopathology from childhood throughout adulthood."…

Lipids constitute approximately sixty percent of the dry weight of the brain. DHA and AA are the most highly concentrated PUFA in neural phospholipids, including subcellular membranes [12,13,14]. Although the circulation contains at least 10 times more n-6 than n-3 PUFA, DHA predominates in the retina, brain and nervous system [14]. Furthermore, DHA is particularly concentrated at neural synapses [15,16,17,18,19].

Importantly, DHA levels in neural membranes vary according to dietary oil intake [4,19,20] and there is evidence that low PUFA and high cholesterol levels reduce phospholipid fluidity [19,20]. Animal studies and human infant autopsies have also shown that when insufficient n-3 PUFA are available during early neural development, there is a decrease in the DHA content of the brain. Furthermore, increased n-6 to n-3 PUFA ratios can also alter the fatty acid composition of neural membranes [21].

Various reviews have outlined biological mechanisms for n-3 PUFA in brain function [22,23,24]. In particular, and in line with a longstanding focus on the role of neurotransmitters such as dopamine and serotonin in mental illness, research has focused on associations between PUFA and central nervous system activity [25]. Evidence points to the role of eicosanoids in healthy brain functioning, and phospholipid membranes in neural cell signaling [12,19,26,27]. Levels of n-3 PUFA have been associated with monoaminergic neurotransmitter levels [27,28,29,30]. n-3 deficiency has also been found, in animal studies, to reduce levels of phosphatidylserine (PS) in the brain, which is thought to play an important function in neural signaling activities [12]. In alcoholics, DHA deficiency has predicted reduced 5-hydroxyindoleacetic acid (5-HIAA) concentrations in cerebrospinal fluid, an indicator of low serotonin turnover rate in the frontal cortex [31].”….

-Nutritional Physiology Research Centre, Sansom Institute for Health Research, University of South Australia
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257637/

Basic neuroanatomy and neuropharmacology of cannabinoids

“Humans have used Cannabis sativa (marijuana) for at least 12,000 years, but researchers have only recently described an endogenous cannabinoid system. The endocannabinoid system modulates an array of physiological and psychological functions. Endocannabinoids are widely distributed throughout the body, including the central nervous system (CNS). This article gives a basic overview of endocannabinoid neuroanatomy and function. Several endocannabinoids have been discovered to date, and their roles are being elucidated. Two G-protein coupled cannabinoid receptors, CB1R and CB2R, have been identified, although other candidate receptors exist, including ion channel and nuclear receptors that might be components of the endocannabinoid system. It appears that cannabinoids are dysregulated in a number of psychiatric disorders and might be involved in their pathogenesis. There is now evidence that manipulation of the endocannabinoid system could be a therapeutic target for a variety of conditions.”

-Department of Pharmaceutical Sciences, Campbell University School of Pharmacy, Buies Creek, North Carolina, USA.
https://pubmed.ncbi.nlm.nih.gov/19367505/

See also Major Depression

Mental Illness

Polyunsaturated Fatty Acids [PUFAs] and Mental Illness

…"PUFA [Polyunsaturated Fatty Acids / Omega-3s] deficiencies have been reported in people with a range of psychiatric problems [22,23,24,39,40,41,24,39], including developmental disorders such as attention deficit hyperactivity disorder (ADHD), depression, bipolar disorder, stress, aggression, hostility and criminality, and dementia."…

-Nutritional Physiology Research Centre, Sansom Institute for Health Research, University of South Australia
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257637/

Metabolic Disorders

…"The beneficial effects of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) on the risk of developing cardiovascular diseases (CVD) [15] and metabolic disorders, such as insulin resistance, fatty liver and hypertension [16], have been extensively studied. The most studied ω-3 PUFAs are eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6), present in the diet as such or biosynthesized from α-linolenic acid (ALA, 18:3) [17]. In contrast, derivatives of ω-6 PUFAs, originated from linoleic acid (LA, 18:2), and of which the major exponent is AA (ω-6 20:4), are known for their pro-inflammatory and other disease-propagating effects [18]. Both ω-3 and ω-6 PUFAs precursors are essential fatty acids because they cannot be synthesized de novo in mammals and have to be obtained through the diet or from dietary precursors. Major sources of ω-3 PUFAs are fish oils, whereas other types of oil, such as flaxseed oil, are a good source of ALA [19]. "…

-Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, CNR, Pozzuoli (NA), Italy
-Dipartimento di Biologia Sperimentale, Università di Cagliari, Italy; and Nutrisearch s.r.l. Pula (CA) Italy
-Aker BioMarine ASA, Oslo, Norway
-Nutrition and Metabolism Group, Heart Research Institute, Sydney, Australia
-Clanet Oy, Helsinki, Finland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3154144/

Phytocannabinoids promote viability and functional adipogenesis of bone marrow-derived mesenchymal stem cells through different molecular targets

“The cellular microenvironment plays a critical role in the maintenance of bone marrow-derived mesenchymal stem cells (BM-MSCs) and their subsequent cell lineage differentiation. Recent studies suggested that individuals with adipocyte-related metabolic disorders have altered function and adipogenic potential of adipose stem cell subpopulations, primarily BM-MSCs, increasing the risk of heart attack, stroke or diabetes. In this study, we explored the potential therapeutic effect of some of the most abundant non-euphoric compounds derived from the Cannabis sativa plant (or phytocannabinoids) including tetrahydrocannabivarin (THCV), cannabidiol (CBD), cannabigerol (CBG), cannabidiolic acid (CBDA) and cannabigerolic acid (CBGA), by analysing their pharmacological activity on viability of endogenous BM-MSCs as well as their ability to alter BM-MSC proliferation and differentiation into mature adipocytes. We provide evidence that CBD, CBDA, CBGA and THCV (5 µM) increase the number of viable BM-MSCs; whereas only CBG (5 µM) and CBD (5 µM) alone or in combination promote BM-MSCs maturation into adipocytes via distinct molecular mechanisms. These effects were revealed both in vitro and in vivo. In addition, phytocannabinoids prevented the insulin signalling impairment induced by palmitate in adipocytes differentiated from BM-MSCs. Our study highlights phytocannabinoids as a potential novel pharmacological tool to regain control of functional adipose tissue in unregulated energy homeostasis often occurring in metabolic disorders including type 2 diabetes mellitus (T2DM), aging and lipodystrophy.”

-Endocannabinoid Research Group, Institute of Biomolecular Chemistry (ICB), National Research Council (CNR), Pozzuoli (NA) Italy.

-Department of Experimental Medicine, Section of Pharmacology L. Donatelli, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy.

-Health, Institut Universitaire de Cardiologie et de Pneumologie de Québec and Institut sur la Nutrition et les Aliments Fonctionnels, Université Laval, Quebec City G1V 0A6, Canada.

-Endocannabinoid Research Group, Institute of Biomolecular Chemistry (ICB), National Research Council (CNR), Pozzuoli (NA) Italy.

https://pubmed.ncbi.nlm.nih.gov/32061773/

Metabolic Syndrome

Dietary Omega-3 Fatty Acid Deficiency and High Fructose intake in the Development of Metabolic Syndrome Brain, Metabolic Abnormalities, and Non-Alcoholic Fatty Liver Disease

“Western diets are characterized by both dietary omega-3 fatty acid deficiency and increased

fructose intake. The latter found in high amounts in added sugars such as sucrose and high fructose corn syrup (HFCS). Both a low intake of omega-3 fatty acids or a high fructose intake contribute to metabolic syndrome, liver steatosis or non-alcoholic fatty liver disease (NAFLD), promote brain insulin resistance, and increase the vulnerability to cognitive dysfunction. Insulin resistance is the core perturbation of metabolic syndrome. Multiple cognitive domains are affected by metabolic syndrome in adults and in obese adolescents, with volume losses in the hippocampus and frontal lobe, affecting executive function. Fish oil supplementation maintains proper insulin signaling in the brain, ameliorates NAFLD and decreases the risk to metabolic syndrome suggesting that adequate levels of omega-3 fatty acids in the diet can cope with the metabolic challenges imposed by high fructose intake in Western diets which is of major public health importance. This review presents the current status of the mechanisms involved in the development of the metabolic syndrome, brain insulin resistance, and NAFLD a most promising area of research in Nutrition for the prevention of these conditions, chronic diseases, and improvement of Public Health."…

"Over the past century, major changes have taken place in the food composition of Western diets, in terms of essential fatty acids and sugar intake, particularly fructose [1,2,3,4,5,6]. Today's Western diets are characterized by increases in total fat, especially in saturated fat and omega-6 fatty acids and decreases in omega-3 fatty acids in comparison to the fatty acid intake during evolution for which our genes were programmed to respond [1,3,6,7]. Omega-3 deficiency contributes to insulin resistance and the metabolic syndrome [1,8,9] brain metabolic abnormalities [10,11,12,13], liver steatosis or non-alcoholic fatty liver disease (NAFLD) [14]. An increase in fructose intake contributes to similar metabolic effects. The largest increase in the intake of fructose occurred with the introduction of high fructose corn syrup (HFCS) in soft drinks and processed foods about 30 years ago [2,5,6]. These dietary changes: the omega-3 fatty acid deficiency and the excessive fructose intake occurred as a result of agribusiness, modern agriculture and food processing, and not because there was any scientific evidence that required decreasing omega-3 fatty acid intake while increasing omega-6 fatty acids and fructose intake. With the decrease in omega-3 fatty acid intake there has been an absolute and relative increase in omega-6 fatty acids leading to an increase in the omega-6/omega-3 ratio from 1–2/1 to about 16/1 in terms of both 18, 20 and 22 carbon atoms (linoleic acid (LA), arachidonic acid (AA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and dochosahexaenoic acid (DHA)) and LA/ALA and AA/EPA + DHA ratios [15]. Omega-3 fatty acids have been studied extensively since 1985 and have been shown to play an important role in growth and development and in health and disease [1,3].

In epidemiological studies, animal experiments and clinical intervention studies the consumption of HFCS, or sugar sweetened beverages has been linked to the presence of unfavorable lipid

levels, high triglycerides, high small dense LDL and low HDL [4], cardiovascular disease [5], type 2 diabetes [6,16,17], insulin resistance [18,19], the metabolic syndrome and liver steatosis [14]. More recently it has been shown that moderate amounts of fructose and sucrose significantly alter hepatic insulin sensitivity and lipid metabolism compared with similar amounts of glucose [20,21,22,23]. Recent studies reveal the broad effects of the metabolic syndrome on mental health disorders, cognitive function, mood changes and depression [10,11,12]. Furthermore, diabetic and obese individuals have increased vulnerability to mental health [13]. For these reasons the effects of metabolic syndrome on brain are being extensively investigated. In this paper I review the effects of the interaction of omega-3 fatty acid deficiency and high fructose intake in the development of metabolic syndrome, brain metabolic abnormalities, cognitive function, mental health, and liver steatosis or NAFLD. Fortunately, these adverse effects may be prevented or ameliorated with dietary repletion of omega-3 fatty acids."…

-The Center for Genetics, Nutrition and Health, 2001 S Street, NW, Suite 530, Washington, DC, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3775234/

Dietary Omega-3 Fatty Acid Deficiency

"In 1991, Storlien et al. studied the influence of dietary fat composition on development of insulin resistance in rats [8]. They showed that impaired insulin action in skeletal muscle is related to triglyceride accumulation, suggesting intracellular glucose-fatty acid cycle involvement, and that long-chain omega-3 fatty acids in phospholipid of skeletal muscle may be important for efficient insulin action. In rats made insulin resistant with a high fat diet, the resistance could be prevented by the inclusion of omega-3 fatty acids in the diet, but only under circumstances in which the EPA and DHA became incorporated in the phospholipid component of the muscle cells. Subsequently, Borkman et al. [9] performed studies in human subjects on the relationship between insulin sensitivity and the fatty acid composition of skeletal muscle membrane phospholipids, and showed that decreased insulin sensitivity is associated with decreased concentrations of long-chain polyunsaturated fatty acids (PUFA) in skeletal-muscle phospholipids, raising the possibility, that changes in the fatty acid composition of muscle cell membrane modulates the action of insulin in human subjects as was shown earlier in rats [8]. Skeletal muscle is the principle site of insulin mediated glucose disposal and the fatty acid composition of membranes influences the action of insulin within the skeletal muscle, whereas the fasting serum insulin concentration was positively correlated with the percentages of LA indicating that high or increased LA is associated with decreased insulin sensitivity [9]. The results of this study, in conjunction with the studies in cell systems and animals, suggest that variations in insulin sensitivity are related to differences in the membrane content of long-chain PUFA within skeletal

muscle phospholipids. Therefore, abnormalities in the fatty-acid composition of membranes may be involved in the pathogenesis of a cluster of disorders linked to insulin resistance and hyperinsulinemia, including obesity, hypertension, type 2 diabetes mellitus, and coronary artery disease, suggesting that diet may influence their development [1,3]. Furthermore, these conditions are known to have genetic determinants for hypertension, type 2 diabetes, some forms of hyperlipidemia, obesity, and insulin resistance (Figure 1) [29] and have a common abnormality in smooth muscle response and insulin resistance [30,31]. Figure 2 is a hypothetical scheme of how a decrease in EPA and DHA in muscle cell membrane phospholipids from (1) a decrease in dietary intake per se, (2) increased dietary intake of trans fatty acids, (3) increased intake of LA, or (4) genetic variants in delta-6 and delta-5 desaturases may lead to a decrease in EPA and DHA muscle cell membrane phospholipids [31]. Such a decrease contributes to insulin resistance and hyperinsulinemia, with the subsequent development of obesity, hypertension, type 2 diabetes, and coronary artery disease (including asymptomatic atherosclerosis and microvascular angina) [31].”

-The Center for Genetics, Nutrition and Health, 2001 S Street, NW, Suite 530, Washington, DC, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3775234/

Capsaicin in Metabolic Syndrome

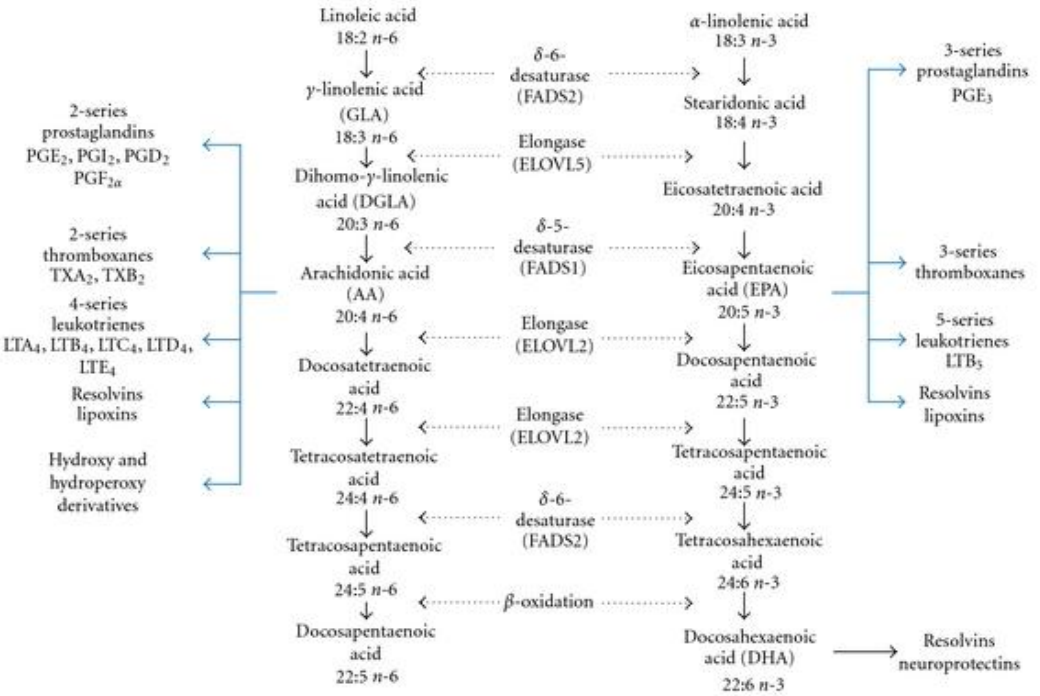
“Capsaicin, the major active constituent of chilli, is an agonist on transient receptor potential vanilloid channel 1 (TRPV1). TRPV1 is present on many metabolically active tissues, making it a potentially relevant target for metabolic interventions. Insulin resistance and obesity, being the major components of metabolic syndrome, increase the risk for the development of cardiovascular disease, type 2 diabetes, and non-alcoholic fatty liver disease. In vitro and pre-clinical studies have established the effectiveness of low-dose dietary capsaicin in attenuating metabolic disorders. These responses of capsaicin are mediated through activation of TRPV1, which can then modulate processes such as browning of adipocytes, and activation of metabolic modulators including AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor α (PPARα), uncoupling protein 1 (UCP1), and glucagon-like peptide 1 (GLP-1). Modulation of these pathways by capsaicin can increase fat oxidation, improve insulin sensitivity, decrease body fat, and improve heart and liver function. Identifying suitable ways of administering capsaicin at an effective dose would warrant its clinical use through the activation of TRPV1. This review highlights the mechanistic options to improve metabolic syndrome with capsaicin.”

-Functional Foods Research Group, University of Southern Queensland, Toowoomba QLD 4350, Australia.

-School of Health and Wellbeing, University of Southern Queensland, Toowoomba QLD 4350, Australia.
https://pubmed.ncbi.nlm.nih.gov/29772784

See also Capsaicin

Metabolism of Omega-6 & Omega-3



…"Metabolism of n-6 and n-3 PUFA. The metabolism of PUFA is a complex process involving several enzymes of desaturation, elongation, and β-oxidation. Shown here is the pathway of both n-6 and n-3 PUFA metabolism to more unsaturated, long-chain members of each family. Also shown are their respective eicosanoid derivatives. Data elaborated from [21]."…

-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland
-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

Methemoglobinemia

"A condition in which a higher-than-normal amount of methemoglobin is found in the blood. Methemoglobin is a form of hemoglobin that cannot carry oxygen. In methemoglobinemia, tissues cannot get enough oxygen. Symptoms may include headache, dizziness, fatigue, shortness of breath, nausea, vomiting, rapid heartbeat, loss of muscle coordination, and blue-colored skin. Methemoglobinemia can be caused by injury or being exposed to certain drugs, chemicals, or foods. It can also be an inherited condition."

-National Cancer Instititue
https://www.cancer.gov/publications/dictionaries/cancer-terms/def/methemoglobinemia

Metmyoglobin promotes arachidonic acid [omega-6] peroxidation at acid pH

…"These observations support the hypothesis that metmyoglobin and other heme proteins can promote significant peroxidation of unsaturated fatty acids under conditions of mildly acidic pH such as may occur at sites of inflammation and during myocardial ischemia and reperfusion. This may be the result of enhanced aggregation of the fatty acid and/or interaction of the fatty acid with heme under acidic conditions."

-Department of Pathology, University of Michigan Medical School, Ann Arbor
https://pubmed.ncbi.nlm.nih.gov/2498331

Microglial & Glial Cells

Endocannabinoid signaling in microglial cells.

"Evidence now shows that microglia, the macrophages of the brain, also express a functional eCBSS [The endocannabinoid signaling system] and that activation of CB receptors expressed by activated microglia controls their immune-related functions. This review summarizes this evidence, discusses how microglia might use the eCBSS to communicate with each other and neighboring cells, and argues that compounds selectively targeting the eCBSS expressed by microglia constitute valuable therapeutics to manage acute and chronic neuroinflammation without inducing the psychotropic effects and underlying addictive properties commonly associated with THC."

-Nephi Stella, Department of Pharmacology, Psychiatry and Behavioral Sciences, Univ. of WA.
https://www.ncbi.nlm.nih.gov/pubmed/18722389

macrophages - white blood cells, of the immune system

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…"One of the striking hallmarks of ongoing inflammation in neurodegenerative diseases is chronic microglial activation [35]. There is a strong interest in unearthing lipid metabolites that can reduce microglial activation and thereby combat neuroinflammation. Several studies indicate that the endocannabinoids reduce microglial-promoted neuroinflammation through CB2 activation. Consequently, there is a strong interest in the discovery of endocannabinoid derivatives that are CB2-preferring/-selective agonists as means of mitigating inflammatory pathologies [8, 36, 37]."…

-Department of Comparative Biosciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Medical Scholars Program, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Biochemistry, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Materials Science and Engineering, University of Illinois at Urbana–Champaign, Champaign, IL,
-Department of Pharmacology, University of Michigan, Ann Arbor, MI;
-Division of Nutritional Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-College of Veterinary Medicine, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Animal Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Bioengineering, University of Illinois at Urbana–Champaign, Champaign IL;
-Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI;
-Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana–Champaign, Champaign, IL,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5544256

The endocannabinoid system in normal and pathological brain ageing

"The role of endocannabinoids as inhibitory retrograde transmitters is now widely known and intensively studied. However, endocannabinoids also influence neuronal activity by exerting neuroprotective effects and regulating glial responses. This review centres around this less-studied area, focusing on the cellular and molecular mechanisms underlying the protective effect of the cannabinoid system in brain ageing. The progression of ageing is largely determined by the balance between detrimental, pro-ageing, largely stochastic processes, and the activity of the homeostatic defence system. Experimental evidence suggests that the cannabinoid system is part of the latter system. Cannabinoids as regulators of mitochondrial activity, as anti-oxidants and as modulators of clearance processes protect neurons on the molecular level. On the cellular level, the cannabinoid system regulates the expression of brain-derived neurotrophic factor and neurogenesis. Neuroinflammatory processes contributing to the progression of normal brain ageing and to the pathogenesis of neurodegenerative diseases are suppressed by

cannabinoids, suggesting that they may also influence the ageing process on the system level. In good agreement with the hypothesized beneficial role of cannabinoid system activity against brain ageing, it was shown that animals lacking CB1 receptors show early onset of learning deficits associated with age-related histological and molecular changes. In preclinical models of neurodegenerative disorders, cannabinoids show beneficial effects, but the clinical evidence regarding their efficacy as therapeutic tools is either inconclusive or still missing."

…"The cannabinoid system also influences ROS levels indirectly through the regulation of glial activity [182]. Both astrocytes and microglia express CB1 and CB2 cannabinoid receptors in an activity-dependent manner [183–185]. In the microglia, the expression of CB2 receptor exceeds the expression of CB1 receptors and correlates with microglial phenotype and activity [186]. Activation of glial CB2 receptors attenuates glial activation [187] and prevents neurodegeneration and reduces symptoms in mouse model of Huntington's disease [188]. These data suggest that cannabinoids regulate glial activity primarily through CB2 receptors. Glial cells not only receive cannabinoid signals but can themselves produce cannabinoids such as anandamide [189], 2-AG [190] and palmitoylethanolamide [191], and also express the enzymes involved in the synthesis and degradation of endocannabinoids [192–194]. Because both neurons and glia express elements of the cannabinoid system, it was hypothesized that the cannabinoid system plays an important role in neuron–glia communication. In support of this hypothesis, it was shown that cannabinoids modulate glial activity by directly binding to the glial cannabinoid receptors [185,195,196] and indirectly by modulating neuronal activities [197]. During central nervous system inflammation, as in multiple sclerosis [195], AD [198] or HIV encephalitis [199], a general upregulation of cannabinoid system activity is observed. Increased activity of the cannabinoid system is generally anti-inflammatory: elevation of anandamide levels [200,201] or activation of the cannabinoid receptor by synthetic receptor agonists [202,203] inhibits the production of pro-inflammatory mediators and reduces microglial migration in vitro. This effect may contribute to the beneficial effect of the cannabinoid system against neurodegeneration [204]. On the other hand, increased 2-AG levels increase inhibitory signalling and impair the control of retrograde neurotransmission thus contributing to the synaptic impairments in AD [198]."…

-Andras Bilkei-Gorzo

-Institute of Molecular Psychiatry, University of Bonn, Bonn 53127, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481530

Migraine

Role of the Cannabinoid System in Pain Control and Therapeutic Implications for the Management of Acute and Chronic Pain Episodes

"Migraine is defined as vasomotor headache characterised by its pulsatile nature, the presentation of crises, and its periodic occurrence. It is usually hemicraneal and accompanied by generalised sensorial hyperestesia, sensitivity to light and noise, and nausea and/or vomiting. Ergot alkaloids and 5-HT1D serotonin receptor agonists are used for its treatment. NSAIDs, codeine, and caffeine are also generally used. Historically, cannabis was prescribed for its management in the early 20th century. At present, the antimigraine properties of cannabis have been recognised [137] and there are studies that affirm that the pain relief it produces is comparable, or better than, that achieved with ergotamine and aspirin [112]. The most effective route of administration is by inhalation because of its rapid action. The antiemetic and vasodilator properties of cannabinoid compounds are additional benefits that support its use as an alternative medication in migraine refractory to conventional therapy."

-Instituto de Neurociencias de Alicante, Universidad Miguel Hernandez-Consejo Superior de Investigaciones Cientificas, Apartado de correos 18, Sant Joan d'Alacant, Spain

-Servicio de Anestesiologia y Reanimacion, Hospital Universitario 12 de Octubre, Avda. Cordoba s/n, Madrid, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2430692/

Molecular mechanisms of omega-3 fatty acids in the migraine headache

"Migraine is a common chronic inflammatory neurological disease with the progressive and episodic course. Much evidence have shown a role of inflammation in the pathogenesis of migraine. Omega-3 fatty acids are an important components of cell membranes phospholipids. The intake of these fatty acids is related to decrease concentration of C-reactive protein (CRP), proinflammatory eicosanoids, cytokines, chemokines and other inflammation biomarkers. Many of clinical trials have shown the beneficial effect of dietary supplementation with omega-3 fatty acids in inflammatory and autoimmune diseases in human, including Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), multiple sclerosis (MS) and migraine headaches. Therefore, omega-3 fatty acids as an alternative therapy can be potentially important. This review focuses on the pathogenesis of a migraine, with an emphasis on the role of omega-3 fatty acid and its molecular mechanisms."

-Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

-Iranian Centre of Neurological Research, Neuroscience institute, Department of Neurology, Imam Khomeini Hospital,

Tehran University of Medical Sciences, Tehran, Iran

-Headache Department, Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

-Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5937007/

■■■

"....Psilocybin is structurally related to migraine medications, and case studies suggest that psilocybin may be efficacious in treatment of cluster headache,"...

-Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences

-Yale University School of Medicine, Department of Psychiatry

-VA Connecticut Healthcare System

-Johns Hopkins University School of Medicine, Department of Neuroscience

https://www.ncbi.nlm.nih.gov/pubmed/22129843

Mitochondrial Dysfunction

Mitochondrial Dysfunction and Multiple Sclerosis

“In recent years, several studies have examined the potential associations between mitochondrial dysfunction and neurodegenerative diseases such as multiple sclerosis (MS), Parkinson's disease and Alzheimer's disease. In MS, neurological disability results from inflammation, demyelination, and ultimately, axonal damage within the central nervous system. The sustained inflammatory phase of the disease leads to ion channel changes and chronic oxidative stress. Several independent investigations have demonstrated mitochondrial respiratory chain deficiency in MS, as well as abnormalities in mitochondrial transport. These processes create an energy imbalance and contribute to a parallel process of progressive neurodegeneration and irreversible disability. The potential roles of mitochondria in neurodegeneration are reviewed. An overview of mitochondrial diseases that may overlap with MS are also discussed, as well as possible therapeutic targets for the treatment of MS and other neurodegenerative conditions.”

-Department of Neurosciences, University of California San Diego, San Diego, CA

https://pubmed.ncbi.nlm.nih.gov/31083577

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…“Cannabinoid system activity influences the amount of intracellular ROS [reactive oxygen

species] not only via their anti-oxidant buffering capacity but also by regulating mitochondrial activity [175]. It has been recently shown that CB1 receptors are also present on mitochondrial membranes and regulate the activity of mitochondria [176]. Whether cannabinoids decrease or increase mitochondrial activity is not fully known: an early study showed that cannabinoids can decrease oxidative metabolism of isolated mitochondria [177], which was later supported by showing that CB1 agonists decrease oxygen consumption, ROS production, membrane potential [175] and oxidative phosphorylation [178]. On the other hand, an increase in brain mitochondrial oxidative phosphorylation was shown ex vivo in anandamide or Δ9-THC treated rats, which was antagonized by the CB1 receptor blocker SR141716A [179]. Under cellular stress, cannabinoids seems to be protective for the mitochondria: the cannabinoid receptor agonist CP55,940 and JWH-015 both attenuated mitochondrial damage against paraquat-induced oxidative stress [180] and the endogenous cannabinoid 2-AG decreased calcium-induced cytochrome c release from mitochondria [181].”…

-Andras Bilkei-Gorzo

-Institute of Molecular Psychiatry, University of Bonn, Bonn 53127, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481530

See also Neurodegenerative Diseases & Disorders , Neuroinflammatory Diseases

Monoacylglycerol Lipase (MAGL or MGL)

…“2-AG is a full agonist towards the cannabinoid receptor type 1 (CB1) and its signaling is terminated primarily by monoacylglycerol lipase (MAGL). “…

-Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy and Management, 115 Wellman Hall, University of California, Berkeley, California, USA

-Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, Virginia, USA

-Department of Anatomy and Cell Biology, Temple University, Philadelphia, Pennsylvania, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2593629/

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”eCBs [endocannabinoids] after their actions are rapidly eliminated by cellular uptake and enzymatic hydrolysis. To this regard, AEA [anandamide] is mainly inactivated by fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996; Dinh et al., 2002), whereas 2-AG [2-arachidonoylglycerol] is predominantly catalyzed by monoacylglycerol lipase (Dinh et al., 2002).”…

-Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy

-Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy
-Laboratory of Virology, The Regina Elena National Cancer Institute, IRCCS, Rome, Italy
-Edited by: Marialessandra Contino, University of Bari Aldo Moro, Italy
-Reviewed by: Luigi Bubacco, University of Padua, Italy; Kevin Donald Broad, UCL Institute for Women's Health, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5288380/

See also Fatty Acid Amide Hydrolase (FAAH)

Monoamine Oxidase & Natural Inhibitors

Monoamine oxidase Inhibitors are commonly refereed to as MAOIs.

"Monoamine oxidase is a type of enzyme that helps neurons fire throughout your body. It's formed in your liver and cleans up neurotransmitters in your brain once they've done their jobs. Besides neurotransmitters, monoamine oxidase cleans out tyramine, a chemical that helps regulate blood pressure."
- HealthLine (Medically reviewed by Alan Carter, PharmD)
https://www.healthline.com/health/depression/what-are-mao-inhibitors

Inhibition of monoamine oxidase activity by cannabinoids.

"Brain monoamines are involved in many of the same processes affected by neuropsychiatric disorders and psychotropic drugs, including cannabinoids. This study investigated in vitro effects of cannabinoids on the activity of monoamine oxidase (MAO), the enzyme responsible for metabolism of monoamine neurotransmitters and affecting brain development and function. The effects of the phytocannabinoid Delta(9)-tetrahydrocannabinol (THC), the endocannabinoid anandamide (N-arachidonoylethanolamide [AEA]), and the synthetic cannabinoid receptor agonist WIN 55,212-2 (WIN) on the activity of MAO were measured in a crude mitochondrial fraction isolated from pig brain cortex. Monoamine oxidase activity was inhibited by the cannabinoids; however, higher half maximal inhibitory concentrations (IC(50)) of cannabinoids were required compared to the known MAO inhibitor iproniazid. The IC(50) was 24.7 micromol/l for THC, 751 micromol/l for AEA, and 17.9 micromol/l for WIN when serotonin was used as substrate (MAO-A), and 22.6 micromol/l for THC, 1,668 micromol/l for AEA, and 21.2 micromol/l for WIN when phenylethylamine was used as substrate (MAO-B). The inhibition of MAOs by THC was noncompetitive. N-Arachidonoylethanolamide was a competitive inhibitor of MAO-A and a noncompetitive inhibitor of MAO-B. WIN was a noncompetitive inhibitor of MAO-A and an uncompetitive inhibitor of MAO-B. Monoamine oxidase activity is affected by cannabinoids at

relatively high drug concentrations, and this effect is inhibitory. Decrease of MAO activity may play a role in some effects of cannabinoids on serotonergic, noradrenergic, and dopaminergic neurotransmission."

Behavioral and Pharmacokinetic Interactions Between Monoamine Oxidase Inhibitors and the Hallucinogen 5-Methoxy-N,N-dimethyltryptamine

"Monoamine oxidase inhibitors (MAOIs) are often ingested together with tryptamine hallucinogens, but relatively little is known about the consequences of their combined use. We have shown previously that monoamine oxidase-A (MAO-A) inhibitors alter the locomotor profile of the hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in rats, and enhance its interaction with 5-HT2A receptors."

…"The present results confirm that 5-MeO-DMT can disrupt PPI by activating 5-HT2A, and indicate that MAOIs alter 5-MeO-DMT pharmacodynamics by increasing its accumulation in the central nervous system."

-Department of Psychiatry, University of California San Diego, La Jolla, CA
-Research Service, VA San Diego Healthcare System, San Diego, CA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5403252/

Peganum harmala L (Syrian Rue), is a seed which has many reported uses in research worldwide. It is a natural Monomine Oxidase Inhibitor (MAOI). This seed goes by many names due to its contents, and region it is found: such as Syrian Rue, Harmine, Harmalin, wild syrian rue. The plant is from the Zygophyllaceae family. *(Ref. Below)*

Pharmacological and therapeutic effects of Peganum harmala and its main alkaloids

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3841998/

…"Another study indicates that the action of harmaline on the prostacyclin pathway also plays a role in its vasoleraxant activity.[12] It has been also shown that harmaline, harmalol and harmine decrease systemic arterial blood pressure and total peripheral vascular resistance obviously not due to activation of cholinergic, beta-adrenergic and histamine (H1) receptors. The harmaline-

evoked decreases were frequently followed by a secondary increase and these two effects of harmalol were inconsistent.[10] Astulla et al. also showed in an in vitro study the vasorelaxant activity of vasicinone, another alkaloid isolated from the seeds of P. harmala, against phenylephrine-induced contraction of isolated rat aorta.[16]”..

-Department of Pharmacology, Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran

-Veterinary Medicine, Faculty of Agriculture and Veterinary, Shabestar Branch, Islamic Azad University, Shabestar, Iran

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3841998

Peganum harmala L.’s anti-growth effect on a breast cancer cell line

…"P. harmala L.’s [syrian rue] seed extract induced cell death and decreased the cell growth in the breast cancer cell line. The cell death was caused by apoptosis which was triggered by both intrinsic and extrinsic pathways which suggest that herb might be useful for preventing the development of tumors."

-National Institute of Genetic Engineering and Biotechnology, Tehran, Iran

-Dipartimenti di Sienze Agraria, Universita degli Studi di Udine, Udine, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4980734/

Monosodium Glutamate (MSG)

Monosodium glutamate (MSG): a villain and promoter of liver inflammation and dysplasia

"Chronic inflammation is a common theme in a variety of disease pathways, including autoimmune diseases”….

“We previously reported that injection of monosodium glutamate (MSG) in ICR mice leads to the development of significant inflammation, central obesity, and type 2 diabetes." .... "These results take on considerable significance in light of the widespread usage of dietary MSG and we suggest that MSG should have its safety profile re-examined and be potentially withdrawn from the food chain."

-Department of Diagnostic Pathology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan.

https://www.ncbi.nlm.nih.gov/pubmed/18178378

Mood Disorders

Omega-6 to omega-3 polyunsaturated fatty acid ratio and subsequent mood disorders in young people with at-risk mental states: a 7-year longitudinal study.

"While cross-sectional studies suggest that patients with mood disorders have a higher ratio of omega-6 to omega-3 polyunsaturated fatty acids (PUFAs) and lower levels of omega-3 PUFAs, it is unknown if a high n-6/3 ratio indicates vulnerability for depression. We tested this hypothesis in a 7-year follow-up study of young individuals with an ultra-high risk (UHR) phenotype. We conducted a secondary analysis of the Vienna omega-3 study, a longitudinal study of omega-3 PUFAs in individuals at UHR for psychosis (n=69)."

…" This association remained significant after adjustment for age, gender, smoking, severity of depressive symptoms at baseline and n-3 supplementation. Consistent results were obtained for individual PUFAs, including lower levels of eicosapentaenoic acid and docosahexaenoic acid. The predictive capacity of these findings was specific to mood disorders as no associations were found for any other psychiatric disorder. To our knowledge, our data provide the first prospective evidence that the n-6/3 PUFA ratio is associated with an increased risk for mood disorders in young people exhibiting an UHR phenotype. These findings may have important implications for treatment and risk stratification beyond clinical characteristics."

-Laboratory of Psychiatric Neuroscience, Australian Institute of Tropical Health and Medicine, Townsville, QLD, Australia.

-College of Public Health, Medical and Veterinary Science, James Cook University, Townsville, QLD, Australia.

-Orygen, The National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, The University of Melbourne, Melbourne, VIC, Australia.

-Department of Psychiatry, University Hospital Jena, Jena, Germany.

-Department of Psychiatry, Chonnam National University Medical School, Gwangju, Korea.

-Department of Child and Adolescent Psychiatry, Medical University Vienna, Vienna, Austria.

-IMPACT Strategic Research Centre, School of Medicine, Deakin University, Barwon Health, Geelong, VIC, Australia.

-Florey Institute for Neuroscience and Mental Health, Parkville, VIC, Australia.

-Department of Psychiatry, The University of Melbourne, Melbourne, VIC, Australia.

https://www.ncbi.nlm.nih.gov/pubmed/28850110

MRSA Super bug

"Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium that causes infections in

different parts of the body. It's tougher to treat than most strains of staphylococcus aureus -- or staph -- because it's resistant to some commonly used antibiotics. The symptoms of MRSA depend on where you're infected."

- WebMD
https://www.webmd.com/skin-problems-and-treatments/understanding-mrsa

■■■

"In the present study, we investigated the antimicrobial activity of the endocannabinoid (EC) anandamide (AEA) and the endocannabinoid-like (EC-like), arachidonoyl serine (AraS) against methicillin resistant S. aureus strains (MRSA). We observed a strong inhibition of biofilm formation of all tested MRSA strains as well as a notable reduction of metabolic activity of pre-formed MRSA biofilms by both agents. Moreover, staphylococcal biofilm-associated virulence determinants such as hydrophobicity, cell aggregation and spreading ability were altered by AEA and AraS. In addition, the agents were able to modify bacterial membrane potential. Importantly, both compounds prevent biofilm formation by altering the surface of the cell without killing the bacteria. Therefore, we propose that EC and EC-like compounds may act as a natural line of defence against MRSA or other antibiotic resistant bacteria. Due to their anti biofilm action these agents could also be a promising alternative to antibiotic therapeutics against biofilm-associated MRSA infections."

-Biofilm Research Laboratory, Institute of Dental Sciences, Faculty of Dental Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
-The Institute for Drug Research, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6283871/

Antibacterial cannabinoids from Cannabis sativa: a structure-activity study.

"Marijuana (Cannabis sativa) has long been known to contain antibacterial cannabinoids, whose potential to address antibiotic resistance has not yet been investigated. All five major cannabinoids (cannabidiol (1b), cannabichromene (2), cannabigerol (3b), Delta (9)-tetrahydrocannabinol (4b), and cannabinol (5)) showed potent activity against a variety of methicillin-resistant Staphylococcus aureus (MRSA) strains of current clinical relevance."…

-Department of Chemical, Food, Pharmaceutical and Pharmacological Sciences,University of Eastern Piedmont, Novara, Italy.
https://pubs.acs.org/doi/abs/10.1021/np8002673

MSG (Monosodium glutamate)

See Chronic Inflammation

Multiple Chemical Sensitivity (MCS)

"Systematic bibliography analysis of about the last 17 years on multiple chemical sensitivity (MCS) was carried out in order to detect new diagnostic and epidemiological evidence. The MCS is a complex syndrome that manifests as a result of exposure to a low level of various common contaminants. The etiology, diagnosis, and treatment are still debated among researchers."....

"From the symptoms point of view, some industrial experts have compiled the following nonexhaustive example of evolutive framework of the syndrome, presented in Italy in Bill N 1922[15]:"

"**Stage 0** - Tolerance: in this stage, the individual is normally able to adapt to the environment that surrounds him, unless limits for certain hazardous substances are exceeded.

Stage 1 - Sensitization: this stage could be experienced as a result of chronic exposure to low doses and/or after individual acute exposures. The patient may complain of the following disorders: dermal, ocular and respiratory tract irritation, itching, fatigue, muscle and joint pain, headache, nausea, tachycardia, changes in blood pressure, balance problems, sensations of cold or fever, dyspnea, cognitive problems and asthma, insufficient peripheral circulation, immune disorders and gastrointestinal diseases, etc.

Stage 2 – Inflammation: chronic inflammation in load of different tissues, organs, and systems. Various disorders development, detectable through specialist examination: dermatitis, vasculitis, immune, endocrine, metabolic diseases, food and environmental allergies (dust, pollen, etc), arthritis, colitis, rhinitis, dyspnea, asthma, muscle fatigue, fainting, cognitive delays, poor peripheral circulation, bleeding, etc. The persistence and aggravation of this stage depends on the exposures, their avoidance, and undergo therapy. After an exposure, symptoms may persist and oscillate for days, if not weeks.

Stage 3 - Deterioration: chronic inflammation produces damage to tissues and organs. CNS (central nervous system), kidneys, liver, lungs, immune system, circulatory, vascular, dermal are affected. Lupus, ischemia, heart failure, cancer, autoimmunity, neurodegenerative and psychiatric syndromes, hemorrhagic forms, porphyria are the most common diseases in this

stage.

Given that most of the chemicals implicated are common environmental pollutants, it is practically impossible to avoid them completely and therefore individuals who have the disease will be, depending on the stage reached, more vulnerable than the general population.

Moreover, given the diagnostic difficulty, in the early stages, it is possible that nor the doctors nor the patients find the causal link between the symptoms reported and the exposures. The MCS could therefore not be diagnosed as such and be confused with other diseases."…

-Department of Environment and Health, Istituto Superiore di Sanità, Rome, Italy.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5794238

Multiple Myeloma

"Multiple myeloma is a cancer that forms in a type of white blood cell called a plasma cell. Healthy plasma cells help you fight infections by making antibodies that recognize and attack germs. In multiple myeloma, cancerous plasma cells accumulate in the bone marrow and crowd out healthy blood cells."

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/multiple-myeloma/symptoms-causes/syc-20353378

Targeting Cannabinoid Receptor-2 Pathway by Phenylacetylamide Suppresses the Proliferation of Human Myeloma Cells Through Mitotic Dysregulation and Cytoskeleton Disruption

…"Despite the development of novel treatment approaches and high-dose therapies, MM [multiple myeloma] remains incurable. There is an urgent need, therefore, for the development of new therapeutic strategies for MM patients. Selective apoptosis induction has been widely accepted as an ideal way to eliminate cancer cells and could provide suitable targets for cancer treatment and prevention [23,36,37]. One of the most exciting and promising areas of current cannabinoid research is the ability of these compounds to control the cell survival/death decision [4,38]. In the present study, we found that the expression of CB2 receptor in MM cells was higher than that in other kinds of non-B cell cancers, which is consistent with the conclusion of dominantly expression of CB2 in plasma B cells [10,11,39]. This finding opens up a new avenue to develop a reasonable strategy to treat MM via the CB2 pathway."...

-Department of Pharmaceutical Sciences and Drug Discovery Institute, University of Pittsburgh, Pittsburgh, PA
-Department of Computational Biology, Joint Pitt/CMU Computational Biology Program, University of Pittsburgh, Pittsburgh, PA

-Division of Hematology/Oncology, Columbia University, NY
-Hematology/Oncology, Department of Medicine, Indiana University, Indianapolis, IN
-Hisun Institute, Zhejiang Hisun Pharmaceutical Co. Ltd., Taizhou, Zhejiang, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504841/

Multiple Sclerosis (MS)

Cannabinoids in health and disease

"Inflammation, autoimmune response, demyelination, and axonal damage are thought to participate in the pathogenesis of MS. Increasing evidence supports the idea of a beneficial effect of cannabinoid compounds for the treatment of this disease. In clinical trials, it has been shown that cannabis derivatives are active on the pain related to MS,[84,85,95,97,98] However, this is not the only positive effect of cannabinoids in this disease. In rat experimental autoimmune encephalomyelitis (EAE), a laboratory model of MS, THC, given once after disease onset, significantly reduced maximal EAE score. Reduction in the inflammatory response in the brain and spinal cord was also noted in animals treated with dexanabinol (HU-211 a nonpsychoactive synthetic cannabinoid).[101] In another trial in rats, all animals treated with placebo developed severe clinical EAE and more than 98% died, while THC-treated animals had either no clinical signs or mild signs, with delayed onset with survival greater than 95%.[102] WIN-55,212-2, another synthetic cannabinoid, also was found to ameliorate the clinical signs of EAE and to diminish cell infiltration of the spinal cord, partially through CB2.[103] Using a chronic model of MS in mice, it was shown that clinical signs and axonal damage in the spinal cord were reduced by the synthetic cannabinoid HU210.[104] To more fully inderstand the involvement of the endocannabinoid system in MS, the status of cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase (FAAH) enzyme in brain tissue samples obtained from MS patients was investigated. Selective glial expression of cannabinoid CB1 and CB2 receptors and FAAH enzyme was found to be induced in MS.[105] In mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), a chronic model of MS that reproduces many of the pathological hallmarks of the human disease, a moderate decrease in the density of CB1 receptors in the caudate-putamen, globus pallidus, and cerebellum was found. These observations may explain the efficacy of cannabinoid agonists in improving motor symptoms (spasticity, tremor, ataxia) typical of MS in both humans and animal models.[106] Spasticity is a common neurologic condition in patients with MS, stroke, cerebral palsy, or an injured spinal cord. Marijuana was suggested as treatment of muscle spasticity as early as the 1980s.[107] In an experiment in mice, control of spasticity in a MS model was found to be mediated by CB1, but not by CB2, cannabinoid

receptors.[108] In clinical trials, patients treated with THC had significant improvement in ratings of spasticity compared to placebo.[109] In one case report nabilone improved muscle spasms, nocturia, and general well-being.[110] In another case report, the chronic motor handicaps of an MS patient acutely improved while he smoked a marijuana cigarette.[111] THC significantly reduced spasticity by clinical measurement. Responses varied, but benefit was seen in patients with tonic spasms.[112] At a progressive stage of illness, oral and rectal THC reduced the spasticity, rigidity, and pain, resulting in improved active and passive mobility.[113] However, in other clinical trials, cannabinoids appeared to reduce tremor but were ineffective in spasticity.[114,115] Moreover, in one trial marijuana smoking further impaired posture and balance in patients with spastic MS.[116] The inconsistent effects noted might be due to dosedependency. Improved motor coordination was seen when patients with MS, seriously disabled with tremor and ataxia, were given oral THC.[117] In another study, cannabis extract did not produce a functionally significant improvement in MS-associated tremor.[118] Suppression of acquired pendular nystagmus (involuntary movement of the eyes) was seen in a patient with MS after smoking cannabis resin, but not after taking nabilone tablets or orally administered capsules containing cannabis oil.[119] There are also findings suggestive of a clinical effect of cannabis on urge incontinence episodes in patients with MS.[120] In the treatment of MS, as well as in pain reduction described earlier, there is a preferential effect of a THC+CBD combination (Sativex).[121] A mixture of 2.5 mg THC and 0.9 mg cannabidiol (CBD) lowered spasm frequency and increased mobility, with tolerable side effects, in MS patients with persistent spasticity not responding to other drugs.[122] Oromucosal sprays of Sativex significantly reduced spasticity scores in comparison with placebo.[123] Long-term use of Sativex maintains its effect in those patients who perceive initial benefit.[124] Zajicek et al originally reported that cannabinoids did not have a beneficial effect on spasticity; however, there was an objective improvement in mobility and some patients reported an improvement in pain.[125] Later the same group also found positive effects on muscle spasticity with prolonged treatment.[126] The subject has been thoroughly reviewed.[99,127,130]”

-Natalya M. Kogan MSc, Medicinal Chemistry and Natural Products Dept, Pharmacy School, Ein-Kerem Medical Campus, the Hebrew University of Jerusalem, Israel;

-Raphael Mechoulam PhD, Medicinal Chemistry and Natural Products Dept, Pharmacy School, Ein-Kerem Medical Campus, the Hebrew University of Jerusalem, Israel;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202504/

Cannabinoid and endocannabinoid system: a promising therapeutic intervention for multiple sclerosis

“Multiple sclerosis (MS) is a chronic and complex neurodegenerative disease, distinguished by

the presence of lesions in the central nervous system (CNS) due to exacerbated immunological responses that inflict oligodendrocytes and the myelin sheath of axons. In recent years, studies have focused on targeted therapeutics for MS that emphasize the role of G protein-coupled receptors (GPCRs), specifically cannabinoids receptors. Clinical studies have suggested the therapeutic potential of cannabinoids derived from Cannabis sativa in relieving pain, tremors and spasticity. Cannabinoids also appear to prevent exaggerated immune responses in CNS due to compromised blood-brain barrier. Both, endocannabinoid system (ECS) modulators and cannabinoid ligands actively promote oligodendrocyte survival by regulating signaling, migration and myelination of nerve cells. The cannabinoid receptors 1 (CB1) and 2 (CB2) of ECS are the main ones in focus for therapeutic intervention of MS. Various CB1/CB2 receptors agonists have been experimentally studied which showed anti-inflammatory properties and are considered to be effective as potential therapeutics for MS. In this review, we focused on the exacerbated immune attack on nerve cells and the role of the cannabinoids and its interaction with the ECS in CNS during MS pathology."

-Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan.

https://pubmed.ncbi.nlm.nih.gov/35182322/

The endocannabinoid system and multiple sclerosis

"Multiple sclerosis (MS) is a neurodegenerative disease that is characterised by repeated inflammatory/demyelinating events within the central nervous system (CNS). In addition to relapsing-remitting neurological insults, leading to loss of function, patients are often left with residual, troublesome symptoms such as spasticity and pain. These greatly diminish "quality of life" and have prompted some patients to self-medicate with and perceive benefit from cannabis. Recent advances in cannabinoid biology are beginning to support these anecdotal observations, notably the demonstration that spasticity is tonically regulated by the endogenous cannabinoid system. Recent clinical trials may indeed suggest that cannabis has some potential to relieve, pain, spasms and spasticity in MS. However, because the CB(1) cannabinoid receptor mediates both the positive and adverse effects of cannabis, therapy will invariably be associated with some unwanted, psychoactive effects. In an experimental model of MS, and in MS tissue, there are local perturbations of the endocannabinoid system in lesional areas. Stimulation of endocannabinoid activity in these areas either through increase of synthesis or inhibition of endocannabinoid degradation offers the positive therapeutic potential of the cannabinoid system whilst limiting adverse events by locally targeting the lesion. In addition, CB(1) and CB(2) cannabinoid receptor stimulation may also have anti-inflammatory and neuroprotective

potential as the endocannabinoid system controls the level of neurodegeneration that occurs as a result of the inflammatory insults. Therefore cannabinoids may not only offer symptom control but may also slow the neurodegenerative disease progression that ultimately leads to the accumulation of disability."

-Neuroimmunology Unit, Neuroscience Centre, Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, London UK.
https://pubmed.ncbi.nlm.nih.gov/18781983/

The endocannabinoid system as a target for the treatment of neurodegenerative disease

"Multiple sclerosis (MS) is an inflammatory CNS disease which in contrast to the other neurodegenerative disorders reviewed here, presents most frequently in early adulthood (Liguori et al., 2000). The CNS infiltration of autoreactive T cells, with specificity for myelin or other CNS proteins, is followed by their clonal expansion. Other immune mediators are recruited, including B cells and microglia, and together with T cells differentiated into 'cytotoxic' effectors, cause demyelination of neurons of the brain and spinal cord (Friese and Fugger, 2005). This is particularly catastrophic for motor and sensory function, and symptoms of MS include spasticity, hyperreflexia, pain and sensory disturbance (Noseworthy et al., 2000). Focal inflammatory lesions or 'plaques' in the white matter are characterized by clusters of immune cells causing axonal demyelination and destruction, death of oligodendrocytes and bystander neurons, and a sclerotic astroglial 'scar' (Frohman et al., 2006)."

…"Interestingly, an up-regulation of CB1 and CB2 levels has also been detected in blood sampled from primary progressive MS patients, suggesting that peripheral immune regulation of the endocannabinoid system paralleled that occurring in the human brain (Jean-Gilles et al., 2009)."

…"All three of these studies suggest a relationship between disease state and the regulation of endocannabinoid levels, and demonstrate induction of the endocannabinoid system by inflammatory cues or neuronal activity. FAAH, which is expressed by macrophages (Di Marzo et al., 1999; Di Marzo et al. 1998), platelets (Maccarrone et al., 2000) and mast cells (Maccarrone et al., 2000) in blood, showed decreased expression in secondary progressive MS and trended towards a decrease in relapsing-remitting and primary progressive MS patient blood (Jean-Gilles et al., 2009). Decreased expression of the inactivating enzyme FAAH may underpin the elevations in AEA detected in human blood and CSF described earlier."

-Centre for Brain Research and Department of Pharmacology, University of Auckland, Auckland, New Zealand
-Department of Anatomy and Cell Biology, Centre foators may hr Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931550/

Glial Cell: A Potential Target for Cellular and Drug Based Therapy in Various CNS Diseases.

…"Oligodendrocytes myelinate the neuronal axons for proper transmission of nerve impulse and microglia are brain immune cells. Multiple sclerosis is a prototype glia mediated disease that manifests demyelination. Fingolimod is already being marketed for this disease, while guanabenz and ibudilast are facing clinical trials."…

-Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University, New Delhi. India.
-Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh. India.
https://www.ncbi.nlm.nih.gov/pubmed/28302022

Peripheral nerve involvement in multiple sclerosis: Demonstration by magnetic resonance neurography.

"Peripheral nerve lesions could be visualized and quantified in MS in vivo by high-resolution MRN. Lesions are defined by an increase of proton spin density and a decrease of T2 relaxation time, indicating changes in the microstructural organization of the extracellular matrix in peripheral nerve tissue in MS. By showing involvement of the peripheral nervous system in MS, this proof-of-concept study may offer new insights into the pathophysiology and treatment of MS."

-Department of Neuroradiology, Heidelberg University Hospital, Heidelberg, Germany.
-Department of Radiology, Hannover Medical School, Hannover, Germany.
-Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany.
-Division of Experimental Radiology, Department of Neuroradiology, Heidelberg, Germany.
-Department of Neurology, University of Michigan, Ann Arbor, MI.
-Department of Neuroradiology, Würzburg University Hospital, Würzburg, Germany.
https://www.ncbi.nlm.nih.gov/pubmed/29023976

The endocannabinoid system is dysregulated in multiple sclerosis and in experimental autoimmune encephalomyelitis

"The ability of cannabinoids to modulate both inflammatory and degenerative neuronal damage prompted investigations on the potential benefits of such compounds in multiple sclerosis (MS)and in animal models of this disorder. Here we measured endocannabinoid levels, metabolism and binding, and physiological activities in 26 patients with MS (17 females, aged 19-43 years),25 healthy controls and in mice with experimental autoimmune encephalomyelitis

(EAE), a preclinical model of MS. Our results show that MS and EAE are associated with significant alterations of the endocannabinoid system. We found that anandamide (AEA),but not 2-arachidonoylglycerol (2-AG), was increased in the CSF of relapsing MS patients. AEA concentrations were also higher in peripheral lymphocytes of these patients, an effect associated with increased synthesis and reduced degradation of this endocannabinoid. Increased synthesis, reduced degradation, and increased levels of AEA were also detected in the brains of EAE mice in the acute phase of the disease, possibly accounting for its anti-excitotoxicaction in this disorder. Accordingly, neurophysiological recordings from single neurons confirmed that excitatory transmission in EAE slices is inhibited by CB1 receptor activation, while inhibitory transmission is not. Our study suggests that targeting the endocannabinoid system might be useful for the treatment of MS."

-Neurological Clinic, Department of Neurosciences, Tor Vergata University, Rome, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/17626034

The use of cannabinoids in multiple sclerosis

"Naturally occurring cannabinoids including Delta9-tetrahydrocannabinol and cannabidiol as well as endocannabinoids and synthetic cannabinoids may have a role in modulating experimental models of multiple sclerosis. Recent clinical studies to treat symptoms of multiple sclerosis have shown varying results, which may reflect issues relating to the way in which such studies were conducted. There is now increasing interest in the potential role of cannabinoids not only in symptom relief, but also for their possible neuroprotective actions."

-Neurology Research Group, Peninsula Medical School,UK
https://pubmed.ncbi.nlm.nih.gov/16022575/

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…"Additionally, fingolimod can inhibit phospholipase A2 (PLA2) activity in mast cells and therefore prostaglandin and thromboxane secretion (Payne et al., 2007). This could contribute to the therapeutic effect of fingolimod in MS, as PLA2 has been shown to be highly expressed in EAE plaques (Kalyvas and David, 2004) and arachidonic acid [omega-6] is increased in cerebrospinal fluid of MS patients (Dore-Duffy et al., 1991)."…

-Cerebrovascular Research Group, Department of Neurology, Frankfurt University Hospital, Frankfurt am Main, Germany
-Institute of General Pharmacology and Toxicology, pharmazentrum frankfurt, Goethe University Frankfurt, Frankfurt am Main, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4162362

Neuroregenerative potential of lion's mane mushroom, Hericium erinaceus (Bull.: Fr.) Pers. (higher Basidiomycetes), in the treatment of peripheral nerve injury (review).

…"Therefore, daily oral administration of H. erinaceus [lion's mane mushroom] could promote the regeneration of injured rat peroneal nerve in the early stage of recovery."

-Department of Anatomy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
https://www.ncbi.nlm.nih.gov/pubmed/23510212

Omega-3 fatty acid supplementation decreases matrix metalloproteinase-9 production in relapsing-remitting multiple sclerosis

"The primary objective was to evaluate the effect of omega-3 fatty acids (omega-3 FA) on matrix metalloproteinase-9 (MMP-9) production by immune cells in multiple sclerosis (MS). Quality of life, fatty acid levels, and safety were also evaluated."

…"Immune cell secretion of MMP-9 decreased by 58% after 3-months of omega-3 FA supplementation when compared to baseline levels ($p < 0.01$). This effect was coupled with a significant increase in omega-3 FA levels in red blood cell membranes."

…"Omega-3 FA significantly decreased MMP-9 levels in RRMS and may act as immune-modulator that has potential therapeutic benefit in MS patients."…

-Department of Neurology, Oregon Health & Science University, Portland, OR, 97239, USA
-Department of Veterans Affairs Medical Center, Portland, OR, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2692605/

Neuroprotective agents: cannabinoids

"Chronic inflammation and neurodegeneration are the main pathological traits of multiple sclerosis that coexist in all stages of the disease course, with complex and still nonclarified relationships. Currently licensed medications have efficacy to control aspects related to inflammation, but have been unable to modify pure progression. Experimental work has provided robust evidence of the immunomodulatory and neuroprotective properties that cannabinoids exert in animal models of multiple sclerosis. Through activation of the CB2

receptor, cannabinoids modulate peripheral blood lymphocytes, interfere with migration across the blood-brain barrier and control microglial/macrophage activation. CB1 receptors present in neural cells have a fundamental role in direct neuroprotection against several insults, mainly excitotoxicity. In multiple sclerosis, several reports have documented the disturbance of the endocannabinoid system. Considering the actions demonstrated experimentally, cannabinoids might be promising agents to target the main aspects of the human disease."

-Neuroimmunology Laboratory and Neurology Service, Hospital Universitario Puerta de Hierro, Majadahonda,Universidad Autónoma de Madrid, Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/21420365

Abnormalities in the cerebrospinal fluid levels of endocannabinoids in multiple sclerosis

"Objective: Endocannabinoids (eCBs) play a role in the modulation of neuroinflammation, and experimental findings suggest that they may be directly involved in the pathogenesis of multiple sclerosis (MS). The objective of our study was to measure eCB levels in the cerebrospinal fluid (CSF) of patients with MS."...

"Results: Significantly reduced levels of all the tested eCBs were found in the CSF of patients with MS compared to control subjects, with lower values detected in the SP MS group. Higher levels of AEA and PEA, although below those of controls, were found in the CSF of RR MS patients during a relapse. Higher levels of AEA, 2-AG and OEA were found in patients with MRI gadolinium-enhancing (Gd+) lesions.

Discussion: The present findings suggest the presence of an impaired eCB system in MS. Increased CSF levels of AEA during relapses or in RR patients with Gd+ lesions suggest its potential role in limiting the ongoing inflammatory process with potential neuroprotective implications. These findings provide further support for the development of drugs targeting eCBs as a potential pharmacological strategy to reduce the symptoms and slow disease progression in MS."

-Centre for Study of Demyelinating Diseases, Department of Medical and Surgical Specialities and Public Health, Ospedale S Maria della Misericordia, University of Perugia, Perugia, Italy.

https://pubmed.ncbi.nlm.nih.gov/18535023

Role of cannabinoids in multiple sclerosis

"Although extracts from the cannabis plant have been used medicinally for thousands of years, it is only within the last 2 decades that our understanding of cannabinoid physiology and the

provision of evidence for therapeutic benefit of cannabinoids has begun to accumulate. This review provides a background to advances in our understanding of cannabinoid receptors and the endocannabinoid system, and then considers how cannabinoids may help in the management of multiple sclerosis (MS). The relative paucity of treatments for MS-related symptoms has led to experimentation by patients with MS in a number of areas including the use of cannabis extracts. An increasing amount of evidence is now emerging to confirm anecdotal reports of symptomatic improvement, particularly for muscle stiffness and spasms, neuropathic pain and sleep and bladder disturbance, in patients with MS treated with cannabinoids. Trials evaluating a role in treating other symptoms such as tremor and nystagmus have not demonstrated any beneficial effects of cannabinoids. Safety profiles of cannabinoids seem acceptable, although a slow prolonged period of titration improves tolerability. No serious safety concerns have emerged. Methodological issues in trial design and treatment delivery are now being addressed. In addition, recent experimental evidence is beginning to suggest an effect of cannabinoids on more fundamental processes important in MS, with evidence of anti-inflammation, encouragement of remyelination and neuroprotection. Trials are currently under way to test whether cannabinoids may have a longer term role in reducing disability and progression in MS, in addition to symptom amelioration, where indications are being established."

-Clinical Neurology Research Group, Peninsula College of Medicine and Dentistry, Plymouth, UK.

https://pubmed.ncbi.nlm.nih.gov/21323391/

News about therapeutic use of Cannabis and endocannabinoid system

"Growing basic research in recent years led to the discovery of the endocannabinoid system with a central role in neurobiology. New evidence suggests a therapeutic potential of cannabinoids in cancer chemotherapy-induced nausea and vomiting as well as in pain, spasticity and other symptoms in multiple sclerosis and movement disorders. Results of large randomized clinical trials of oral and sublingual Cannabis extracts will be known soon and there will be definitive answers to whether Cannabis has any therapeutic potential. Although the immediate future may lie in plant-based medicines, new targets for cannabinoid therapy focuses on the development of endocannabinoid degradation inhibitors which may offer site selectivity not afforded by cannabinoid receptor agonists."

-Catalan Institute of Pharmacology Foundation, Vall d'Hebron Hospital, Autonomous University of Barcelona, Barcelona

https://pubmed.ncbi.nlm.nih.gov/15033046/

Towards cannabis and cannabinoid treatment of multiple sclerosis

"Multiple sclerosis is a common human demyelinating disease of the central nervous system (CNS), and it is thought to involve autoimmune responses to CNS myelin antigens. Current symptomatic therapies for multiple sclerosis are in some cases ineffective and may have a high risk of serious side effects. This has led some multiple sclerosis patients to self-medicate with cannabis, which anecdotal evidence suggests may be beneficial in controlling symptoms such as spasticity, pain, tremor and bladder dysfunction. In support of these claims, results from experimental studies have suggested that cannabinoid-based treatments may be beneficial in a wide number of diseases. Furthermore, recent research in animal models of multiple sclerosis has demonstrated the efficacy of cannabinoids in controlling disease-induced symptoms such as spasticity and tremor, as well as in ameliorating the severity of clinical disease. However, these initially promising results have not yet been fully translated into the clinic. Although cannabinoid treatment of multiple sclerosis symptoms has been shown to be both well tolerated and effective in a number of subjective tests in several small-scale clinical trials, objective measures demonstrating the efficacy of cannabinoids are still lacking. Currently, a number of large-scale phase III clinical trials are under way to further elucidate the use of cannabinoids in the symptomatic treatment of multiple sclerosis. This review highlights the recent advances in our understanding of the endocannabinoid system, discusses both the experimental and clinical evidence for the use of cannabinoids to treat multiple sclerosis and explores possible future strategies of cannabinoid therapy in multiple sclerosis."

-Department of Microbiology and Immunology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, USA.

https://pubmed.ncbi.nlm.nih.gov/15510238/

Cannabinoid signaling in glial cells

"The cannabinoid signaling system is composed of cannabinoid (CB) receptors, their endogenous ligands, the endocannabinoids, and the enzymes that produce and inactivate them. It is well known that neurons communicate between each other through this signaling system. Delta 9-tetrahydrocannabinol, the main psychoactive compound of marijuana, interacts with CB receptors, impinging on this communication and inducing profound behavioral effects such as memory impairment and analgesia. Recent evidence suggests that glial cells also express components of the cannabinoid signaling system and marijuana-derived compounds act at CB receptors expressed by glial cells, affecting their functions. This review summarizes this evidence, discusses how glial cells might use the cannabinoid signaling system to communicate with neighboring cells, and argues that nonpsychotropic cannabinoids, both marijuana-derived and synthetic, likely constitute lead compounds for therapy aimed at reducing acute and chronic

neuroinflammation, such as occurs in multiple sclerosis."

-Department of Pharmacology, Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98195-7280

https://pubmed.ncbi.nlm.nih.gov/15390110/

Cannabinoid system and neuroinflammation: implications for multiple sclerosis

"There is a growing amount of evidence suggesting that cannabinoids may be neuroprotective in central nervous system inflammatory conditions. Advances in the understanding of the physiology and pharmacology of the cannabinoid system have potentiated the interest in cannabinoids as potential therapeutic targets. Here our aim was to update the actions of cannabinoids on immune system and glial cells and their implications on multiple sclerosis. We also show our results on the modulation of cytokines of the IL-12 family by cannabinoids in macrophages and brain microglia. We used murine primary cultures of macrophage and microglia activated by lipopolysaccharide/IFN-gamma and Theiler's virus to study the effects of cannabinoids on the regulation of IL-12 and IL-23 mRNA and protein IL-12p40, evaluated by RT-PCR and ELISA, respectively. Cannabinoids negatively regulate the production of these cytokines by microglial cells in part due to the activation of CB(2) receptors. The effects of cannabinoids on cytokine brain work and on the regulation of neuroinflammatory processes may affect chronic inflammatory demyelinating diseases such as multiple sclerosis.

-Neuroimmunology Group, Functional and Systems Neurobiology Department, Instituto Cajal, Consejo Superior de Investigaciones Científicas, Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/18073512

Myocardial Infarction (MI)

"Myocardial infarction (MI) (ie, heart attack) is the irreversible death (necrosis) of heart muscle secondary to prolonged lack of oxygen supply (ischemia). Approximately 1.5 million cases of MI occur annually in the United States. See the images below."…

- Dr. A Maziar Zafari, MD, PhD, FACC, FAHA; Chief Editor: Dr. Eric H Yang, MD

-Medscape

https://emedicine.medscape.com/article/155919-overview

…"Studies using dietary fish consumption have found beneficial effects similar to those observed in studies with n-3 PUFA supplements. The United States Physicians' Health Study recruited male physicians with no prior history of MI, cerebrovascular disease or cancer to maintain a dietary record and allow follow-up for 11 years [9]. Sudden cardiac death was significantly reduced by consumption of at least one meal of fish weekly, while nonfatal MI levels were unchanged [10]. The Nurses' Health Study [11], which followed female nurses with no prior CVD or cancer for 16 years, identified a significant inverse relationship between fish consumption and CAD. Dietary ALA appeared to be the most protective PUFA [10]. Yuan et al [12] examined fish and shellfish consumption in Chinese men and found that the ingestion of over 200 g/week reduced fatal MI risk by 59% compared with those consuming less than 50 g/week. Secondary cardiovascular complications were greatly reduced by adopting a 'Mediterranean-style' diet in the Lyon Heart Study [13]. Analysis of the Finnish, Dutch and Italian cohorts of the Seven Countries Study [14] revealed an inverse relationship between fatty fish consumption and 20-year CAD mortality [15]."…

-National Centre for Agri-Food Research in Medicine and the Division of Stroke and Vascular Disease, St Boniface Hospital Research Centre

-Department of Physiology, Faculties of Medicine and Pharmacy, University of Manitoba, Winnipeg, Manitoba

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719153/

Myocardial Ischemia

"Myocardial ischemia occurs when blood flow to the heart muscle (myocardium) is obstructed by a partial or complete blockage of a coronary artery by a buildup of plaques (atherosclerosis). If the plaques rupture, you can have a heart attack (myocardial infarction)."

-Mayo Clinic

https://www.mayoclinic.org/diseases-conditions/myocardial-ischemia/symptoms-causes/syc-20375417

Cardiovascular pharmacology of cannabinoids.

"Cannabinoids and their synthetic and endogenous analogs affect a broad range of physiological functions, including cardiovascular variables, the most important component of their effect being profound hypotension. The mechanisms of the cardiovascular effects of cannabinoids in vivo are complex and may involve modulation of autonomic outflow in both the central and peripheral nervous systems as well as direct effects on the myocardium and vasculature. Although several lines of evidence indicate that the cardiovascular depressive effects of cannabinoids are mediated by peripherally localized CB1 receptors, recent studies provide strong

support for the existence of as-yet-undefined endothelial and cardiac receptor(s) that mediate certain endocannabinoid-induced cardiovascular effects. The endogenous cannabinoid system has been recently implicated in the mechanism of hypotension associated with hemorrhagic, endotoxic, and cardiogenic shock, and advanced liver cirrhosis. **Furthermore, cannabinoids have been considered as novel antihypertensive agents. A protective role of endocannabinoids in myocardial ischemia has also been documented.**"

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda

https://www.ncbi.nlm.nih.gov/pubmed/16596789

Myopia

"Nearsightedness, or myopia, as it is medically termed, is a vision condition in which people can see close objects clearly, but objects farther away appear blurred. People with myopia can have difficulty clearly seeing a movie or TV screen, a whiteboard in school or while driving."

-American Optometric Association

https://www.aoa.org/patients-and-public/eye-and-vision-problems/glossary-of-eye-and-vision-conditions/myopia

See: Retina

N

N-Acetylcysteine (NAC)

…"N-Acetylcysteine (NAC) has been reported to protect the kidney from injury induced by contrast media, ischemia, and toxins. In all these studies, glomerular filtration rate (GFR) is the surrogate marker of kidney injury and serum creatinine changes are the measured metric of GFR."…

-Division of Nephrology, Fletcher Allen Health Care
-University of Vermont, Burlington, Vermont;
-St. David's Hospital, Georgetown, Texas

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2572274

…"N-acetyl cysteine treats acetaminophen (Tylenol) poisoning by binding the poisonous forms of acetaminophen that are formed in the liver. It is also an antioxidant, so it may play a role in preventing cancer."

-*WebMD.com*
https://www.webmd.com/vitamins/ai/ingredientmono-1018/n-acetyl-cysteine-nac

"Impaired endothelial activity and/or cell death play a critical role in the development of vascular dysfunction associated with congestive heart failure, diabetic complications, hypertension, coronary artery disease and atherosclerosis. Increasing evidence suggests that cannabinoid 1 (CB1) receptor inhibition is beneficial in atherosclerosis and cardiovascular inflammation both in experimental models, as well as in humans. Here, we investigated the effects of CB1 receptor activation with the endocannabinoid anandamide (AEA) or synthetic agonist HU210 on cell death and interrelated signal transduction pathways in human primary coronary artery endothelial cells (HCAECs)."…

Key results:

…"The AEA- [anandamide] or HU210-induced cell death and MAPK activation were attenuated by CB1 antagonists [SR141716 (rimonabant) and AM281], inhibitors of p38 and JNK–MAPKs or the antioxidant the antioxidant N-acetylcysteine. N-acetylcysteine alone prevented AEA- or HU210-induced ROS generation, but only partially attenuated MAPK activation and cell death. In contrast, in combination with CB1 antagonists, N-acetylcysteine completely prevented these effects.

Conclusions and Implications

CB1 receptor activation in endothelial cells may amplify the ROS–MAPK activation–cell death pathway in pathological conditions when the endocannabinoid synthetic or metabolic pathways are dysregulated by excessive inflammation and/or oxidative/nitrosative stress, thereby contributing to the development of endothelial dysfunction and pathophysiology of multiple cardiovascular diseases."…

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

-Department of Surgery, University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ,

USA

-Department of Intensive Care Medicine, University Medical Center and Faculty of Biology and Medicine, Lausanne, Switzerland

-Gill Center and the Department of Psychological & Brain Sciences, Indiana University, Bloomington, IN, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931568

■■■

…"In addition to promising preclinical findings, NAC also has a favorable safety profile. NAC is approved by the US Food and Drug Administration (FDA) as a mucolytic agent for bronchopulmonary disorders [44] and as an oral or intravenous antidote to treat acetaminophen poisoning [45]. NAC is also available as an inexpensive over-the-counter product commonly sold as a nutritional supplement. Preliminary clinical studies have suggested efficacy for NAC as a pharmacotherapuetic agent for several psychiatric disorders, including compulsive disorders and SUDs [46, 47]. "…

-Medical University of South Carolina School of Medicine, United States

-Addiction Sciences Division, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, United States

-Yale University School of Medicine, United States

-Center for the Clinical Trials Network, National Institute on Drug Abuse, United States

-The EMMES Corporation, Rockville, MD, United States

-Johns Hopkins University, School of Medicine, 5510 Nathan Shock Dr., Baltimore, MD, United States

-Columbia University/New York State Psychiatric Institute, New York, NY 10032, United States

-Division of Alcohol and Drug Abuse, McLean Hospital, United States; Department of Psychiatry, Harvard Medical School, Boston, MA, United States

-University of California, David Geffen School of Medicine, United States

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252394

N-acetylcysteine exerts therapeutic action in a rat model of allergic rhinitis

"**Background**: The pathophysiologic mechanism of allergy is dependent on the action of many redox-sensitive proinflammatory mediators. However, even though redox disturbances are believed to be a hallmark of inflammation, little is known of the effect of redox imbalance to the pathophysiology of allergic rhinitis. We thus opted to investigate the relation of oxidative stress and allergic rhinitis, through the utilization of a potent antioxidant substance (N-acetylcysteine [NAC]) in a rat model of allergic rhinitis and the evaluation of its action on specific markers of inflammation.

Results: Intranasal OVA [ovalbumin sensitized] challenges lead to mucosal inflammation, induction of the mucosal expression of iNOS and COX-2 and elevation of TNF-α blood levels. NAC

significantly inhibited accumulation of inflammatory cells and downregulated iNOS expression and TNF-α serum levels. The role of COX-2 appeared to be 2-fold and its expression was divergently modulated by NAC.

Conclusion: Our findings suggest that redox balance is involved in the pathophysiology of allergic rhinitis in rats and that NAC can potentially suppress the allergen-induced nasal inflammatory cascade. The investigation of the role of oxidative stress in atopy could help in the evaluation of the therapeutic potential of antioxidant substances in allergic diseases."

-Laboratory of Experimental Physiology, School of Medicine, Aristotle University, Thessaloniki, Greece.
https://pubmed.ncbi.nlm.nih.gov/23307410

Inhibitory effects of N-acetylcysteine on the functional responses of human eosinophils in vitro

"Background: Oxidative stress appears to be relevant in the pathogenesis of inflammation in allergic diseases like bronchial asthma. Eosinophils are oxidant-sensitive cells considered as key effectors in allergic inflammation."...

"Conclusion: Inhibition by NAC of human eosinophil functions in vitro is potentially useful in the treatment of allergic inflammation."

-Department of Pharmacology, University of Valencia, Valencia, Spain.
https://pubmed.ncbi.nlm.nih.gov/17456219

Interactions between exosomes from breast cancer cells and primary mammary epithelial cells leads to generation of reactive oxygen species which induce DNA damage response, stabilization of p53 and autophagy in epithelial cells

"Exosomes are nanovesicles originating from multivesicular bodies and are released by all cell types. They contain proteins, lipids, microRNAs, mRNAs and DNA fragments, which act as mediators of intercellular communications by inducing phenotypic changes in recipient cells. Tumor-derived exosomes have been shown to play critical roles in different stages of tumor development and metastasis of almost all types of cancer. One of the ways by which exosomes affect tumorigenesis is to manipulate the tumor microenvironments to create tumor permissive "niches". Whether breast cancer cell secreted exosomes manipulate epithelial cells of the

mammary duct to facilitate tumor development is not known. To address whether and how breast cancer cell secreted exosomes manipulate ductal epithelial cells we studied the interactions between exosomes isolated from conditioned media of 3 different breast cancer cell lines (MDA-MB-231, T47DA18 and MCF7), representing three different types of breast carcinomas, and normal human primary mammary epithelial cells (HMECs). Our studies show that exosomes released by breast cancer cell lines are taken up by HMECs, resulting in the induction of reactive oxygen species (ROS) and autophagy. **Inhibition of ROS by N-acetyl-L-cysteine (NAC) led to abrogation of autophagy**. HMEC-exosome interactions also induced the phosphorylation of ATM, H2AX and Chk1 indicating the induction of DNA damage repair (DDR) responses. Under these conditions, phosphorylation of p53 at serine 15 was also observed. Both DDR responses and phosphorylation of p53 induced by HMEC-exosome interactions were also inhibited by NAC. Furthermore, exosome induced autophagic HMECs were found to release breast cancer cell growth promoting factors. Taken together, our results suggest novel mechanisms by which breast cancer cell secreted exosomes manipulate HMECs to create a tumor permissive microenvironment."

-H. M. Bligh Cancer Research Laboratories, Department of Microbiology and Immunology, Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois, USA.
https://pubmed.ncbi.nlm.nih.gov/24831807

See also Substance Abuse , Cerebral Palsy

Narcolepsy

"Narcolepsy is a rare long-term brain condition that causes a person to suddenly fall asleep at inappropriate times."

-NHS UK
https://www.nhs.uk/conditions/narcolepsy

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"Narcolepsy is a chronic neurological disorder caused by autoimmune destruction of hypocretin-producing neurons inhibiting the brain's ability to regulate sleep-wake cycles normally [1,2]. People with narcolepsy often experience frequent excessive daytime sleepiness, sleep paralysis, hypnagogic hallucinations and cataplexy, these symptoms may not present in all patients [3]. It severely interferes with every aspect of patients' life, in work and social settings. Narcolepsy occurs in approximately 1 in 2000 individuals, while most cases are sporadic and can be

substantially helped but not cured [4]."…

-Department of Neurology and Shandong Sleep Medical Center, Provincial Hospital Affiliated to Shandong University, Jinan 250021, China

-Department of Neurology, Provincial Hospital Affiliated to Shandong University, Jinan 250021, China

-Shandong Sleep Medical Center, Provincial Hospital Affiliated to Shandong University, Jinan 250021, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4538164

Effects of Omega-3 Fatty Acid Supplementation on Neurocognitive Functioning and Mood in Deployed U.S. Soldiers: A Pilot Study

The omega-3 fatty acid (FA) docosahexaenoic acid (DHA) is a major structural component of the brain,[1] and reduced levels are associated with deficits in cognition and mood in animal models.[2,3] In humans, higher omega-3 FA intakes are linked to improvements in a number of mood disorders including major depressive disorder and bipolar disorder.[4–6] Omega-3 levels are lower in red blood cells, tissues, and/or plasma from individuals diagnosed with depression.[7–9] Some studies provide evidence that omega-3 supplementation can improve both mood[10,11] and cognitive functioning.[12,13] The link between omega-3 levels and mood has important implications for the military considering that as high as 31% of U.S. Soldiers with a deployment history show signs of depression.[14] Compared to civilian populations, U.S. Soldiers appear to have low omega-3 levels,[15] but whether this is due to low intakes or other factors is currently unknown."….

-Comprehensive Soldier & Family Fitness/Performance, Headquarters Department of the Army, 251 18th Street South, Suite 210, Crystal Park 5, Arlington, VA 22202.

-Walter Reed National Naval Medical Center (WRNNMC), 8901 Wisconsin Boulevard, Bethesda, MD 20889.

-Natural Science Division, Pepperdine University, 24255 Coast Highway, Malibu, CA 90263.

-Consortium for Health and Military Performance, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814.

-Sanford School of Medicine, University of South Dakota, 1400 W 22nd Street, Sioux Falls, SD 57105.

https://watermark.silverchair.com/milmed-d-13-00395.pdf

https://pubmed.ncbi.nlm.nih.gov/24690964

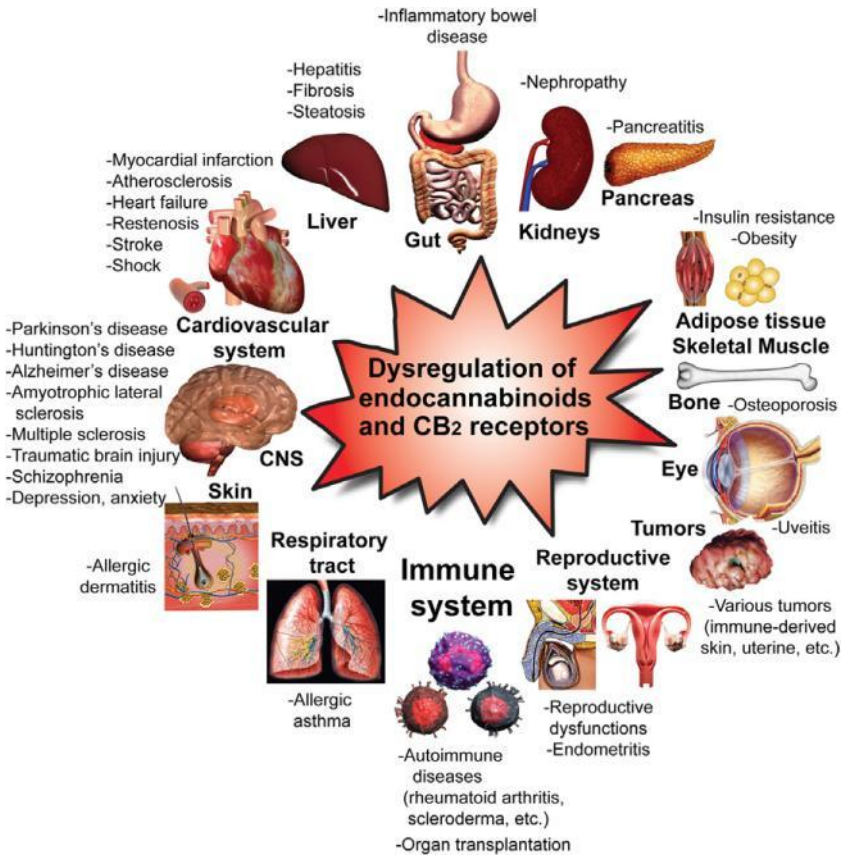
National Institute of Health

Is lipid signaling through cannabinoid 2 receptors part of a protective system?

"The mammalian body has a highly developed immune system which guards against continuous invading protein attacks and aims at preventing, attenuating or repairing the inflicted damage. It is conceivable that through evolution analogous biological protective systems have been evolved

against non-protein attacks. There is emerging evidence that lipid endocannabinoid signaling through cannabinoid 2 (CB2) receptors may represent an example/part of such a protective system/armamentarium. Inflammation/tissue injury triggers rapid elevations in local endocannabinoid levels, which in turn regulate signaling responses in immune and other cells modulating their critical functions. Changes in endocannabinoid levels and/or CB2 receptor expressions have been reported in almost all diseases affecting humans, ranging from cardiovascular, gastrointestinal, liver, kidney, neurodegenerative, psychiatric, bone, skin, auto-immune, lung disorders to pain and cancer, and modulating CB2 receptor activity holds tremendous therapeutic potential in these pathologies. While CB2 receptor activation in general mediates immunosuppressive effects, which limit inflammation and associated tissue injury in large number of pathological conditions, in some disease states activation of the CB2 receptor may enhance or even trigger tissue damage, which will also be discussed alongside the protective actions of the CB2 receptor stimulation with endocannabinoids or synthetic agonists, and the possible biological mechanisms involved in these effects."

…"The mammalian body has a highly developed immune system, whose main role is to guard against protein attack and prevent, reduce or repair a possible injury. It is inconceivable that through evolution analogous biological protective systems have not been developed against non-protein attacks. Are there mechanisms through which our body lowers the damage caused by various types of neuronal as well as non-neuronal insults? The answer is of course positive. Through evolution numerous protective mechanisms have been evolved to prevent and limit tissue injury.



We believe that lipid signaling through cannabinoid 2 (CB2) receptors is a part of such a protective machinery and CB2 receptor stimulation leads mostly to sequences of activities of a protective nature. Inflammation/tissue injury triggers rapid elevations in local endocannabinoid levels, which in turn regulate fast signaling responses in immune and other cells

modulating their critical functions. Endocannabinoids and endocannabinoid-like molecules acting through the CB2 cannabinoid receptor have been reported to affect a large number of pathological conditions, ranging from cardiovascular [1,2], gastrointestinal [3,4], liver [5–7], kidney [8,9], lung [10], neurodegenerative [11–14] and psychiatric [15–20] disorders to pain [21,22], cancer [23–26], bone [27,28], reproductive system [29–31] and skin pathologies [32] (Fig. 1). This receptor works in conjunction with the immune system and with various other physiological systems. As numerous excellent reviews have been published on the actions of the endocannabinoid system on specific topics, in this Review we aim to summarize some of the protective actions of the CB2 receptor stimulation with endocannabinoids or synthetic agonists, and the possibly biological mechanisms involved in these effects. While CB2 receptor activation in general mediates immunosuppressive effects, which limit inflammation and associated tissue injury in large number of pathological conditions, in some disease states activation of the CB2 receptor may enhance or even trigger tissue damage, which will also be discussed alongside the protective actions."…

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, MD, USA
-Institute of Drug Research, Hebrew University Medical Faculty, Jerusalem, Israel
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3062638/

The Endocannabinoid System as an Emerging Target of Pharmacotherapy

"The recent identification of cannabinoid receptors and their endogenous lipid ligands has triggered an exponential growth of studies exploring the endocannabinoid system and its regulatory functions in health and disease. Such studies have been greatly facilitated by the introduction of selective cannabinoid receptor antagonists and inhibitors of endocannabinoid metabolism and transport, as well as mice deficient in cannabinoid receptors or the endocannabinoid-degrading enzyme fatty acid amidohydrolase. In the past decade, the endocannabinoid system has been implicated in a growing number of physiological functions, both in the central and peripheral nervous systems and in peripheral organs. More importantly, modulating the activity of the endocannabinoid system turned out to hold therapeutic promise in a wide range of disparate diseases and pathological conditions, ranging from mood and anxiety disorders, movement disorders such as Parkinson's and Huntington's disease, neuropathic pain, multiple sclerosis and spinal cord injury, to cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity/metabolic syndrome, and osteoporosis, to name just a few. An impediment to the development of cannabinoid medications has been the socially unacceptable psychoactive properties of plant-derived or synthetic agonists, mediated

by CB1 receptors. However, this problem does not arise when the therapeutic aim is achieved by treatment with a CB1 receptor antagonist, such as in obesity, and may also be absent when the action of endocannabinoids is enhanced indirectly through blocking their metabolism or transport. The use of selective CB2 receptor agonists, which lack psychoactive properties, could represent another promising avenue for certain conditions. The abuse potential of plant-derived cannabinoids may also be limited through the use of preparations with controlled composition and the careful selection of dose and route of administration. The growing number of preclinical studies and clinical trials with compounds that modulate the endocannabinoid system will probably result in novel therapeutic approaches in a number of diseases for which current treatments do not fully address the patients' need. Here, we provide a comprehensive overview on the current state of knowledge of the endocannabinoid system as a target of pharmacotherapy."

-Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2241751/

Cannabinoids cool the intestine

"Cannabinoids inhibit motility and secretion in the intestine. They are now assigned the additional task of curbing excessive inflammation, suggesting that drugs targeting the endogenous cannabinoid system could be exploited for inflammatory bowel disease."

"Inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn's disease affects over a million people in the United States1, with an estimated indirect cost from work loss of $3.6 billion annually[2]. Many of these individuals suffer from pain, diarrhea and poor ability to digest their food, and in up to half of those with IBD, the disease is so severe that it ultimately requires surgery to remove the affected bowel segment.

Despite recent therapeutic advances and improved understanding of the underlying pathologies, patients with IBD are often resistant to treatment, justifying the continued search for new therapeutic approaches. Although the mechanisms underlying ulcerative colitis and Crohn's disease are different, they share one pathological feature: chronic inflammation. In a recent issue of the Journal of Clinical Investigation, Massa et al. provide evidence that stimulation of cannabinoid receptors protects against colonic inflammation[3].

As their model, the authors induced bowel inflammation in mice by treatment with different chemical agents, an approach commonly used to explore endogenous protective mechanisms and to screen potential therapeutic agents. The authors began with an experiment testing chemical agents in mice lacking the CB1 subtype of cannabinoid receptor; such agents induced

more severe colitis in the CB1 knockout mice than in wild-type mice. Moreover, pretreatment of wild-type mice with a CB1 antagonist caused a similar increase in the inflammatory response.

The authors then performed the converse experiments. They found that either treatment of wild-type mice with a CB1 receptor agonist or genetic ablation of fatty acid amidohydrolase (FAAH), the enzyme that degrades the endogenous cannabinoid agonist anandamide4, reduced inflammation in response to chemicals. The authors also observed an increase in the expression of CB1 receptors in intrinsic neurons of the inflamed mouse colon. Together, these findings suggest that anandamide counteracts inflammation. Another endocannabinoid, 2-arachidonoylglycerol, is unlikely to be involved because its abundance in tissue is unaffected by genetic ablation of FAAH5.

These findings may offer a new therapeutic approach to IBD. CB1 receptors in the brain mediate the addictive psychological effects of marijuana, so treating a chronic disease with a drug that directly stimulates CB1 receptors would be socially objectionable. Recent evidence indicates, however, that drugs which target endogenous cannabinoids may not have the same potential for abuse. A potent FAAH inhibitor, for example, elicits cannabinoid-like antianxiety effects in mice without producing many of the other behavioral effects of psychoactive cannabinoids[6].”

-George Kunos & Pál Pacher
-National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2516444/

Nausea and Vomiting

Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system

“Nausea and vomiting (emesis) are important elements in defensive or protective responses that animals use to avoid ingestion or digestion of potentially harmful substances. However, these neurally-mediated responses are at times manifested as symptoms of disease and they are frequently observed as side-effects of a variety of medications, notably those used to treat cancer. Cannabis has long been known to limit or prevent nausea and vomiting from a variety of causes. This has led to extensive investigations that have revealed an important role for cannabinoids and their receptors in the regulation of nausea and emesis. With the discovery of the endocannabinoid system, novel ways to regulate both nausea and vomiting have been discovered that involve the production of endogenous cannabinoids acting centrally. Here we review recent progress in understanding the regulation of nausea and vomiting by cannabinoids

and the endocannabinoid system, and we discuss the potential to utilize the endocannabinoid system in the treatment of these frequently debilitating conditions."

…"One of the oldest pharmacological remedies for nausea and vomiting is the plant cannabis (Kalant, 2001). In clinical trials, cannabis-based medicines have been found to be effective anti-emetics and even surpass some modern treatments in their potential to alleviate nausea (Cotter, 2009; Tramèr et al., 2001). "

-Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, Canada

-Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, California, USA

-Department of Psychology, University of Guelph, Guelph, Ontario, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883513/

■■■

…"Accumulating evidence indicates that the endocannabinoid system is a key modulator of gastrointestinal physiology, influencing satiety, **emesis**, immune function, mucosal integrity, motility, secretion, and visceral sensation." …

-College of Pharmacy, Pusan National University, Busan, Korea; and.

-Section of Inflammatory Bowel Disease & Inflammatory Bowel Disease Center, Division of Digestive Diseases, David Geffen School of Medicine, UCLA, Los Angeles, California.

-College of Pharmacy, Pusan National University, Busan, Korea;

https://pubmed.ncbi.nlm.nih.gov/27538961/

Nerve Function

Omega-6 and omega-3 fatty acids predict accelerated decline of peripheral nerve function in older persons

"Pre-clinical studies suggest that both omega-6 and omega-3 fatty acids have beneficial effects on peripheral nerve function."…

…"Low plasma omega-6 and omega-3 fatty acids levels were associated with accelerated decline of peripheral nerve function with aging."..

-Tuscany Regional Health Agency, Florence, Italy

-Geriatric Rehabilitation, Azienda Sanitaria Firenze, Florence, Italy

-Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA

-Institute of Gerontology and Geriatrics, Perugia University Medical School, Perugia, Italy

-Laboratory of Clinical Epidemiology, Department of Medicine and Sciences of Aging, University G. D'Annunzio, Chieti,

Italy

-Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, MD, USA

-Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, MD, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2646099/

Long-Chain Omega-3 Fatty Acids Supplementation Accelerates Nerve Regeneration and Prevents Neuropathic Pain Behavior in Mice

"Fish oil (FO) is the main source of long chain omega-3 polyunsaturated fatty acids (ω-3 PUFAs), which display relevant analgesic and anti-inflammatory properties. Peripheral nerve injury is driven by degeneration, neuroinflammation, and neuronal plasticity which results in neuropathic pain (NP) symptoms such as allodynia and hyperalgesia. We tested the preventive effect of an EPA/DHA-concentrate fish oil (CFO) on NP development and regenerative features. Swiss mice received daily oral treatment with CFO 4.6 or 2.3 g/kg for 10 days after NP was induced by partial sciatic nerve ligation. Mechanical allodynia and thermal hypernociception were assessed 5 days after injury. CFO 2.3 g/kg significantly prevented mechanical and thermal sensitization, reduced TNF levels in the spinal cord, sciatic MPO activity, and ATF-3 expression on DRG cells. CFO improved Sciatic Functional Index (SFI) as well as electrophysiological recordings, corroborating the increased GAP43 expression and total number of myelinated fibers observed in sciatic nerve. No locomotor activity impairment was observed in CFO treated groups. These results point to the regenerative and possibly protective properties of a combined EPA and DHA oral administration after peripheral nerve injury, as well as its anti-neuroinflammatory activity, evidencing ω-3 PUFAs promising therapeutic outcomes for NP treatment."

-Laboratory of Studies in Experimental Pharmacology, Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

-Neurodegeneration and Repair Laboratory, Department of Pathology, Faculty of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

-Edited by: Weien Yuan, Shanghai Jiao Tong University, China

-Reviewed by: Hong Zhan, University of Wisconsin-Madison, United States; Anna Maria Pittaluga, Università di Genova, Italy; Chong Li, Southwest University, United States

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5651013/

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See Supplements for related research quotes.

Effect of eicosapentaenoic acids-rich fish oil supplementation on motor nerve function after eccentric contractions

"Eight weeks of EPA and DHA supplementation may play a protective role against motor nerve function and may attenuate muscle damage after eccentric contractions."

-Faculty of Bioscience and Applied Chemistry, Hosei University, Japan
-Faculty of Modern life, Teikyo Heisei University, Tokyo, Japan
-Human Life Science R&D Center, Nippon Suisan Kaisha, Ltd, Tokyo, Japan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5508798/

Omega-3 polyunsaturated fatty acid supplementation for improving peripheral nerve health: protocol for a systematic review

"Damage to peripheral nerves occurs in a variety of health conditions. Preserving nerve integrity, to prevent progressive nerve damage, remains a clinical challenge. Omega-3 polyunsaturated fatty acids (PUFAs) are implicated in the development and maintenance of healthy nerves and may be beneficial for promoting peripheral nerve health. The aim of this systematic review is to assess the effects of oral omega-3 PUFA supplementation on peripheral nerve integrity, including both subjective and objective measures of peripheral nerve structure and/or function."…

"The term 'peripheral neuropathy' describes a heterogeneous group of disorders that cause damage to the peripheral nervous system. Currently, management approaches for peripheral neuropathy are aimed primarily at addressing the underlying cause and/or managing symptoms. For many causes of peripheral neuropathy, including diabetes, reversing or even limiting the progression of nerve damage remains a challenge with currently available therapeutics.

Omega-3 PUFAs are reported to be associated with a range of general health benefits that include reducing the risk of cardiovascular disease,[38 39] lowering systemic triglycerides40 and improving clinical symptoms of dry eye disease.[44] In animal models of experimental peripheral nerve injury, increasing endogenous levels of omega-3 PUFAs have been shown to improve sciatic blood flow and accelerate the recovery of neuronal function.[50 52 53]

The aim of this systematic review is to assess the safety and efficacy of oral omega-3 PUFA supplementation for improving peripheral nerve health. If it is demonstrated that omega-3 supplements can improve measures of peripheral nerve function and/or quality of life, it is anticipated that this therapy would make a valuable contribution to the current clinical management of peripheral neuropathy."

- Department of Optometry and Vision Sciences, University of Melbourne, Parkville, Victoria, Australia,
- Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia,

- Department of Medicine, University of Melbourne, Parkville, Victoria, Australia,

- Centre for Clinical Neurosciences and Neurological Research, St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia,

- Department of Ophthalmology, New Zealand National Eye Centre, The University of Auckland, Auckland, New Zealand,

- Institute for Health and Ageing, Australian Catholic University, Fitzroy, Victoria,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5875591

See also Omega Ratio

Nervous System

Cannabinoid signalling in the enteric nervous system

"Cannabinoid signalling is an important mechanism of synaptic modulation in the nervous system. Endogenous cannabinoids (anandamide and 2-arachidonyl-glycerol) are synthesized and released via calcium-activated biosynthetic pathways. Exogenous cannabinoids and endocannabinoids act on CB1 and CB2 receptors. CB1 receptors are neuronal receptors which couple via G-proteins to inhibition of adenylate cyclase or to activation or inhibition of ion channels. CB2 receptors are expressed by immune cells and cannabinoids can suppress immune function. In the central nervous system, the endocannabinoids may function as retrograde signals released by the postsynaptic neuron to inhibit neurotransmitter release from presynaptic nerve terminals. Enteric neurons also express CB receptors. Exogenously applied CB receptor agonists inhibit enteric neuronal activity but it is not clear if endocannabinoids released by enteric neurons can produce similar responses in the enteric nervous system (ENS). In this issue of Neurogastroenterology and Motility, Boesmans et al. show that CB1 receptor activation on myenteric neurons maintained in primary culture can suppress neuronal activity, inhibit synaptic transmission and mitochondrial transport along axons. They also provide initial evidence that myenteric neurons (or other cell types present in the cultures) release endocannabinoids and which activate CB1 receptors constitutively. These data provide new information about targets for cannabinoid signalling in the ENS and highlight the potential importance of CB receptors as drug targets. It is necessary that future work extends these interesting findings to intact tissues and ideally to the in vivo setting."

-Department of Pharmacology & Toxicology and the Neuroscience Program, Michigan State University

https://pubmed.ncbi.nlm.nih.gov/19689654

Neu5Gc

A red meat-derived glycan promotes inflammation and cancer progression

“We present an unusual mechanism for the well-known association between red meat consumption and carcinoma risk involving the nonhuman sialic acid N-glycolylneuraminic acid (Neu5Gc). We first evaluate the Neu5Gc content of various foods to show that red meats are particularly rich in orally bioavailable Neu5Gc and then investigate human-like Neu5Gc-deficient mice fed this form of Neu5Gc. When such mice were challenged with anti-Neu5Gc antibodies, they developed evidence of systemic inflammation. Long-term exposure to this combination resulted in a significantly higher incidence of carcinomas (five-fold increase) and an association with Neu5Gc accumulation in the tumors. Similar mechanisms may contribute to the association of red meat consumption with other diseases, such as atherosclerosis and type 2 diabetes, which are also exacerbated by inflammation.

A well known, epidemiologically reproducible risk factor for human carcinomas is the long-term consumption of “red meat” of mammalian origin. Although multiple theories have attempted to explain this human-specific association, none have been conclusively proven. We used an improved method to survey common foods for free and glycosidically bound forms of the nonhuman sialic acid N-glycolylneuraminic acid (Neu5Gc), showing that it is highly and selectively enriched in red meat. The bound form of Neu5Gc is bioavailable, undergoing metabolic incorporation into human tissues, despite being a foreign antigen. Interactions of this antigen with circulating anti-Neu5Gc antibodies could potentially incite inflammation. Indeed, when human-like Neu5Gc-deficient mice were fed bioavailable Neu5Gc and challenged with anti-Neu5Gc antibodies, they developed evidence of systemic inflammation. Such mice are already prone to develop occasional tumors of the liver, an organ that can incorporate dietary Neu5Gc. Neu5Gc-deficient mice immunized against Neu5Gc and fed bioavailable Neu5Gc developed a much higher incidence of hepatocellular carcinomas, with evidence of Neu5Gc accumulation. Taken together, our data provide an unusual mechanistic explanation for the epidemiological association between red meat consumption and carcinoma risk. This mechanism might also contribute to other chronic inflammatory processes epidemiologically associated with red meat consumption.”

“There is a long-standing epidemiological link between the consumption of red meat (beef, pork, and lamb) and the incidence of carcinomas, atherosclerosis, type 2 diabetes, and all-cause mortality [1–4]. Although such diseases have multifactorial origins, all are aggravated by chronic

inflammation [5, 6]. Red meat-rich diets also correlate with circulating markers of inflammation and endothelial dysfunction [7]. Here, we focus on red meat-related risk of carcinomas (further citations regarding the association are provided in Table S1). Corroboration comes from the low rates of carcinomas in populations that consume very low levels or no red meat [8–10].”…

“Another unexplained fact is the human specificity of this risk (i.e., other vertebrate carnivores do not suffer a high incidence of carcinomas). In this regard, we have suggested an unusual human-specific mechanism, involving inflammation associated with metabolic incorporation of a nonhuman sialic acid, N-glycolylneuraminic acid (Neu5Gc), and interaction with circulating anti-Neu5Gc antibodies [16–19]. Despite the fact that humans are genetically unable to produce Neu5Gc, this molecule is detectable on surfaces of human epithelia and endothelia, and in higher amounts in malignant tissues [20]. In the absence of an alternate pathway for Neu5Gc biosynthesis [21], the only possible source for incorporation is dietary intake [22]. An initial food survey showed a prominent presence of Neu5Gc in red meat [23]. Metabolic incorporation of dietary Neu5Gc into tissues [24] makes this glycan the first example, to our knowledge, of a xeno-autoantigen, which can react with circulating anti-Neu5Gc antibodies (i.e., xeno-autoantibodies) [25]. The resulting antigen–antibody interaction is hypothesized to generate or promote chronic inflammation or “xenosialitis,” which could contribute to carcinogenesis or to other diseases exacerbated by chronic inflammation.”

-Departments of Medicine Pathology and Cellular and Molecular Medicine, Glycobiology Research and Training Center, University of California, San Diego, La Jolla, CA

-Edited by Stuart A. Kornfeld, Washington University School of Medicine

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4299224/

Loss of N-glycolylneuraminic acid in humans: Mechanisms, consequences, and implications for hominid evolution

“The surface of all mammalian cells is covered with a dense and complex array of sugar chains, which are frequently terminated by members of a family of molecules called sialic acids. One particular sialic acid called N-glycolylneuraminic acid (Neu5Gc) is widely expressed on most mammalian tissues, but is not easily detectable on human cells. In fact, it provokes an immune response in adult humans. The human deficiency of Neu5Gc is explained by an inactivating mutation in the gene encoding CMP-N-acetylneuraminic acid hydroxylase, the rate-limiting enzyme in generating Neu5Gc in cells of other mammals. This deficiency also results in an excess of the precursor sialic acid N-acetylneuraminic acid (Neu5Ac) in humans. This mutation appears universal to modern humans, occurred sometime after our last common ancestor with the great apes, and happens to be one of the first known human-great ape genetic differences with an

obvious biochemical readout. While the original selection mechanisms and major biological consequences of this human-specific mutation remain uncertain, several interesting clues are currently being pursued. First, there is evidence that the human condition can explain differences in susceptibility or resistance to certain microbial pathogens. Second, the functions of some endogenous receptors for sialic acids in the immune system may be altered by this difference. Third, despite the lack of any obvious alternate pathway for synthesis, Neu5Gc has been reported in human tumors and possibly in human fetal tissues, and traces have even been detected in normal human tissues. One possible explanation is that this represents accumulation of Neu5Gc from dietary sources of animal origin. Finally, a markedly reduced expression of hydroxylase in the brains of other mammals raises the possibility that the human-specific mutation of this enzyme could have played a role in human brain evolution."

-Glycobiology Research and Training Center and Departments of Medicine and Cellular and Molecular Medicine, University of California, San Diego, La Jolla, California

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7159735/pdf/AJPA-116-54.pdf

Sugar Molecule Links Red Meat Consumption and Elevated Cancer Risk in Mice

Neu5Gc, a non-human sugar found in red meat, promotes inflammation and cancer progression in rodents

"While people who eat a lot of red meat are known to be at higher risk for certain cancers, other carnivores are not, prompting researchers at the University of California, San Diego School of Medicine to investigate the possible tumor-forming role of a sugar called Neu5Gc, which is naturally found in most mammals but not in humans.

In a study published in the Dec. 29 online early edition of the Proceedings of the National Academy of Sciences, the scientists found that feeding Neu5Gc to mice engineered to be deficient in the sugar (like humans) significantly promoted spontaneous cancers. The study did not involve exposure to carcinogens or artificially inducing cancers, further implicating Neu5Gc as a key link between red meat consumption and cancer.

"Until now, all of our evidence linking Neu5Gc to cancer was circumstantial or indirectly predicted from somewhat artificial experimental setups," said principal investigator Ajit Varki, MD, Distinguished Professor of Medicine and Cellular and Molecular Medicine and member of the UC San Diego Moores Cancer Center. "This is the first time we have directly shown that mimicking the exact situation in humans — feeding non-human Neu5Gc and inducing anti-Neu5Gc antibodies — increases spontaneous cancers in mice."

Red meat is rich in Neu5Gc, a non-human sugar found to promote inflammation and cancer

progression in rodents.

Varki's team first conducted a systematic survey of common foods. They found that red meats (beef, pork and lamb) are rich in Neu5Gc, affirming that foods of mammalian origin such as these are the primary sources of Neu5Gc in the human diet. The molecule was found to be bio-available, too, meaning it can be distributed to tissues throughout the body via the bloodstream.

The researchers had previously discovered that animal Neu5Gc can be absorbed into human tissues. In this study, they hypothesized that eating red meat could lead to inflammation if the body's immune system is constantly generating antibodies against consumed animal Neu5Gc, a foreign molecule. Chronic inflammation is known to promote tumor formation.

To test this hypothesis, the team engineered mice to mimic humans in that they lacked their own Neu5Gc and produced antibodies against it. When these mice were fed Neu5Gc, they developed systemic inflammation. Spontaneous tumor formation increased fivefold and Neu5Gc accumulated in the tumors.

"The final proof in humans will be much harder to come by," Varki said. "But on a more general note, this work may also help explain potential connections of red meat consumption to other diseases exacerbated by chronic inflammation, such as atherosclerosis and type 2 diabetes.

"Of course, moderate amounts of red meat can be a source of good nutrition for young people. We hope that our work will eventually lead the way to practical solutions for this catch-22."

-Dr Heather Buschman, PhD

-Study co-authors include Annie N. Samraj, Oliver M. T. Pearce, Heinz Läubli, Alyssa N. Crittenden, Anne K. Bergfeld, Kalyan Banda, Christopher J. Gregg, Andrea E. Bingman, Patrick Secrest, Sandra L. Diaz and Nissi M. Varki, all at UC San Diego School of Medicine.

https://health.ucsd.edu/news/releases/Pages/2014-12-29-sugar-molecule-in-red-meat-linked-to-cancer.aspx

Neurodevelopment

Omega-3 Fatty Acid and Nutrient Deficits in Adverse Neurodevelopment and Childhood Behaviors

"Nutritional insufficiencies of omega-3 highly unsaturated fatty acids (HUFAs) may have adverse effects on brain development and neurodevelopmental outcomes. A recent meta-analysis of ten randomized controlled trials of omega-3 HUFAs reported a small to modest effect size for the efficacy of omega-3 for treating symptoms of ADHD in youth. Several controlled trials of omega-3 HUFAs combined with micronutrients (vitamins, minerals) show sizeable reductions in aggressive, antisocial, and violent behavior in youth and in young adult prisoners. Meta-analyses

report efficacy for depressive symptoms in adults, and preliminary findings suggest anti-suicidal properties in adults, but studies in youth are insufficient to draw any conclusions regarding mood. Dietary adjustments to increase omega-3 and reduce omega-6 HUFA consumption are sensible recommendations for youth and adults based on general health considerations, while the evidence base for omega-3 HUFAs as potential psychiatric treatments develops."…

…"A large body of research has confirmed the essential role of DHA in the development and function of the brain. The negative impact of inadequate DHA during critical periods of brain development has been well studied in animals and, to a lesser extent, in humans. Maternal nutritional deficiencies during neurogenesis and angiogenesis have long been associated with behavioral impairments in both animal models [57–59] and in humans [40, 60, 61]. It appears that HUFA insufficiency during lactation can lead to some irreversible changes [62], presumably due to impaired connectivity.

In animal studies, prenatal and postnatal DHA insufficiency has been associated with a variety of structural changes, such delayed neuronal migration, disrupted dendritic arborization, abnormal neuronal development in the hippocampus [52], and abnormalities in timed apoptosis. Neurochemical studies have shown alterations of several neurotransmission systems, including the dopaminergic and serotonergic systems [63]. The resulting altered or impaired connectivity may result in permanent disturbances [64]. Subsequent functional deficits include cognitive impairments, such as memory and learning [57] as well as deficits in emotional regulation and behavior, such as depression, anxiety, and aggression in animal models [65, 66]. Repletion of both omega-3 and omega-6 fatty acids into the diet during lactation in animals restores the brain fatty acid composition and some parameters of neurotransmitter function [62], but only partially."

-Section of Nutritional Neurosciences, Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, 5625 Fishers Lane, Rockville, MD 20892

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4175558/

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"Omega-3 (n-3) long-chain polyunsaturated fatty acids (LCPUFA), particularly eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), can offer many health benefits when regularly consumed in sufficient quantities. Health benefits of n-3 LCPUFA include reduction of preterm birth, decreased risk for low birth weight in infants, improved visual acuity in infants, facilitation of early childhood neurodevelopment, inflammation modulation such as with chronic disease or cancer-related complications, risk reduction of cardiovascular disease (CVD), prevention of dementia and cognitive decline, and a decreased risk for developing age-related macular

degeneration [1,2,3,4,5,6,7,8,9,10,11,12,13].”…

-Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE 68198, USA; (M.T.)
-College of Public Health, University of Nebraska Medical Center, Omaha, NE 68198, USA;
-Department of Nutritional Sciences, University of Arizona, Tucson, AZ 85721, USA;
-Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA 16802, USA;
-Division of Biomedical Sciences, School of Medicine, University of California Riverside, Riverside, CA 92521, USA
-College of Allied Health Professions, University of Nebraska Medical Center, Omaha, NE 68198, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7400855/

Neurodegenerative Diseases

“The endocannabinoid system (ECS) plays key modulatory roles during synaptic plasticity and homeostatic processes in the brain. Based on anecdotal evidence obtained from cannabis use, laboratory studies, and from emerging clinical work, modulation of the ECS has been proposed as a promising therapeutic target to treat numerous central nervous system (CNS) disorders including neurodegenerative diseases, epilepsy and cognitive deficits among others (Scotter et al., 2010; Fernández-Ruiz et al., 2011; Bilkei-Gorzo, 2012).”

…”CB1 receptors are indicated in many disorders that impact the CNS including several neurodegenerative disorders such as Huntington’s disease (HD), multiple sclerosis (MS) and AD (Fernández-Ruiz et al., 2011; Di Marzo et al., 2014).”

…”At the molecular level, these improvements are generally linked to the activation of both CB1 receptors and CB2 receptors by agonist, resulting in their dual anti-inflammatory and neuroprotective effects throughout the CNS (Baker et al., 2000; Maresz et al., 2007). These effects include up-regulation of prosurvival molecules such as interleukines in astroglia, and the reduction of cytotoxic factors such as nitric oxide, reactive oxygen species and proinflammatory cytokines in microglia (Fernández-Ruiz et al., 2011).”

-Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, USA
-Department of Anatomy and Neurobiology, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico
-Institute of Neurobiology, University of Puerto Rico, San Juan, Puerto Rico
-Edited by: Hansen Wang, University of Toronto, Canada
-Reviewed by: Carla Cannizzaro, University of Palermo, Italy; Eilís Dowd, National University of Ireland, Galway, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209363/

Prospects for cannabinoid therapies in viral encephalitis

"Cannabinoids are promising therapies to support neurogenesis and decelerate disease progression in neuroinflammatory and degenerative disorders."

…"Thus, HU-308 [a synthetic cannabinoid agonist] action on CB2 receptors, receptors known to be renewed during microglia proliferation and action, is a nontolerizing mechanism of controlling CNS inflammation during viral encephalitis by reducing microglia activation, as well as partially limiting viral infection, and uses a nonpsychotropic cannabinoid agonist."

…"Neuroinflammation is recognized as early event or key accelerant in the pathobiology of persistent CNS infections, HIV associated cognitive decline, prion diseases, and neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's Diseases. The discovery of cannabinoid receptors, identification of their naturally occurring ligands, and increase in understanding of the physiologic role of the endogenous cannabinoid (endocannabinoid) system, has advanced the exploration of cannabinoid receptor compounds for novel CNS therapies (Piomelli, 2003, Mechoulam and Parker, 2013).

The CB1 receptor is abundant in the brain (Howlett et al., 2002), signals progenitor cells, neurogenesis and development (Aguado et al., 2007, Diaz-Alonso et al., 2012), can be neuroprotective, and mediates many of the psychoactive effects of cannabinoids (Mackie, 2005, Monory et al., 2007). The CB2 receptor is present mainly on immune cells of both the periphery and CNS (Howlett et al., 2002). Its activation is immunomodulatory, regulatory and neuroprotective (Atwood and Mackie, 2010), through reduction of microglia/macrophage activation, migration (Romero-Sandoval et al., 2009, Fraga et al., 2011), and decrease in proinflammatory cytokines and toxins (Cabral and Griffin-Thomas, 2009, Bouchard et al., 2012). That CB2 expression increases in disease states associated with neural inflammation (Benito et al., 2008, Pacher and Mechoulam, 2011) adds to its appeal as a therapeutic target."

-Department of Medicine (Neurology), University of Manitoba, Winnipeg, MB, Canada
-Department of Medical Microbiology, University of Manitoba, Winnipeg, MB, Canada
https://www.sciencedirect.com/science/article/pii/S0006899313011694

The Gut-Brain Axis in Alzheimer's Disease and Omega-3. A Critical Overview of Clinical Trials

…"Increasing clinical findings [13,14] reveal that the pathogenesis of many neurodegenerative diseases may depend on the gut microbiota and that the resident commensal microbiota modulates CNS autoimmunity [43,44], beyond neuroinflammation [45,46].

A common trait between theories investigating the causes of neurodegenerative diseases is the presence of neuroinflammation [47,48] that has been associated with activation of microglia and

peripheral monocytes that cross the BBB. These cells produce inflammatory cytokines and several neurotoxic molecules, such as TNF-α and IL-1β [49,50,51,52,53,54] in an attempt to counteract the formation and/or extend misfolding of neuronal proteins and the formation of insoluble fibrillary aggregates [55,56,57].

AD is associated with impaired cognition and cerebral accumulation of amyloid-β peptides (Aβ). Indeed, recent studies published, respectively, by Italian and American researchers described interactions between brain protein misfolding and microbiota [58,59].

Larsen et al. [60,61] and Jordal et al. [62] have described an abundance of functional bacterial amyloids; amyloid is used by bacteria such as Proteobacteria, Bacteroidetes, Chloroflexi, Actinobacteria and Firmicutes as structural and adhesive material, toxin, and protection against host innate immunological defenses [63]. The human innate immune system recognizes bacterial amyloid proteins by using several pathways involving TLR 1/2, Nod-like receptor-3 protein (NLRP3), nuclear factor kappa-B (NF-kb), CD14, and inducible nitric oxide synthase [57,64,65]. Other misfolded proteins produced by bacteria could predispose to tissue damage and to the production of proinflammatory cytokines associated with the development of dementia [66].

Other Authors [67,68] have shown that in a mouse model of Huntington's disease treatment with butyrate-like analogues such as phenylbutyrate, histone deacetylase inhibitor or sodium butyrate used to modulate transcription prevents neuronal death and lengthens the life of mice in a dose-dependent manner.

As described above, the gut microbiota could influence the integrity of the blood-brain barrier (BBB). For example, this can be observed in a microbiota dysbiotic condition that induces increased permeability of the gut (the so-called "leaky gut") in both foetal and adult mouse brains. Braniste et al. [69] conducted a study in adult and embryonic animals showing the relationship between the lack of a normal gut flora in germ-free mice and increased BBB permeability. This study highlighted the importance of gut microbiota integrity on the CNS, especially in the progression of neurodegenerative diseases. Studies by Diaz et al. in mice have shown that the normal gut microbiota modulates brain development and subsequent adult behaviour, investigated as motor control and anxiety behaviours, suggesting that the microbial colonization process triggers cellular pathways that affect specific neuronal circuits [11]. Other authors have shown that the disruption or absence of the microbiota in mice impaired the function of the BBB and altered cortical myelination and hippocampal neurogenesis, decreased cognitive function and memory formation, and decreased social behaviour [70].

According to Alkasir et al. [13] that proposed a schematic representation of the gut-microbiota and neuroinflammation axis in AD, we can speculate that dysfunction of the gut epithelial barrier results in peripheral inflammation. This condition is linked with dementia onset because the

production of inflammatory cytokines, like IL-1β, reduces Aβ phagocytosis, induces NLRP3-inflammasome activation with consequent release of NLRP3-related cytokines such as caspase-1 and IL-18 [71], thus increasing amyloid-beta deposits.

Therefore, modulation of innate immune responses through changes in microbiota composition may exert healthy effects especially on cognitive decline in MCI patients, possibly slowing down or avoiding the progression to AD."

-IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy;
-Department of Physiopathology and Transplants, University of Milano, Milan, Italy
-Department of Biology and Biotechnology, University of Pavia, Pavia, Italy;
-Istituto per lo Studio e la Cura del Diabete [ISCD], Casagiove, Caserta, Italy;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164598/

The endocannabinoid system as a target for the treatment of neurodegenerative disease

"Aside from this crucial regulatory role in the activity of neurons, endocannabinoids also play a key role in peripheral and brain immune function. As mentioned, CB2 [cannabinoid type 2 receptors] is expressed on various circulating and resident immune cells, particularly when these cells are activated, and its agonism is typically associated with a dampening of their pro-inflammatory activities. This includes the inhibition of release of inflammatory mediators, including nitric oxide, interleukin-2 and TNF-α, inhibition of the activation of the cell-mediated immune processes, and inhibition of proliferation and chemotaxis (Ehrhart et al., 2005; Coopman et al., 2007; Maresz et al., 2007; Romero-Sandoval et al., 2009; and reviewed in Walter and Stella, 2004a)."

-Centre for Brain Research and Department of Pharmacology, University of Auckland, Auckland, New Zealand
-Department of Anatomy and Cell Biology, Centre for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931550/

■■■

…"There is increasing evidence that DHA specifically plays a significant role in neurological development and disease prevention. DHA is an important component of brain development, and DHA deficiencies have been found in patients with neurological conditions. For example, there is a strong correlation between depression and DHA deficiency (Horrocks and Yeo 1999). Deficiency in DHA has also been strongly correlated with neurodegenerative diseases common in the elderly population, particularly Alzheimer's disease (Freemantle et al. 2006)."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

Cannabinoids and neurodegenerative diseases

"Although significant advances have taken place in recent years on our understanding of the molecular mechanisms of different neurodegenerative diseases, its translation into effective therapeutic treatments has not been as successful as could be expected. There is still a dramatic lack of curative treatments for the most frequent disorders and only symptomatic relief for many others. Under this perspective, the search for novel therapeutic approaches is demanding and significant attention and efforts have been directed to studying additional neurotransmission systems including the endocannabinoid system (ECS). The neuroprotective properties of exogenous as well as endogenous cannabinoids have been known for years and the underlying molecular mechanisms have been recently unveiled. As discussed later, antioxidative, antiglutamatergic and antiinflammatory effects are now recognized as derived from cannabinoid action and are known to be of common interest for many neurodegenerative processes. Thus, these characteristics make cannabinoids attractive candidates for the development of novel therapeutic strategies [1]. The present review will focus on the existing data regarding the possible usefulness of cannabinoid agents for the treatment of relevant neurological pathologies for our society such as Alzheimer's disease, multiple sclerosis, Huntington's disease and amyotrophic lateral sclerosis."

-Research Laboratory, Alcorcón Foundation University Hospital and Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED)
https://pubmed.ncbi.nlm.nih.gov/19839933/

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"Neuroinflammation has been implicated in the pathogenesis of neurodegenerative diseases. Cyclooxygenase-2 (COX-2), an inducible enzyme converting arachidonic acid (AA) [omega-6] to prostaglandins, is the key player in neuroinflammation. It has been long thought that the COX-2-mediated neuronal injury/degeneration is attributed to the increased production of AA-derived prostaglandins."…

"Inflammation in the CNS is referred to as neuroinflammation, which has been implicated in many brain disorders such as epilepsy and neurodegenerative diseases (e.g. multiple sclerosis, Alzheimer's diseases, and Parkinson's diseases), and in the contribution to the traumatic brain injury- and ischemia-induced neuronal damage. Accumulated information indicates that

cyclooxygenase-2 (COX-2)-mediated neuronal injury/degeneration is likely attributed to the increased production of arachidonic acid (AA)-derived prostaglandins, mainly prostaglandin E2 (PGE2) (Hurley et al. 2002; Manabe et al. 2004; Chen and Bazan 2005a,b; Liang et al. 2005; Sang et al. 2005; Kawano et al. 2006). While PGE2 is believed to promote neuronal injury in neuroinflammation, it may also protect neurons from glutamate-induced excitotoxicity and inflammation- or ischemia-induced neurodegeneration (Akaike et al. 1994; Kim et al. 2002; Lee et al. 2004; McCullough et al. 2004). The use of selective COX-2 inhibitors or the deletion of the COX-2 gene has been shown to protect neurons from harmful insults, implying that there are undefined mechanisms related to the COX-2-mediated neurodegenerative process."...

-Nan Sang, Jian Zhang, Chu Chen

-Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA.

https://onlinelibrary.wiley.com/doi/full/10.1111/j.1471-4159.2007.04668.x

The endocannabinoid system in neurodegeneration

"Endocannabinoids are bioactive lipids, that comprise amides, esters and ethers of long chain polyunsaturated fatty acids. Anandamide (N-arachidonoylethanolamine; AEA) and 2-arachidonoylglycerol (2-AG) are the best studied endocannabinoids, and act as agonists of cannabinoid receptors. Thus, AEA and 2-AG mimic several pharmacological effects of the exogenous cannabinoid delta9-tetrahydrocannabinol, the psychoactive principle of hashish and marijuana. It is known that the activity of endocannabinoids at their receptors is limited by cellular uptake through specific membrane transporters, followed by intracellular degradation by a fatty acid amide hydrolase (for AEA and partly 2-AG) or by a monoacylglycerol lipase (for 2-AG). Together with AEA, 2-AG and congeners, the proteins that bind, transport and metabolize these lipids form the "endocannabinoid system". This new system will be briefly presented in this review, in order to put in a better perspective the role of the endocannabinoid pathway in neurodegenerative disorders, like Parkinson's disease, Huntington's disease, and multiple sclerosis. In addition, the potential exploitation of antagonists of endocannabinoid receptors, or of inhibitors of endocannabinoid metabolism, as next-generation therapeutics will be discussed."

-Department of Biomedical Sciences, University of Teramo, Teramo, Italy.

https://pubmed.ncbi.nlm.nih.gov/17274532

Endocannabinoid System: Emerging Role from Neurodevelopment to Neurodegeneration

…"The ECs, their receptors, synthesizing and degrading enzymes, as well as transporter molecules, have been detected from the earliest stages of embryonic development and throughout pre- and postnatal development. ECs such as AEA and 2-AG are bioactive lipids that mimic several pharmacological effects of Δ9-THC. Many of the effects of cannabinoids and ECs are mediated by two G protein-coupled receptors (GPCRs), CB1 and CB2, although additional receptors may be implicated. Both CB1 and CB2 couple primarily to inhibitory G proteins and are subject to the same pharmacological influences as other GPCRs. As summarized in this review, several lines of evidence have suggested that the EC system may play an important role in early neuronal development along with a widespread role in neurodegeneration disorders. The development of EC research is also very important from a clinical point of view because the EC system may provide potential targets not only for the treatment of habit-forming behaviors but also for neurological disorders."

-Division of Analytical Psychopharmacology, Nathan Kline Institute for Psychiatric Research, Orangeburg, Orangeburg, NY, USA

-Center for Dementia Research, Nathan Kline Institute for Psychiatric Research, Orangeburg, Orangeburg, NY, USA

-New York State Psychiatric Institute, College of Physicians & Surgeons, Columbia University, New York, NY, USA

-Department of Psychiatry, Taub Institute and Department of Pathology, College of Physicians & Surgeons, Columbia University, New York, NY, USA

-Departments of Psychiatry and Cell Biology, New York University School of Medicine, New York, NY, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4739730

Current Aspects of the Endocannabinoid System and Targeted THC and CBD Phytocannabinoids as Potential Therapeutics for Parkinson's and Alzheimer's Diseases: a Review

"Neurodegeneration leading to Parkinson's disease (PD) and Alzheimer's disease (AD) has become a major health burden globally. Current treatments mainly target controlling symptoms and there are no therapeutics available in clinical practice to preventing the neurodegeneration or inducing neuronal repairing. Thus, the demand of novel research for the two disorders is imperative. This literature review aims to provide a collection of published work on PD and AD and current uses of endocannabinoid system (ECS) as a potential drug target for neurodegeneration. PD is frequently treated with L-DOPA and deep brain stimulation. Recent gene modification and remodelling techniques, such as CRISPR through human embryonic stem cells and induced pluripotent stem cells, have shown promising strategy for personalised medicine. AD characterised by extracellular deposits of amyloid β-senile plaques and

neurofibrillary tangles of tau protein commonly uses choline acetyltransferase enhancers as therapeutics. The ECS is currently being studied as PD and AD drug targets where overexpression of ECS receptors exerted neuroprotection against PD and reduced neuroinflammation in AD. The delta-9-tetrahydrocannabinoid (Δ9-THC) and cannabidiol (CBD) cannabinoids of plant Cannabis sativa have shown neuroprotection upon PD and AD animal models yet triggered toxic effects on patients when administered directly. Therefore, understanding the precise molecular cascade following cannabinoid treatment is suggested, focusing especially on gene expression to identify drug targets for preventing and repairing neurodegeneration."

-Faculty of Science, Engineering and Built Environment, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria 3216 Australia

-Faculty of Health, School of Medicine, Deakin University, Waurn Ponds, Victoria 3216 Australia

-Section of Genetics, Institute for Research & Development in Health & Social Care, Colombo, Sri Lanka

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7515854

■■■

"In addition to PD [Parkinson's Disease] and AD [Alzheimer's Disease], the ECS has been intensively studied as high potential target for therapeutics for other disease conditions as well. The involvement of ECS in pain perception and reward processing makes the ECS a target for treatment for chronic pain [111]. The ECS genetics have shown close association with energy and glucose metabolism, thereby affecting the diabetes conditions [112]. The published literature also evidence that the ECS exerts a neuroprotective effect on stroke where CB1R and CB2R antagonists have the potential to be developed into therapeutics for stroke [113]. A summary of collection of published data for other diseases associated with ECS component is given in Table 1."

-Faculty of Science, Engineering and Built Environment, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria 3216 Australia

-Faculty of Health, School of Medicine, Deakin University, Waurn Ponds, Victoria 3216 Australia

-Section of Genetics, Institute for Research & Development in Health & Social Care, Colombo, Sri Lanka

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7515854

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7515854/table/Tab1

Associations between Use of Specific Analgesics and Concentrations of Amyloid-β 42 or Phospho-Tau in Regions of Human Cerebral Cortex.

..."People with high opioid usage had significantly greater concentration of phospho-tau in middle frontal gyrus than people with little-to-no opioid usage. Consistent with our previous studies, findings suggest that high levels of NSAID use in older individuals may promote Aβ42

accumulation in cerebral cortex"

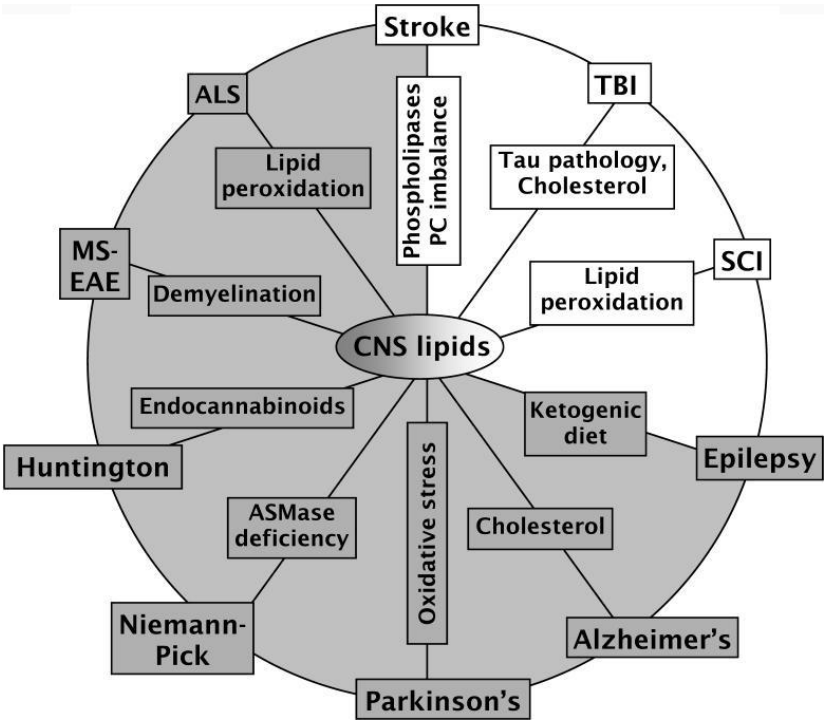
-Department of Pathology, Stanford University, Stanford, CA, USA.
-Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA.
-Department of Medicine, University of Washington, Seattle, WA, USA.
-Department of Pathology, University of Washington, Seattle, WA, USA.
-Department of Pathology, University of Utah, Salt Lake City, UT, USA.
-Department of Epidemiology, University of Washington, Seattle, WA, USA.
https://www.ncbi.nlm.nih.gov/pubmed/29226863

The Cannabinoid CB2 Receptor as a Target for Inflammation-Dependent Neurodegeneration

…"CB2 is believed to be devoid of psychoactivity, and has significant anti-inflammatory functions. Inflammation is known to be a critical part of many types of neurodegeneration [10]. However, non-steroidal antinflammatory drugs (NSAIDS) inhibit clot formation, and increase haemorrhaging during brain injury [58]. Because of this, novel drug targets for the control of inflammation in the brain are of considerable interest and, therefore, the CB2 receptor has recently attracted attention as a potential target for neuroprotection. The rationale for CB2 as a target for neuroinflammatory neurodegeneration will be discussed in detail in the remainder of this article."…

-Department of Pharmacology & Toxicology, University of Otago, New Zealand
-Department of Pharmacology, University of Auckland, New Zealand
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2435344/

…"Neurodegenerative diseases, mental disorders, stroke and CNS traumas are problems of vast clinical importance. The crucial role of lipids in tissue physiology and cell signaling is demonstrated by the many neurological disorders, including bipolar disorders and schizophrenia, and neurodegenerative diseases such as Alzheimer's, Parkinson's, Niemann-Pick and Huntington diseases, that involve deregulated lipid metabolism (Fig. 1) (Adibhatla and Hatcher, 2007, and references cited therein). Altered lipid metabolism is also believed to be a key event which contributes to CNS injuries such as stroke (Adibhatla and Hatcher, 2008, and references cited therein; Adibhatla, et al., 2006a)."…



- Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- Cardiovascular Research Center, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- Neuroscience Training Program, University of Wisconsin School of Medicine and Public Health, Madison, WI.
- William S. Middleton Veterans Affairs Hospital, Madison, WI.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2293298/

Neurogensis

…"Given that eCBs [endocannabinoids] elicit their activities through receptor activation, it was hypothesized that DHA-EA [omega-3] promoted synaptogenesis by acting as an endogenous ligand of GPR110. In the study, use of GPR110 KO mice abolished DHA-EA bioactivity by significantly reducing synaptic protein expression and synapse number in developing brains. DHA-EA also induced neurogenic differentiation and neurite outgrowth, which were also dependent upon GPR110 activation. Hence, the DHA-EA/GPR110 signaling is hypothesized to be an essential mechanism for active neurogenesis and synaptogenesis, proving vital for the development of brain function [42].

The role of DHA-EA in neural development may further be supported by the detection of DHA-EA in murine embryonic stem cells and neural stem cells (NSCs) [43, 44]. In NSCs, DHA-EA treatment induced neuronal differentiation for seven days. The maximum effect for DHA-EA was measured

at 10 nM alone and at 5 nM in the presence of a FAAH inhibition. At nanomolar concentrations, DHA-EA was 50 to 100-fold more effective, than DHA, at increasing expression of neuron-specific markers, microtubule-associated protein 2 (MAP2) and class III beta-tubulin (Tuj-1). Interestingly, DHA-EA also increased phosphorylation of protein kinase A (PKA) substrates, which have been demonstrated to mediate the CREB signaling pathway [44]. For instance, ethanol reduced levels of cAMP and hindered the ability of NSCs to differentiate, yet, DHA-EA treatment reversed these ethanol-induced effects. Additionally, at concentrations between 1 and 10 nM, DHA-EA significantly increased the cellular cAMP production and upregulated expression of adenylyl cyclase's, AC7 and AC8, which are important regulators of cAMP levels. Notably, in the presence of 25 mM ethanol, 1 to 5 nM of DHA-EA completely reversed cAMP reduction [45]."

-Department of Comparative Biosciences, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States

-Department of Biochemistry, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States

-Division of Nutritional Sciences, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States

-Beckman Institute for Advanced Science, Neuroscience Program, Center for Biophysics and Quantitative Biology, Department of Bioengineering, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6685292

Cannabinoid receptor subtype influence on neuritogenesis in human SH-SY5Y cells

…."We propose that basal endogenous production of 2-AG provides autocrine stimulation of CB1 receptor signaling through Gi/o, Gβγ, and β-arrestin mechanisms to promote neuritogenesis, and rho kinase influences process extension."

-Department of Physiology and Pharmacology, Wake Forest School of Medicine, One Medical Center Blvd., Winston-Salem, USA.

-Discovery Sciences, RTI International, Research Triangle Park, USA.

https://pubmed.ncbi.nlm.nih.gov/33049367/

The cannabinoid WIN55212-2 promotes neural repair after neonatal hypoxia-ischemia

…"Our results suggest that the activation of the endocannabinoid system promotes white and gray matter recovery after neonatal HI injury."…

-Unidad de Investigación Neurovascular, Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/21115947/

Neuroinflammatory Diseases

The influence of cannabinoids on generic traits of neurodegeneration

“In an increasingly ageing population, the incidence of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and Huntington's disease are rising. While the aetiologies of these disorders are different, a number of common mechanisms that underlie their neurodegenerative components have been elucidated; namely neuroinflammation, excitotoxicity, mitochondrial dysfunction and reduced trophic support. Current therapies focus on treatment of the symptoms and attempt to delay the progression of these diseases but there is currently no cure. Modulation of the endogenous cannabinoid system is emerging as a potentially viable option in the treatment of neurodegeneration. Endocannabinoid signalling has been found to be altered in many neurodegenerative disorders. To this end, pharmacological manipulation of the endogenous cannabinoid system, as well as application of phytocannabinoids and synthetic cannabinoids have been investigated. Signalling from the CB1 and CB2 receptors are known to be involved in the regulation of Ca(2+) homeostasis, mitochondrial function, trophic support and inflammatory status, respectively, while other receptors gated by cannabinoids such as PPARγ, are gaining interest in their anti-inflammatory properties. Through multiple lines of evidence, this evolutionarily conserved neurosignalling system has shown neuroprotective capabilities and is therefore a potential target for neurodegenerative disorders. This review details the mechanisms of neurodegeneration and highlights the beneficial effects of cannabinoid treatment.”

-Trinity College Institute of Neuroscience, Department of Physiology, School of Medicine, University of Dublin, Trinity College, Dublin 2, Ireland.

https://pubmed.ncbi.nlm.nih.gov/24172185/

Cannabinoids and neuroinflammation (fix ABBREVIATIONS)

“Growing evidence suggests that a major physiological function of the cannabinoid signaling system is to modulate neuroinflammation. This review discusses the anti-inflammatory properties of cannabinoid compounds at molecular, cellular and whole animal levels, first by examining the evidence for anti-inflammatory effects of cannabinoids obtained using in vivo animal models of clinical neuroinflammatory conditions, specifically rodent models of multiple sclerosis, and second by describing the endogenous cannabinoid (endocannabinoid) system components in immune cells. Our aim is to identify immune functions modulated by cannabinoids that could account for their anti-inflammatory effects in these animal models.”…

"Cells involved in neuroinflammation express functional cannabinoid receptors and produce and degrade endocannabinoids, suggesting that the endocannabinoid signaling system has a regulatory function in the inflammatory response. Specifically, during neuroinflammation, there is an upregulation of components involved in the cannabinoid signaling system. This suggests that the cannabinoid signaling system participates in the complex development of this disease, which includes a tight orchestration of the various immune cells involved. If this is the case, the cannabinoid signaling machinery may provide ideal targets, since these would be more susceptible to pharmacological effects than those in the same system under healthy conditions. In line with this, cannabinoid compounds alter the functions of these cells, generally by eliciting anti-inflammatory effects. In the case of MS [multiple sclerosis], neuroinflammation is accompanied by autoimmunity and suppressing the immune response may halt or even prevent associated symptoms. As seen in rodent models of MS, cannabinoids ameliorate the progression of and symptoms associated with neuroinflammation. Future experiments into the components that alter endocannabinoid production and degradation, cannabinoid receptor expression, and effects of cannabinoid receptor agonists on immune cells will provide the necessary information to design more effective treatments for neuroinflammation."

-Department of Pharmacology, University of Washington, Seattle, WA 98195, U.S.A.
-Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98195, U.S.A.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1574256

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…"Neuroinflammation is a pivotal determinant in the pathogenesis and progression of multiple acute and chronic neurodegenerative diseases. Microglial activation, reactive astrogliosis, production of inflammatory mediators (cytokines, chemokines, nitric oxide [NO], reactive oxygen and nitrogen species [ROS/RNS]), BBB breakdown and subsequent brain infiltration of circulating immune cells characterize this process (Becher et al., 2017). Both microglial activation and reactive astrogliosis constitute graded and multistage conserved glial reactions that counteract acute damage, restoring the homeostasis and limiting the brain parenchyma injury (Kettenmann et al., 2011; Pekny and Pekna, 2014). Nevertheless, during severe challenges and chronic brain damage, microglia and astrocytes may turn in uncontrolled source of inflammatory mediators rather than exhibiting a repair-oriented activity profile. While an efficient immune response is necessary to resolve brain threats, under the above circumstances, astrocytes and microglia may worsen disease progression by altering synaptic function, ion homeostasis, antioxidant defense and neuronal survival.

A growing body of data support the idea that eCBs are endowed with powerful immunoregulatory and anti-inflammatory properties, influencing both the CNS and peripheral

tissues (Walter and Stella, 2003; Rom and Persidsky, 2013; Turcotte et al., 2015). eCBs and synthetic CB receptor agonists decrease the production of NO, ROS/RNS, free radicals and pro-inflammatory cytokines in activated glial cells, while facilitate the switching of dysfunctional microglia towards an anti-inflammatory phenotype (Waksman et al., 1999; Molina-Holgado E. et al., 2002; Molina-Holgado et al., 2003; Sheng et al., 2005; Mecha et al., 2015). Remarkably, brain levels of eCBs and glial CB receptors increase during neuroinflammation and neurodegenerative conditions, which may reflect self-neuroprotective and adaptive processes aimed at limiting the deleterious effects of inflammatory responses. In this line, CBs have been proposed as therapeutic tools to tackle several brain pathologies such as AD, multiple sclerosis (MS), Huntington's disease (HD), traumatic brain injury (TBI), Parkinson's disease (PD), among others (Kendall and Yudowski, 2016; Lu and Mackie, 2016). Supporting this notion, CB administration greatly mitigates the symptoms generated in animal models of MS (Lyman et al., 1989), HD (Palazuelos et al., 2009) and AD (Ramírez et al., 2005; Martín-Moreno et al., 2012), as well as a well-characterized model of chronic neuroinflammation produced by the infusion of lipopolysaccharide (LPS; Marchalant et al., 2007). Accumulating evidence suggests that neuroprotective actions of CBs depend on cellular and molecular events modulating the dysfunctional status of glial cells (Stella, 2004, 2010). At this point, one line of thought has argued that CBs may favor neuronal survival by inhibiting the uncontrolled activity of glial hemichannels and pannexons (Orellana et al., 2012c)."...

-Departamento de Neurología, Escuela de Medicina, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

-Centro de Investigación y Estudio del Consumo de Alcohol en Adolescentes, Santiago, Chile

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5890195

See also Cytokine Network , Neurodegenerative Disorders & Diseases

Neurological Disease

Endocannabinoid dysfunction in neurological disease: neuro-ocular DAGLA-related syndrome (NODRS)

"The endocannabinoid system is a highly conserved and ubiquitous signaling pathway with broad ranging effects. Despite critical pathway functions, gene variants have not previously been conclusively linked to human disease. We identified nine children from eight families with heterozygous, de novo truncating variants in the last exon of DAGLA with a neuro-ocular phenotype characterized by developmental delay, ataxia, and complex oculomotor abnormality.

All children displayed paroxysms of nystagmus or eye deviation accompanied by compensatory head posture and worsened incoordination most frequently after waking. RNAseq showed clear expression of the truncated transcript and no differences were found between mutant and wild type DAGLA activity. Immunofluorescence staining of patient-derived fibroblasts and HEK cells expressing the mutant protein showed distinct perinuclear aggregation not detected in control samples. This report establishes truncating variants in the last DAGLA exon as the cause of a unique pediatric syndrome. Because enzymatic activity was preserved, the observed mis-localization of the truncated protein may account for the observed phenotype. Potential mechanisms include DAGLA haploinsufficiency at the plasma membrane or dominant negative effect. To our knowledge, this is the first report directly linking an endocannabinoid system component with human genetic disease and sets the stage for potential future therapeutic avenues."

-Rady Children's Institute for Genomic Medicine (RCIGM), San Diego, USA.

-Sanford Burnham Prebys Medical Discovery Institute, La Jolla, USA.

-The Scripps Research Translational Institute, The Scripps Research Institute, La Jolla, USA.

-Institute of Human Genetics, University Medical Center Leipzig, Germany.

-Department of Neurology and Neurosurgery, McGill University, Montreal, Canada.

-Department of Pediatrics and Human Genetics, McGill University, Montreal, Canada.

-Department of Human Genetics, McGill University, Montreal, Canada.

-Department Specialized Medicine, Division of Medical Genetics, McGill University Health Center, Montreal, Canada.

-Child Health and Human Development Program, Research Institute of the McGill University Health Center, Montreal, Canada.

-Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences Bambino Gesu' Children's Research Hospital, IRCCS, Rome, Italy.

-Centre de Référence Malformations et Maladies Congénitales du Cervelet, Département de génétique, AP-HP.Sorbonne Université, Hôpital Trousseau, Paris, France.

-Developmental Brain Disorders Laboratory, Imagine Institute, INSERM UMR, Paris, France.

-Duke University Medical Center, Department of Pediatrics, Division Medical Genetics Durham, NC USA.

-Illumina, San Diego, USA.

-Division of Pediatric Neurology, Department of Pediatrics, University of Alabama, USA.

-Department of Genetics, University of Alabama at Birmingham; Birmingham, USA.

-Vestische Kinder- und Jugendklinik, Germany.

-Department of Neurology, Boston Children's Hospital, USA.

-Translational Cytogenomics Research Unit, Bambino Gesù Children's Hospital, IRCCS, Italy.

-Sorbonne Université, AP-HP.SU, Centre de Référence Maladies Rares Malformations et Maladies Congénitales du Cervelet & Service de Neuropédiatrie, Hôpital Trousseau, Paris, France.

-Ratner Children's Eye Center at the Shiley Eye Institute; Viterbi Family Department of Ophthalmology, University of California San Diego, La Jolla, USA.

-Department of Developmental Neuroscience, IRCCS Stella Maris Foundation, Italy.

-Tuscan PhD Program of Neuroscience, University of Florence, Italy.

-Genomic Medicine Center, Children's Mercy Hospital, Kansas City, USA.

-Faculty of Medicine, University of Missouri Kansas City, USA.
-Department of Pathology, Children's Mercy Hospital, USA.
-Institute of Human Genetics, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany.
-Rady Children's Hospital San Diego, USA.
-Department of Neurosciences, University of California, USA.
-Department of Pediatrics, University of California, USA.
https://pubmed.ncbi.nlm.nih.gov/35737950/

Neurotransmitters

"The endocannabinoid system is involved in memory, cognition, and pain perception by the presynaptic cannabinoid CB(1) receptor, which is expressed at high levels in many brain regions. Functional studies have shown that activation of cannabinoid CB(1) receptors inhibits the synaptic release of many neurotransmitters such as gamma-aminobutyric acid, glutamate, acetylcholine and monoamines. Monoamines, however, are known not only to be released from and taken back up at nerve terminals but also at extrasynaptic axonal and somatodendritic sites. Here we present immunocytochemical data documenting cannabinoid CB(1) receptor expression on neurite extensions and over cell bodies of serotonergic and dopaminergic neurons."

-Biochemical Laboratory, Central Institute of Mental Health, Mannheim, Germany.
https://pubmed.ncbi.nlm.nih.gov/17931621/

Neuropathic Pain (Nerve Pain)

The endocannabinoid system and neuropathic pain.

"The research of new therapeutic strategies for neuropathic pain represents a major current priority. Important drawbacks to advance in the development of these therapies are the limited translational value of the animal models now available and the elucidation of the complex neuronal and immune pathophysiological mechanisms underlying neuropathic pain. One of the neurotransmitter systems participating in neuropathic pain control that has recently raised a particular interest is the endocannabinoid system. This system is highly expressed in neurons and immune cells, and it plays a crucial role in the development of neuropathic pain. Preclinical studies have provided important findings, revealing the potential interest of the endocannabinoid system for the treatment of neuropathic pain. These studies have reported the analgesic effects of cannabinoid agonists in multiple neuropathic pain models, and they have

identified specific targets within this system to develop more effective and safe analgesic compounds. However, further studies using more relevant neuropathic pain animal models are required to confirm these interesting results. Several clinical studies suggest that cannabinoids significantly reduced neuropathic pain, although most of these trials fail the required standards of quality. The different pain patient populations included in the systematic reviews also make it difficult to get adequate conclusions. Therefore, additional clinical trials that consider an adequate number of patients, the use active treatments as controls, and longer duration of administration are required to have an adequate profile of the effectiveness and safety of cannabinoids in neuropathic pain."

-*Laboratory of Neuropharmacology, Department of Experimental and Health Sciences (CEXS), Faculty of Health and Life Sciences, Pompeu Fabra University, Barcelona, Spain.*
(Laboratori de Neurofarmacologia, Departament de Ciències Experimentals i de la Salut (CEXS), Facultat de Ciències de la Salut i de la Vida…)
https://www.ncbi.nlm.nih.gov/pubmed/26785153

Protection against Neuropathic Pain

…"Currently, there is a growing realization that lesions to the peripheral or central nervous system could lead to neuropathic pain [48]. Currently, both ionotropic P2X receptors and metabotropic P2Y receptors have been identified as key receptors in mediating neuropathic pain [49]. As H. erinaceus mycelium [from lion's main mushroom] has a crucial role in nerve regeneration via the stimulation of neurotrophic factors, the analgesic potential of this mycelium using both a P2 purinergic receptor-coupled Ca2+ signaling platform and an in vivo model was investigated. The results indicated that the extracts of H. erinaceus mycelium could completely block ATP-induced Ca2+ signaling in human HOS cells, suggesting its inhibitory potential as a modulator of pain-related P2X receptors [50]. In addition, administration of the extracts of H. erinaceus mycelium in heat-induced mice could significantly postpone the tail-flick response to heat stimulation as well as the paw-lifting response to a hot plate, indicating that it has an excellent potential for pain relief."

-*Grape King Bio Ltd, Zhong-Li Dist., Taoyuan City, Taiwan*
-*Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei City, Taiwan*
-*Institute of Food Science and Technology, National Taiwan University, Taipei City, Taiwan*
-*Department of Food Science, Nutrition and Nutraceutical Biotechnology, Shih Chien University, Taipei City, Taiwan*
-*Institute of Biotechnology, National Changhua University of Education, Changhua, Taiwan*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987239/

Neuroprotection

“Neuroprotection is defined as the ability for a therapy to prevent neuronal cell death by intervening in and inhibiting the pathogenetic cascade that results in cell dysfunction and eventual death.”

- Blue Books of Neurology, 2010
https://www.sciencedirect.com/topics/neuroscience/neuroprotection

■■■

..."As n-3 [omega-3] and n-6 [omega-6] shares the same elongation/desaturation enzymes for their synthesis, chronic deprivation of n-6 PUFAs in rats decreases the loss of arachidonic acid and increases DHA metabolism to promote neuroprotection and alter neurotransmission [9–11], while deficiency in n-3 PUFAs induces the turnover of n-6 long chain unsaturated fatty acids [12]. Their metabolic cascades are altered reciprocally by the change of dietary PUFAs [11, 13, 14]. Therefore, diminishment of brain DHA (C22:6n-3) can lead to the increase of DPA (C22:5n-6), with one fewer double bond at the terminal methyl end of the chain [15, 16]. The replacement of DHA (n-3) with DPA (n-6) may alter the properties of neural membranes and the function of integral receptor proteins[17]. n-3 PUFAs compete with n-6 fatty acids for elongation/desaturation enzymes that catalyze them; thus, dietary supplementation of n-3 PUFAs significantly increases the concentration of DHA, and leads to a decrease in n-6 derived PUFAs such as AA in the cerebral cortex of rodents [18–20]. This shift in fatty acid make up can contribute to development of a neuroprotective state. "...

-State Key Laboratory of Medical Neurobiology, Institute of Brain Sciences and Collaborative Innovation Center for Brain Science, Fudan University, Shanghai, China

-Pittsburgh Institute of Brain Disorders & Recovery and Department of Neurology University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

-Geriatric Research, Education and Clinical Center Veterans Affairs Pittsburgh Health Care System, Pittsburgh, PA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5650946/

Cannabinoids and cell fate

“Cannabinoids recently have been shown to control the cell survival/death decision. Thus, cannabinoids induce growth arrest or apoptosis in a number of transformed neural and non-neural cells in culture. In addition, cannabinoid administration induces regression of malignant gliomas in rodents by a mechanism that may involve sustained ceramide generation and

extracellular signal-regulated kinase activation. In contrast, most of the experimental evidence indicates that cannabinoids may protect normal neurons from toxic insults, such as glutamatergic overstimulation, ischaemia, and oxidative damage. Regarding immune cells, low doses of cannabinoids may enhance proliferation, whereas high doses of cannabinoids usually induce growth arrest or apoptosis. The potential therapeutic applications of these findings are discussed."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain
https://pubmed.ncbi.nlm.nih.gov/12182964/

Control of the cell survival/death decision by cannabinoids

"Cannabinoids, the active components of Cannabis sativa (marijuana), and their derivatives produce a wide spectrum of central and peripheral effects, some of which may have clinical application. The discovery of specific cannabinoid receptors and a family of endogenous ligands of those receptors has attracted much attention to cannabinoids in recent years. One of the most exciting and promising areas of current cannabinoid research is the ability of these compounds to control the cell survival/death decision. Thus cannabinoids may induce proliferation, growth arrest, or apoptosis in a number of cells, including neurons, lymphocytes, and various transformed neural and nonneural cells. The variation in drug effects may depend on experimental factors such as drug concentration, timing of drug delivery, and type of cell examined. Regarding the central nervous system, most of the experimental evidence indicates that cannabinoids may protect neurons from toxic insults such as glutamaergic overstimulation, ischemia and oxidative damage. In contrast, cannabinoids induce apoptosis of glioma cells in culture and regression of malignant gliomas in vivo. Breast and prostate cancer cells are also sensitive to cannabinoid-induced antiproliferation. Regarding the immune system, low doses of cannabinoids may enhance cell proliferation, whereas high doses of cannabinoids usually induce growth arrest or apoptosis. The neuroprotective effect of cannabinoids may have potential clinical relevance for the treatment of neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, and ischemia/stroke, whereas their growth-inhibiting action on transformed cells might be useful for the management of malignant brain tumors. Ongoing investigation is in search for cannabinoid-based therapeutic strategies devoid of nondesired psychotropic effects."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain
https://pubmed.ncbi.nlm.nih.gov/11269508/

Cannabinoid receptors and their role in neuroprotection

"Two G protein-coupled receptors for marijuana's psychoactive component, Delta9-tetrahydrocannabinol, have been cloned to date, the cannabinoid CB1 and CB2 receptors. These two proteins, the endogenous lipids that activate them, also known as endocannabinoids, and the proteins for the biosynthesis and inactivation of these ligands constitute the endocannabinoid system. Evidence has accumulated over the last few years suggesting that endocannabinoid-based drugs may potentially be useful to reduce the effects of neurodegeneration. In fact, exogenous and endogenous cannabinoids were shown to exert neuroprotection in a variety of in vitro and in vivo models of neuronal injury via different mechanisms, such as prevention of excitotoxicity by cannabinoid CB1-mediated inhibition of glutamatergic transmission, reduction of calcium influx, anti-oxidant activity, activation of the phosphatidylinositol 3-kinase/protein kinase B pathway, induction of phosphorylation of extracellular regulated kinases and the expression of transcription factors and neurotrophins, lowering of cerebrovasoconstriction and induction of hypothermia. The release of endocannabinoids during neuronal injury may constitute a protective response. If this neuroprotective function of cannabinoid receptor activation can be transferred to the clinic, it might represent an interesting target to develop neuroprotective agents."

-Endocannabinoid Research Group, Institute of Biomolecular Chemistry, National Research Council, Pozzuoli, NA, Italy.
https://pubmed.ncbi.nlm.nih.gov/16052037/

Using the endocannabinoid system as a neuroprotective strategy in perinatal hypoxic-ischemic brain injury

"One of the most important causes of brain injury in the neonatal period is a perinatal hypoxic-ischemic event. This devastating condition can lead to long-term neurological deficits or even death. After hypoxic-ischemic brain injury, a variety of specific cellular mechanisms are set in motion, triggering cell damage and finally producing cell death. Effective therapeutic treatments against this phenomenon are still unavailable because of complex molecular mechanisms underlying hypoxic-ischemic brain injury. After a thorough understanding of the mechanism underlying neural plasticity following hypoxic-ischemic brain injury, various neuroprotective therapies have been developed for alleviating brain injury and improving long-term outcomes. Among them, the endocannabinoid system emerges as a natural system of neuroprotection. The endocannabinoid system modulates a wide range of physiological processes in mammals and has demonstrated neuroprotective effects in different paradigms of acute brain injury, acting as a natural neuroprotectant. The aim of this review is to study the use of different therapies to induce long-term therapeutic effects after hypoxic-ischemic brain injury, and analyze the

important role of the endocannabinoid system as a new neuroprotective strategy against perinatal hypoxic-ischemic brain injury."….

-Department of Cell Biology and Histology, School of Medicine and Dentistry, University of the Basque Country, Leioa, Bizkaia, Spain

-GAIKER Technology Centre, Bizkaia Science and Technology Park, Bizkaia, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4146074/

Neurological benefits of omega-3 fatty acids

"The central nervous system is highly enriched in long-chain polyunsaturated fatty acid (PUFA) of the omega-6 and omega-3 series. The presence of these fatty acids as structural components of neuronal membranes influences cellular function both directly, through effects on membrane properties, and also by acting as a precursor pool for lipid-derived messengers. An adequate intake of omega-3 PUFA is essential for optimal visual function and neural development. Furthermore, there is increasing evidence that increased intake of the long-chain omega-3 PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may confer benefits in a variety of psychiatric and neurological disorders, and in particular neurodegenerative conditions. However, the mechanisms underlying these beneficial effects are still poorly understood. Recent evidence also indicates that in addition to the positive effects seen in chronic neurodegenerative conditions, omega-3 PUFA may also have significant neuroprotective potential in acute neurological injury. Thus, these compounds offer an intriguing prospect as potentially new therapeutic approaches in both chronic and acute conditions. The purpose of this article is to review the current evidence of the neurological benefits of omega-3 PUFA, looking specifically at neurodegenerative conditions and acute neurological injury."

-British College of Osteopathic Medicine, Lief House, London, UK.

https://pubmed.ncbi.nlm.nih.gov/18543124/

Neutrophils

Omega-3 Fatty acids and inflammation: novel interactions reveal a new step in neutrophil recruitment.

"Inflammation is a physiological response to tissue trauma or infection, but leukocytes, which are the effector cells of the inflammatory process, have powerful tissue remodelling capabilities. Thus, to ensure their precise localisation, passage of leukocytes from the blood into inflamed tissue is tightly regulated. Recruitment of blood borne neutrophils to the tissue stroma occurs

during early inflammation. In this process, peptide agonists of the chemokine family are assumed to provide a chemotactic stimulus capable of supporting the migration of neutrophils across vascular endothelial cells, through the basement membrane of the vessel wall, and out into the tissue stroma. Here, we show that, although an initial chemokine stimulus is essential for the recruitment of flowing neutrophils by endothelial cells stimulated with the inflammatory cytokine tumour necrosis factor-alpha, transit of the endothelial monolayer is regulated by an additional and downstream stimulus. This signal is supplied by the metabolism of the omega-6-polyunsaturated fatty acid (n-6-PUFA), arachidonic acid, into the eicosanoid prostaglandin-D(2) (PGD(2)) by cyclooxygenase (COX) enzymes. This new step in the neutrophil recruitment process was revealed when the dietary n-3-PUFA, eicosapentaenoic acid (EPA), was utilised as an alternative substrate for COX enzymes, leading to the generation of PGD(3). This alternative series eicosanoid inhibited the migration of neutrophils across endothelial cells by antagonising the PGD(2) receptor. Here, we describe a new step in the neutrophil recruitment process that relies upon a lipid-mediated signal to regulate the migration of neutrophils across endothelial cells. PGD(2) signalling is subordinate to the chemokine-mediated activation of neutrophils, but without the sequential delivery of this signal, neutrophils fail to penetrate the endothelial cell monolayer. Importantly, the ability of the dietary n-3-PUFA, EPA, to inhibit this process not only revealed an unsuspected level of regulation in the migration of inflammatory leukocytes, it also contributes to our understanding of the interactions of this bioactive lipid with the inflammatory system. Moreover, it indicates the potential for novel therapeutics that target the inflammatory system with greater affinity and/or specificity than supplementing the diet with n-3-PUFAs"…
“

Neutrophils, which circulate in the blood stream, are the first inflammatory cells to be recruited to a site of tissue inflammation. In response to recruitment signals provided by chemotactic peptides called chemokines, neutrophils traverse the endothelial cell lining of blood vessels. This process involves a multistep cascade of neutrophil adhesion and activation events on the endothelial barrier. While investigating the anti-inflammatory functions of the omega-3 fatty acid , EPA, which is found, for instance, in dietary fish oil, we identified an additional unexpected lipid-derived signal that is essential for neutrophil migration across the endothelium. Our experiments show that a chemokine delivered the first signal needed to bind neutrophils firmly to the endothelial surface. However, in order to traverse the endothelium, a subsequent signal delivered by prostaglandin-D2 (PGD2), a lipid derived from the omega-6 fatty acid arachidonic acid, was essential. When EPA, was introduced into the experiment, it was used to form PGD3. This alternative lipid blocked interactions between PGD2 and its receptor on neutrophils, preventing the process of migration across the endothelial barrier. Thus, we reveal a new step in

the recruitment of neutrophils during inflammation, and a novel anti-inflammatory mechanism of action of dietary EPA."…

-Centre for Cardiovascular Sciences, School of Clinical and Experimental Medicine, The Medical School, The University of Birmingham, Birmingham, United Kingdom

-Department of Medical Biochemistry and Immunology, School of Medicine, Cardiff University, Cardiff, United Kingdom

-Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, United Kingdom

-NIH/NIAID, United States of America

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2718617/

Effects of Omega-3 Fatty Acids on Neutrophil Function

.."The most abundant leukocyte in humans is the neutrophil. The vast majority of mature neutrophils are found in the circulation, blood, and the marginal pools (bone marrow, spleen, and liver), whereas a small portion is found in tissues [55,56,57]. Neutrophils are the first cells to be recruited to the site of inflammation [58] and have an important role in the clearance of pathogens. However, neutrophils can also interact with the adaptive immune system by promoting naïve T cells to transition into T helper 1 cells and can present antigens to B-cells in the spleen [59].

Omega-3 fatty acids have been shown to be incorporated into phospholipids in the cell membrane of neutrophils at the expense of the omega-6 fatty acids linoleic and arachidonic acid [13,60]. Once the omega-3 fatty acids have been incorporated into the phospholipids, they can be metabolized by neutrophils into prostaglandins, leukotrienes, thromboxanes, maresins, protectins, and resolvins [10,61,62]. Omega-3 fatty acids, and their metabolites, modulate neutrophil function in several ways, including neutrophil migration, phagocytic capacity, as well as the production of reactive oxygen species and cytokines."…

-Department of Physiology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Sweden

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6834330/

Neutropenia

"Neutropenia is when a person has a low level of neutrophils. Neutrophils are a type of white blood cell. All white blood cells help the body fight infection. Neutrophils fight infection by destroying harmful bacteria and fungi (yeast) that invade the body. Neutrophils are made in the bone marrow. Bone marrow is the spongy tissue found in larger bones such as the pelvis,

vertebrae, and ribs.

Half of people with cancer who are receiving chemotherapy have some level of neutropenia. It is a common side effect in people with leukemia. People who have neutropenia have a higher risk of getting serious infections. This is because they do not have enough neutrophils to kill organisms that cause infection. People with severe or long-lasting neutropenia are most likely to develop an infection."…

-American Society of Clinical Oncology (ASCO).
https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/neutropenia

Nicotine & Tobacco

"a toxic colorless or yellowish oily liquid that is the chief active constituent of tobacco. It acts as a stimulant in small doses, but in larger amounts blocks the action of autonomic nerve and skeletal muscle cells. Nicotine is also used in insecticides." - *Oxford Languages / Google*

Nicotinic receptor contributions to smoking: insights from human studies and animal models

"It is becoming increasingly evident that a variety of factors contribute to smoking behavior. Nicotine is a constituent of tobacco smoke that exerts its psychoactive effects via binding to nicotinic acetylcholine receptors (nAChRs) in brain. Human genetic studies have identified polymorphisms in nAChR genes, which predict vulnerability to risk for tobacco dependence. In vitro studies and animal models have identified the functional relevance of specific polymorphisms. Together with animal behavioral models, which parse behaviors believed to contribute to tobacco use in humans, these studies demonstrate that nicotine action at a diversity of nAChRs is important for expression of independent behavioral phenotypes, which support smoking behavior."

-Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4540370

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.."Several studies have demonstrated that nAChR [nicotinic acetylcholine receptors] activation results in a significantly increase of tau phosphorylation, whereas mAChR activation, may

prevent tau phosphorylation."…

-Centro de Biología Molecular Severo Ochoa, Universidad Autónoma de Madrid, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/16900665

Tau protein has been linked to Alzheimer's Disease.

Alzheimer's disease and cigarette smoke components:

"Cigarette smoking is a significant risk factor for Alzheimer's disease (AD), which is associated with extracellular brain deposits of amyloid plaques containing aggregated amyloid-β (Aβ) peptides. Aβ aggregation occurs via multiple pathways that can be influenced by various compounds."….

-Department of Biochemistry and Biophysics, Arrhenius Laboratories, Stockholm University, Stockholm, Sweden
-Department of Anthropology, National Museum of Natural History, Smithsonian Institution, Washington, DC USA
-Department of Environmental Science and Analytical Chemistry, Arrhenius Laboratories, Stockholm University, Stockholm, Sweden
-Chemical Research Laboratory, University of Oxford, UK
-The National Institute of Chemical Physics and Biophysics, Tallinn, Estonia
-Institute of Environmental Medicine, Karolinska Institutet, Sweden
-Department of Clinical Physiology, Capio St.Göran Hospital, Stockholm,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5663743

The endogenous cannabinoid system modulates nicotine reward and dependence

"A growing body of evidence suggests that the endogenous cannabinoid system modulates the addictive properties of nicotine, the main component of tobacco that produces rewarding effects."…

"These findings indicate that endocannabinoids play a role in the rewarding properties of nicotine as well as nicotine dependence liability. Specifically, increasing endogenous cannabinoid levels magnifies, although disrupting CB(1) receptor signaling, attenuates nicotine reward and withdrawal. Taken together, these results support the hypothesis that cannabinoid receptor antagonists may offer therapeutic advantages to treat tobacco dependence."…

-Department of Pharmacology and Toxicology, Virginia Commonwealth University, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746999/

"Evidence shows that the endocannabinoid system modulates the addictive properties of nicotine" …

…."Together, the results indicate that pharmacological strategies aimed at enhancing endocannabinoid signaling may offer therapeutic advantages to treat the negative affective state produced by nicotine withdrawal, which is critical for the maintenance of tobacco use."

School of Pharmacy, Pharmacology Unit, University of Camerino, Camerino, Italy
http://www.ncbi.nlm.nih.gov/pubmed/20087854

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"One neurobiological system implicated in the addictive properties of nicotine is the endocannabinoid (EC) system. This system consists of two receptors (CB1 and CB2), which are members of the superfamily of G protein coupled, and exert their actions predominantly through Gi/o proteins (Howlett et al., 2002, 2005), and several endogenous lipid-based signaling molecules (endocannabinoids) that bind to these receptors"

-Department of Pharmacology and Toxicology, Medical College of Virginia Campus, Virginia Commonwealth University, USA
-Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, USA
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3477273

■■■

"The endocannabinoid system has been recently identified as having critical involvement in drug taking and relapse phenomenon for various drugs of abuse and notably nicotine."…
"CONCLUSIONS: These results indicate that the integrity of the CB(1) receptors is necessary for the incentive motivation of the rats for nicotine and that FAAH inhibition may be as effective as CB(1) receptor blockade to prevent reinstatement of nicotine seeking"...

-Translational Addiction Research Laboratory, Centre for Addiction and Mental Health (CAMH), Canada
http://www.ncbi.nlm.nih.gov/pubmed/19484221

■■■

..."Accumulating evidence suggests that the endocannabinoid system might play a major role in neuronal mechanisms underlying the rewarding properties of drugs of abuse, including nicotine."….
"These data indicate for the first time that the anorexic lipids OEA and PEA possess neuromodulatory properties as endogenous ligands of PPAR-α in the brain and provide a potential new target for the treatment of nicotine addiction."…

-B. B. Brodie Department of Neuroscience

-Consiglio Nazionale delle Richerche Institute of Neuroscience, University of Cagliari, Monserrato, Italy,

-Division of Geriatric Medicine and Gerontology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

-Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, Intramural Research Program, Department of Health and Human Services, National Institute on Drug Abuse–National Institutes of Health, Baltimore, Maryland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169176

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…"It has been suggested that nicotine acts on the endocannabinoid system by triggering the release of anandamide and 2-AG in the mesolimbic reward circuitry involving the ventral tegmental area (VTA) and nucleus accumbens (NAcc)[25]. An increase in the levels of endogenous cannabinoids can lead to the presynaptic inhibition of neurotransmitters such as γ-amino butyric acid (GABA), which may subsequently lead to an increase in dopamine levels that enhances the rewarding effects of nicotine. This perspective has been supported Gonzalez and colleagues who demonstrated an increase in anandamide levels in limbic regions following chronic administration of nicotine in rats [26]."...

-Interdepartmental Program in Neuroscience, University of Utah, Salt Lake City, UT, USA

-Diagnostic Neuroimaging, University of Utah, Salt Lake City, UT USA

-Department of Psychiatry, University of Utah, Salt Lake City, UT

-George E. Whalen Department of Veterans Affairs Medical Center, VA VISN 19 Mental Illness Research, Education and Clinical Center (MIRREC), Salt Lake City, UT, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4861316

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"The endocannabinoid system regulates neurotransmission in brain regions relevant to neurobiological and behavioral actions of addicting drugs. We recently demonstrated that inhibition by URB597 of fatty acid amide hydrolase (FAAH), the main enzyme which degrades the endogenous cannabinoid N-acylethanolamine (NAE) anandamide and the endogenous non-cannabinoid NAEs oleoylethanolamide and palmitoylethanolamide, blocks nicotine-induced excitation of ventral tegmental area (VTA) dopamine (DA) neurons and DA release in the shell of the nucleus accumbens (ShNAc), as well as nicotine-induced drug self-administration, conditioned place preference and relapse in rats."

-B.B.Brodie Department of Neuroscience, University of Cagliari, 09042, Monserrato, Italy

-CNR Neuroscience Institute-Cagliari, University of Cagliari, 09042, Monserrato, Italy

-Center of Excellence for the Neurobiology of Addiction, University of Cagliari, 09042, Monserrato, Italy

-Division of Geriatric Medicine and Gerontology, Department of Medicine, John Hopkins University School of Medicine, Baltimore, Maryland 21224

-Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, Intramural Research Program, Department of Health and Human Services,

-National Institute on Drug Abuse,National Institutes of Health, Baltimore, Maryland, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3167063/

Involvement of Arachidonic Acid [omega-6] Metabolites Pathway and Nicotinic Acetylcholine Receptors (nAChRs) on Nicotine-induced Contractions (or Relaxations) in the Basilar Artery

"Smoking is one of the most important risk factors for cerebral circulatory disorders and nicotine is considered to be the major pathogenic compound in cigarette smoke. Amelioration of nicotine-induced vasoconstrictions (or vasodilations) may provide a therapeutic target for the treatment of stroke. This study will review the involvement of arachidonic acid [omega-6] metabolites pathway and nicotinic acetylcholine receptors (nAChRs) on nicotine-induced contractions (or relaxations) in the basilar artery. Arachidonic acid metabolites pathway and nAChRs may be new drug targets and their selectivity antagonists (or agonists) may be new therapeutic drugs for the treatment of stroke."…

-International Journal of Pharmacology, Vol 13, Issue 1, Page. No 1-10

-Yifan Li, Dan Luo, Xuejiao Chen, Jie Li, Liang Yan, Tong Li, Yingliang Zhao, Hui Liu,, Xu Ji and Xiao Ma

https://scialert.net/abstract/?doi=ijp.2017.1.10

Waking a Sleeping Giant: The Tobacco Industry's Response to the Polonium-210 Issue

"The major tobacco manufacturers discovered that polonium was part of tobacco and tobacco smoke more than 40 years ago and attempted, but failed, to remove this radioactive substance from their products. Internal tobacco industry documents reveal that the companies suppressed publication of their own internal research to avoid heightening the public's awareness of radioactivity in cigarettes. Tobacco companies continue to minimize their knowledge about polonium-210 in cigarettes in smoking and health litigation. Cigarette packs should carry a radiation-exposure warning label."…

"In 1964, PO-210 was reported to be a tobacco smoke constituent.[13] PO-210 emits a carcinogenic form of radiation called alpha radiation.[14,15] Inhalation experiments showed PO-210

to be a cause of lung cancers in animals.[16,17] PO-210 is thought to deposit in the bronchial segmental bifurcations, resulting in substantial doses of high-energy alpha radiation in the pulmonary sites where bronchogenic carcinomas frequently arise.[18,19] Alpha radiation has also been shown to induce signaling pathways in cells that are not directly exposed (the so-called bystander effect).[20] Mean tissue concentrations of PO-210 in cigarette smokers have been observed to be more than double those of nonsmokers.[21] It is estimated that smokers of 1.5 packs of cigarettes a day are exposed to as much radiation as they would receive from 300 chest X-rays a year."….

-Monique E. Muggli MPH / Nicotine Research Program, Mayo Clinic, Rochester, MN.
-Jon O. Ebbert MD and Richard D. Hurt MD/ Nicotine Dependence Center, Mayo Clinic, Rochester.
-Channing Robertson PhD / Department of Chemical Engineering, Stanford University, Stanford, CA.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2509609/

Secondhand smoke alters arachidonic acid metabolism and inflammation in infants and children with cystic fibrosis

"Mechanisms that facilitate early infection and inflammation in cystic fibrosis (CF) are unclear. We previously demonstrated that children with CF and parental-reported secondhand smoke exposure (SHSe) have increased susceptibility to bacterial infections. SHSe hinders arachidonic acid (AA) metabolites that mediate immune function in patients without CF, and may influence CF immune dysfunction. We aimed to define SHSe's impact on inflammation mediators and infection in children with CF."….

"Hair nicotine concentrations were elevated in 63% of patients. Of the AA metabolites measured by plasma lipidomics, prostaglandin D2 (PGD2) concentrations were decreased in children with CF exposed to SHSe, and associated with more frequent hospitalisations (p=0.007) and worsened weight z scores (p=0.008). Children with CF exposed to SHSe demonstrated decreased expression of the prostaglandin genes PTGES3 and PTGR2 and overexpression of inflammatory pathways. These findings were confirmed using an in vitro model, where SHSe was associated with a dose-dependent decrease in PGD2 and increased methicillin-resistant Staphylococcus aureus survival in human CF macrophages."

"Infants and young children with CF and SHSe have altered AA metabolism and dysregulated inflammatory gene expression resulting in impaired bacterial clearance. Our findings identified potential therapeutic targets to halt early disease progression associated with SHSe in the young population with CF."

-Division of Pulmonary Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA
-Center for Microbial Pathogenesis, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio, USA

-Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio, USA
-Center for Perinatal Research, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio, USA
-Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA
-Division of Gastroenterology, Hepatology and Nutrition, Nationwide Children's Hospital, Columbus, Ohio, USA
-Riley Children's Hospital, Indianapolis, Indiana, USA
-Section of Ambulatory Pediatrics, Nationwide Children's Hospital, Columbus, Ohio, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7642975

See also Drugs of Abuse

Nightmares

See also Dreams

Nitric Oxide

"Nitric oxide is produced by nearly every type of cell in the human body and one of the most important molecules for blood vessel health. It's a vasodilator, meaning it relaxes the inner muscles of your blood vessels, causing the vessels to widen. In this way, nitric oxide increases blood flow and lowers blood pressure."

https://www.healthline.com/nutrition/nitric-oxide-supplements

The endocannabinoid system: 'NO' longer anonymous in the control of nitrergic signalling?

"The endocannabinoid system (ECS) is a key cellular signalling system that has been implicated in the regulation of diverse cellular functions. Importantly, growing evidence suggests that the biological actions of the ECS may, in part, be mediated through its ability to regulate the production and/or release of nitric oxide, a ubiquitous bioactive molecule, which functions as a versatile signalling intermediate. Herein, we review and discuss evidence pertaining to ECS-mediated regulation of nitric oxide production, as well as the involvement of reactive nitrogen

species in regulating ECS-induced signal transduction by highlighting emerging work supporting nitrergic modulation of ECS function. Importantly, the studies outlined reveal that interactions between the ECS and nitrergic signalling systems can be both stimulatory and inhibitory in nature, depending on cellular context. Moreover, such crosstalk may act to maintain proper cell function, whereas abnormalities in either system can undermine cellular homoeostasis and contribute to various pathologies associated with their dysregulation. Consequently, future studies targeting these signalling systems may provide new insights into the potential role of the ECS–nitric oxide signalling axis in disease development and/or lead to the identification of novel therapeutic targets for the treatment of nitrosative stress-related neurological, cardiovascular, and metabolic disorders."…

-Division of Cell Signalling and Immunology, Sir James Black Centre, School of Life Sciences, University of Dundee, Dundee, DD1 5EH, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5439392/

Increased Contextual Fear Conditioning in iNOS Knockout Mice: Additional Evidence for the Involvement of Nitric Oxide in Stress-Related Disorders and Contribution of the Endocannabinoid System

"Background: Inducible or neuronal nitric oxide synthase gene deletion increases or decreases anxiety-like behavior in mice, respectively. Since nitric oxide and endocannabinoids interact to modulate defensive behavior, the former effect could involve a compensatory increase in basal brain nitric oxide synthase activity and/or changes in the endocannabinoid system. Thus, we investigated the expression and extinction of contextual fear conditioning of inducible nitric oxide knockout mice and possible involvement of endocannabinoids in these responses."…

Conclusion:

"These data reinforce the involvement of the nitric oxide and endocannabinoids (anandamide) in stress-related disorders and point to a deregulation of the endocannabinoid system in situations where nitric oxide signaling is increased."

-Department of Pharmacology, Medical School of Ribeirão Preto (Drs Lisboa, Gomes, Silva, Cunha, and Resstel, Ms Uliana and Ms Camargo), Department of Pharmacology, School of Pharmaceutical Sciences of Ribeirão Preto (Dr Joca), and Center for Interdisciplinary Research on Applied Neurosciences, University of São Paulo, Brazil (Drs Lisboa, Gomes, Guimarães, Joca, and Resstel).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4571624

Crosstalk Between Nitric Oxide and Endocannabinoid Signaling Pathways in Normal and Pathological Placentation

“Endocannabinoids are a group of endogenous lipid mediators that act as ligands of cannabinoid and vanilloid receptors, activating multiple signal transduction pathways. Together with enzymes responsible for their synthesis and degradation, these compounds constitute the endocannabinoid system (ECS), which is involved in different physiological processes in reproduction. The placenta, which is essential for the success of gestation and optimal fetal growth, undergoes constant tissue remodeling. ECS members are expressed in trophoblast cells, and current evidence suggests that this system is involved in placental development, apoptosis, and syncytialization. Impairment of endocannabinoid signaling has been associated with several pathological conditions such as intrauterine growth restriction and preeclampsia. Both clinical entities are characterized by dysregulation on vascular perfusion where nitrergic system performs a pivotal role. Nitric oxide (NO) is a potent local vasodepressor that exerts a critical role in the regulation of hemodynamic flow, contributing to the maintenance of low vascular resistance in the feto-placental circulation. NO production could be affected by different factors and growing evidence suggests that the endocannabinoid mediators may regulate nitrergic signaling. Herein, we review emerging knowledge supporting ECS-mediated regulation of NO production in normal placentation. Finally, we discuss how alterations in these systems could affect homoeostasis and contribute to the occurrence of placental-mediated pregnancy complications. Given the impact on women and perinatal heath, we will focus on current knowledge regarding the effects of ECS on nitrergic system in normal and pathological placentation.”…

-Laboratory for Research Applied to Neurosciences (LIAN), FLENI - CONICET, Belén de Escobar, Argentina
-Laboratory of Placental Physiopathology, CEFyBO-UBA-CONICET, Buenos Aires, Argentina
-High Risk Pregnancy Unit, CEMIC, Buenos Aires, Argentina
-Laboratory of Reproduction Biology, IFIBIO-UBA-CONICET, Buenos Aires, Argentina
-Iberoamerican Network of Vascular Alterations Associated with Pregnancy Disorders (RIVA-TREM), Buenos Aires, Argentina
https://www.frontiersin.org/articles/10.3389/fphys.2018.01699/full

Nitric oxide production from macrophages is regulated by arachidonic acid metabolites

“In activated macrophages the inducible form of the enzyme nitric oxide (NO) synthase generates high amounts of the toxic mediator NO. After 20 h of treatment with LPS rat peritoneal macrophages release 12-16 nmol NO2-/10(5) cells which is detectable in the culture

supernatant by the Griess reaction as a measure of NO formation. The addition of aminoguanidine (1 mM), a preferential inhibitor of the inducible NO-synthase, completely abolished NO2-accumulation. Incubation with indomethacin or acetyl-salicylic acid, preferential inhibitors of the cyclooxygenase pathway of the arachidonic acid metabolism, did not influence NO2- levels. Nordihydro-guaiaretic acid (50 microM), a preferential inhibitor of the lipoxygenase pathway, caused strong reduction of NO2- accumulation to 1.9 +/- 0.3 nmol/200 microliter. Simultaneous inhibition of cyclo- and lipoxygenase by BW755c resulted in an intermediate effect (7.3 +/- 1.1 nmol/200 microliter NO2-). These results show that the induction of NO production in activated macrophages is regulated by products of the lipoxygenase-pathway of the arachidonic acid metabolism."

-Diabetes Research Institute, University of Düsseldorf, Germany.
https://pubmed.ncbi.nlm.nih.gov/7504482/

Non-Alcoholic Fatty Liver Disease (NAFLD)

…"The most common type of liver disease, nonalcoholic fatty liver disease (NAFLD), alone affects more than 65 million Americans with a cost burden of $103 billion annually within the US itself."…

-Division of Biological Sciences, University of California, San Diego, La Jolla, CA, USA
-Department of Pediatrics, University of California San Diego, CA
-Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, CA
-NAFLD Research Center, Division of Gastroenterology, Department of Medicine, University of California at San Diego, San Diego, CA
-Department of Computer Science and Engineering, University of California San Diego, CA
-Department of Medicine, University of California San Diego, La Jolla, CA
-Department of Medicine, VA San Diego Healthcare System, San Diego, CA
-Center for Microbiome Innovation, University of California San Diego, CA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6319369/

Cannabidiol protects liver from binge alcohol-induced steatosis by mechanisms including inhibition of oxidative stress and increase in autophagy

"Acute alcohol drinking induces steatosis, and effective prevention of steatosis can protect liver from progressive damage caused by alcohol. Increased oxidative stress has been reported as one mechanism underlying alcohol-induced steatosis. We evaluated whether cannabidiol, which has been reported to function as an antioxidant, can protect the liver from alcohol-generated

oxidative stress-induced steatosis. Cannabidiol can prevent acute alcohol-induced liver steatosis in mice, possibly by preventing the increase in oxidative stress and the activation of the JNK MAPK pathway. Cannabidiol per se can increase autophagy both in CYP2E1-expressing HepG2 cells and in mouse liver. Importantly, cannabidiol can prevent the decrease in autophagy induced by alcohol. In conclusion, these results show that cannabidiol protects mouse liver from acute alcohol-induced steatosis through multiple mechanisms including attenuation of alcohol-mediated oxidative stress, prevention of JNK MAPK activation, and increasing autophagy."

-School of Public Health, Sun Yat-sen University, Guangzhou, Guangdong, China
-Mount Sinai School of Medicine, New York, NY, USA
-State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4112960/

Omega 3 - Omega 6: What is right for the liver?

"Linoleic and alpha-linolenic acids are the fatty acids designated as "essential" since they are not synthesized by mammalian cells and must be provided in the diet. The recent dietary shift towards the consumption of n-6 (omega-6) at the expense of n-3 (omega-3) polyunsaturated fatty acids (PUFAs) is thought to be a primary cause of many diseases related to the Western diet. The body converts linoleic acid to arachidonic acid and derives eicosapentaenoic acid from alpha-linolenic acid. Ideally the effects of these fatty acids and their eicosanoid derivatives are tailored to the specific biological needs of the body. The balance between n-3 and n-6 PUFAs is essential for metabolism and maintenance of the functions of both classes. The availability of n-3 long chain PUFAs plays a major role in regulating both fat accumulation and its elimination by the liver. Derangement of hepatic n-6:n-3 PUFA ratio impacts on the histological pattern of fatty liver through modulation of the amount of intrahepatic lipids. Moreover, the influence of PUFAs and their eicosanoid products on hepatic microcirculation and ischemia/reperfusion injury has been demonstrated in many studies. This concise review article will focus on the role of PUFAs and eicosanoids in hepatic steatosis, microcirculation and ischemia/reperfusion injury."

-Swiss HPB (Hepato-Pancreatico-Biliary) Centre, Department of Visceral and Transplant Surgery, University Hospital Zurich, Zurich, Switzerland.
https://pubmed.ncbi.nlm.nih.gov/17869370

Arachidonic Acid as an Early Indicator of Inflammation during Non-Alcoholic Fatty Liver Disease Development

"Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease characterized by excessive

lipid deposition. Lipid metabolism disturbances are possibly associated with hepatocyte inflammation development and oxidative balance impairment. The aim of our experiment was to examine the first moment when changes in plasma and liver arachidonic acid (AA) levels as a pro-inflammatory precursor may occur during high-fat diet (HFD)-induced NAFLD development. Wistar rats were fed a diet rich in fat for five weeks, and after each week, inflammation and redox balance parameters were evaluated in the liver. The AA contents in lipid fractions were assessed by gas–liquid chromatography (GLC). Protein expression relevant to inflammatory and lipogenesis pathways was determined by immunoblotting. The oxidative system indicators were determined with assay kits. Our results revealed that a high-fat diet promoted an increase in AA levels, especially in the phospholipid (PL) fraction. Importantly, rapid inflammation development via increased inflammatory enzyme expression, elevated lipid peroxidation product content and oxidative system impairment was caused by the HFD as early as the first week of the experiment. Based on these results, we may postulate that changes in AA content may be an early indicator of inflammation and irreversible changes in NAFLD progression."

-Department of Physiology, Medical University of Bialystok, 15-089 Bialystok, Poland;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7464179/

The importance of the long-chain polyunsaturated fatty acid n-6/n-3 ratio in development of non-alcoholic fatty liver associated with obesity

"Non-alcoholic fatty liver disease (NAFLD) is the most important cause of chronic liver disease that is characterized by hepatocyte triacylglycerol accumulation (steatosis), which can progress to inflammation, fibrosis, and cirrhosis (steatohepatitis). Overnutrition triggers the onset of oxidative stress in the liver due to higher availability and oxidation of fatty acids (FA), with development of hyperinsulinemia and insulin resistance (IR), and n-3 long-chain polyunsaturated FA (n-3 LCPUFA) depletion, with enhancement in the n-6/n-3 LCPUFA ratio favouring a pro-inflammatory state. These changes may lead to hepatic steatosis by different mechanisms, namely, (i) IR-dependent higher peripheral lipolysis and FA flux to the liver, (ii) n-3 LCPUFA depletion-induced changes in DNA binding activity of sterol regulatory element-binding protein 1c (SREBP-1c) and peroxisome proliferator-activated receptor α (PPAR-α) favouring lipogenesis over FA oxidation, and (iii) hyperinsulinemia-induced activation of lipogenic factor PPAR-γ. Supplementation with n-3 LCPUFA appears to reduce nutritional hepatic steatosis in adults, however, other histopathologic features of NAFLD remain to be studied."

-School of Nutrition and Dietetics, Faculty of Medicine, Santiago-7, Chile.
https://pubmed.ncbi.nlm.nih.gov/22008843/

Increase in long-chain polyunsaturated fatty acid n - 6/n - 3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease

"Hepatic steatosis is a major feature associated with NAFLD (non-alcoholic fatty liver disease). The aims of the present study were to assess the levels of PUFA (polyunsaturated fatty acids) in liver total lipids, triacylglycerols (triglycerides) and phospholipids of NAFLD patients in relation to those in adipose tissue and hepatic indexes related to oxidative stress as factors contributing to hepatic steatosis. Eleven control subjects and 19 patients with NAFLD were studied. Analysis of liver and abdominal adipose tissue fatty acids was carried out by GLC. The liver content of protein carbonyl groups and malondialdehyde were taken as indexes related to oxidative stress. NAFLD patients had a depletion in LCPUFA (long-chain PUFA) of the n -6 and n -3 series in liver triacylglycerols, with decreased 20:4, n -6/18:2, n -6 and (20:5, n -3+22:6, n -3)/18:3, n -3 ratios, whereas liver phospholipids contained higher n -6 and lower n -3 LCPUFA. These findings were accompanied by an enhancement of (i) n -6/ n -3 ratio in liver and adipose tissue, (ii) 18:1, n -9 trans levels in adipose tissue, and (iii) hepatic lipid peroxidation and protein oxidation indexes. It is concluded that a marked enhancement in LCPUFA n -6/ n -3 ratio occurs in the liver of NAFLD patients, a condition that may favour lipid synthesis over oxidation and secretion, thereby leading to steatosis. Depletion of hepatic LCPUFA may result from both defective desaturation of PUFA, due to inadequate intake of precursors, such as 18:3, n -3, and higher intake of the 18:1, n -9 trans isomer leading to desaturase inhibition, and from an increased peroxidation of LCPUFA due to oxidative stress."

-Department of Nutrition, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Casilla, Santiago 7, Santiago, Chile.

https://pubmed.ncbi.nlm.nih.gov/14720121/

Oxidative stress and depletion of hepatic long-chain polyunsaturated fatty acids may contribute to nonalcoholic fatty liver disease

"Human nonalcoholic fatty liver disease (NAFLD) associated with obesity is characterized by depletion of hepatic n-3 long-chain polyunsaturated fatty acids (LCPUFA), with lower LCPUFA product/precursor ratios and higher 18:1n-9 trans levels in adipose tissue, both in patients with steatosis and in those with steatohepatitis. These changes point to modification of gene expression, with decreased fatty acid oxidation and triacylglycerol export and enhanced lipid synthesis, thereby leading to fat accumulation in the liver. Changes in oxidative stress-related parameters indicate a moderate enhancement in the pro-oxidant status of the liver in steatosis, which is further exacerbated in steatohepatitis. It is proposed that oxidative stress plays a dual role in NAFLD by contributing to steatosis due to higher peroxidation of LCPUFA, in addition to

defective fatty acid desaturation and diet imbalance, and by promoting progression of steatosis to steatohepatitis, features that might involve changes in the activity of transcriptional mediators."

-Molecular and Clinical Pharmacology Program, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Chile.
https://pubmed.ncbi.nlm.nih.gov/15454290/

Health Implications of High Dietary Omega-6 Polyunsaturated Fatty Acids

…"In summary, the depletion of n-3 LC-PUFA, the decrease in the ratio of product/precursors of LC-PUFA, the increase in n-6 PUFA, and the increase in n-6 LC-PUFA derived eicosanoid production within the liver all contribute to the development of NAFLD and related pathophysiologies such as insulin resistance. Recently, the relationship between the n-6:n-3 PUFA ratio within the liver and severity of steatosis was demonstrated [108]. In this study, patients with NAFLD showed significant correlation between the n-6:n-3 PUFA ratio and the quantity of hepatic triglycerides, as a marker of the severity of hepatic steatosis [108]. Defective desaturation of PUFA due to inadequate intake of n-3 PUFA, and a higher intake of n-6 PUFA further enhances the contribution of desaturase inhibition in NAFLD."

-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland
-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol. Consider acquiring EPA/DHA only from diet. See Supplements for related research quotes.

See also Enlarged Spleen

Non-Hodgkins Lymphoma (NHL)

Nutrient intake and risk of non-Hodgkin's lymphoma.

"The mechanisms through which diet may influence the development of non-Hodgkin's

lymphoma (NHL) are unclear but can be better understood by examining associations between nutrient consumption and NHL risk. Between 2000 and 2002, 591 NHL cases and 460 population-based controls in Sweden completed a semiquantitative food frequency questionnaire. Unconditional logistic regression was performed to estimate odds ratios and 95% confidence intervals for associations with nutrient intake; all statistical tests were two sided. Dietary intake of most macronutrients was not associated with risk of NHL or its common subtypes. Consumption of omega-3 or marine fatty acids was associated with decreased risk of NHL and chronic lymphocytic lymphoma, and dietary fiber was associated with lower risk of all subtypes examined. When the highest and the lowest quartiles of marine fat intake were compared, the odds ratio for NHL risk was 0.6 (95% confidence interval: 0.4, 0.9), ptrend=0.03; for dietary fiber intake, the corresponding odds ratio was 0.5 (95% confidence interval: 0.3, 0.7), ptrend<0.001. Dietary consumption of beta-carotene or alpha-tocopherol was associated with lower NHL risk, whereas intake of calcium or retinol was associated with increased NHL risk. Nutrients that affect inflammation, vitamin D activity, oxidative DNA damage, or DNA methylation may be associated with risk of NHL."

-Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.
https://www.ncbi.nlm.nih.gov/pubmed/17005624

Carotenoid intake and risk of non-Hodgkin lymphoma: a systematic review and dose-response meta-analysis of observational studies.

…"In conclusion, our findings suggest that higher intakes of alpha-carotene, beta-carotene, and lutein/zeaxanthin might protect against NHL [non-Hodgkin lymphoma] development. Further cohort studies with a control of plausible confounding are needed to confirm these associations."

-Department of Hematology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai,People's Republic of China.

-Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center, Shanghai, China.

-Department of Medicine, Division of Nephrology, University of Calgary, Calgary, AB, Canada.

-School of Nursing, Southwest Medical University, Luzhou, Sichuan, China.

-Department of Hematology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai, People's Republic of China.

https://www.ncbi.nlm.nih.gov/pubmed/28011986

Prediagnostic circulating carotenoid levels and the risk of non-Hodgkin lymphoma: the Multiethnic Cohort

…"These data provide support for a protective role of carotenoid-rich fruits and vegetables in the etiology of NHL [non-Hodgkin lymphoma]."…

-University of Hawaii Cancer Center, Honolulu, HI;
-Department of Public Health Sciences, University of Hawaii, Honolulu, HI; and
-Keck School of Medicine, University of Southern California, Los Angeles, CA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3382940/

"**Carotenoids** are pigments in plants, algae, and photosynthetic bacteria. These pigments produce the bright yellow, red, and orange colors in plants, vegetables, and fruits. Carotenoids act as a type of antioxidant for humans. There are more than 600 different types of carotenoids."

-Healthline
https://www.healthline.com/health/carotenoids

Vegetables, fruit, and antioxidant-related nutrients and risk of non-Hodgkin lymphoma: a National Cancer Institute–Surveillance, Epidemiology, and End Results population-based case-control study

…"Higher intakes of vegetables, lutein and zeaxanthin, and zinc are associated with a lower NHL risk."

-The American Journal of Clinical Nutrition, Volume 83, Issue 6, June 2006, Pages 1401–1410
https://academic.oup.com/ajcn/article/83/6/1401/4633001

Trans fatty acid intake is associated with increased risk and n3 fatty acid intake with reduced risk of non-hodgkin lymphoma.

…"In conclusion, diets high in TFAs [trans Fatty acid], processed meats, and higher fat dairy products were positively associated with NHL [non-Hodgkin lymphoma] risk, whereas diets high in n3 [omega-3] fatty acids and total seafood were inversely associated with risk."...

-Department of Health Sciences Research and Divisions of
-Nutrition Research
-Biomedical Statistics and Informatics
-General Internal Medicine
-Hematology
-Anatomic Pathology, and

-Epidemiology, Mayo Clinic, Rochester, MN
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3738236/

N-oleoylethanolamine (OEA)

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs: eNdocannabinoid stimulating anti-inflammatory drugs?

"Read any pharmacology textbook and the message is clear: nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the activity of cyclooxygenase (COX) and thereby the production of prostaglandins. However, evidence is accumulating that NSAIDs involve the endocannabinoid system in their actions, and that such effects may pave the way towards the design of new analgesics that are not plagued with the gastrointestinal and cardiovascular adverse actions that are associated with this class of drugs. In this Opinion article, our current understanding of the involvement of the endocannabinoid system in the actions of NSAIDs is described, and the ways in which this can lead to novel drug development is discussed."

-Prof. Christopher J. Fowler
-Department of Pharmacology and Clinical Neuroscience, Umeå University, SE-901 87 Umeå, Sweden.
https://pubmed.ncbi.nlm.nih.gov/22664342

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"Some NSAIDs have additional influences on the cannabinoid system either by inhibiting fatty acid amide hydrolase (FAAH) or by inhibiting a possible intracellular transporter of endocannabinoids. All the NSAIDs that inhibit COX2 can influence the cannabinoid system because a possible important degradative pathway for anandamide and 2–arachidonoyl glycerol might involve COX 2. One of the causes for the variety of experimental results presented might be due to pharmacokinetic mechanisms, depending on the route of administration and the dose."

-Department of Pharmacology and Pharmacotherapy, 'Carol Davila' University of Medicine and Pharmacy, Romania
-Department of Physiology, 'Carol Davila' University of Medicine and Pharmacy, Romania
-Department of Dermatology, 'Carol Davila' University of Medicine and Pharmacy, Romania
-Department of Anatomy, 'Carol Davila' University of Medicine and Pharmacy, Romania
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056416

Non-Steroidal Anti-Inflammatory Drugs: An Overview of Cardiovascular Risks

”While aspirin may offer protection, other non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) can cause serious cardiovascular side effects and complications. This has led to a general "black box" warning for cardiovascular adverse events for NSAIDs. This review explores the different mechanisms underlying the protective effects of aspirin, the NSAID associated renovascular effects causing hypertension, edema and heart failure, the cardiovascular effects causing myocardial infarction and stroke, and the possible deleterious interaction between NSAIDs and aspirin.”…

-Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente and University of Twente, Ariensplein 1, The Netherlands
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4036661/

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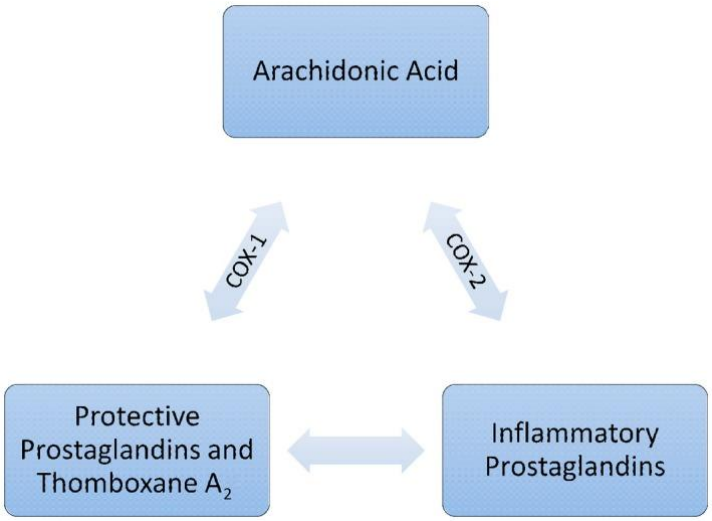
“The reddening and swelling of areas in the body generally occurs because of the release of omega-6 (AA) eicosanoids and cytokines. This happens when AA is metabolised by cycloxygenases (COX1 and COX2) or LOXs. Aspirin, for example, a well-known pain reliever and fever reducer, inhibits COX1 from breaking down AA, thereby preventing the inflammatory response. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen inhibit both COX1 and COX2 and are the most popular over-the-counter pain relievers showing just how powerful the proinflammatory metabolites are from AA. Instead of using NSAIDs to inhibit the formation of omega-6 AA metabolites, eating more EPA/DHA [omega-3] can provide a similar effect. Omega-3s PUFAs act to prevent chronic low-grade inflammation. Indeed, supplementing with fish oil is known to inhibit inflammatory cytokines such as TNF-alpha and IL-1 beta and proinflammatory/proaggregatory eicosanoids such as thromboxane-2 and prostaglandin E2.[32] Using longchain omega-3s to suppress low-grade inflammation may benefit numerous chronic diseases such as rheumatoid arthritis, atherosclerosis, dyslipidaemia, diabetes, obesity and heart failure.[32] The consumption of omega-6 seed oils may have the opposite effect.”

-Saint Luke’s Mid America Heart Institute, Kansas, Missouri, USA
-Dr James J DiNicolantonio & James H O’Keefe
https://openheart.bmj.com/content/openhrt/5/2/e000946.full.pdf

Risk of Nonsteroidal Anti-inflammatory Drugs and Safety of Acetaminophen in Patients with Advanced Liver Disease

"Several factors have contributed to misconceptions regarding nonsteroidal anti-inflammatory drug (NSAID) and acetaminophen use in patients with advanced liver disease. NSAIDs are commonly recommended as first- or second-line therapy for pain management by several societies and organizations. Their use remains uncontrolled, and the vast array of over-the-counter agents lend to a preconceived notion that NSAIDs are generally safe. Furthermore, awareness of acetaminophen toxicity as a common cause of acute liver failure has resulted in distortions regarding the safety and tolerability of these drugs in patients with advanced liver disease."…"Prostaglandins and nitric oxide synthase are essential compounds that play a central role in maintaining GI mucosal integrity through protective and repair mechanisms (Fig. (Fig.1).1). NSAID-induced mucosa GI injury can range from mild gastritis to the development of complicated peptic ulcer disease (Fig. (Fig.2).2). The risk for portal and nonportal hypertensive bleeding is further increased as a result of decreased platelet aggregation stemming from a reduction in thromboxane A2 production and can be further augmented by coexisting coagulopathy and thrombocytopenia.6, 7 Thus, patients and providers must exercise cautionary use of NSAIDs given the increased risk for GI bleeding in patients with cirrhosis and particularly in those with portal hypertension."



-Dr Miguel H. Malespin, M.D, Division of Gastroenterology and Hepatology, Department of Medicine, University of Florida Health, Jacksonville, FL

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6385913/

…"NSAIDs inhibit two cyclooxygenase (COX) enzymes, COX1 and COX2, and thereby block the conversion of arachidonic acid (AA) into inflammatory prostaglandins. Ibuprofen, ketorolac, and flurbiprofen also block the hydrolysis of AEA into arachidonic acid and ethanolamine [27]. See Figure 2. A binding site for some NSAIDs on FAAH has also been identified [28]. NSAID inhibition of

COX2 blocks the metabolism of AEA and 2-AG into prostaglandin ethanolamides (PG-EAs) and prostaglandin glycerol esters (PG-GEs), respectively [29]. PG-EAs and PG-GEs increase the frequency of miniature inhibitory postsynaptic currents (mIPSCs) in primary cultured mouse hippocampal neurons, an effect opposite to that of their parent molecules [30]."...

- GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom,
- Department of Family Medicine, University of Vermont, Burlington, Vermont, United States of America,
- Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei, Pozzuoli, Napoli, Italy,
-St. Joseph's Hospital and Medical Center, United States of America,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951193

See also Acetaminophen , Cyclooxygenase (COX) , Interstitial Nephritis , Prostaglandins

N-palmitoylethanolamine (PEA)

Also refered to as palmitoylethanolamide or PEA

N-Palmitoylethanolamine and Neuroinflammation: a Novel Therapeutic Strategy of Resolution

"Inflammation is fundamentally a protective cellular response aimed at removing injurious stimuli and initiating the healing process. However, when prolonged, it can override the bounds of physiological control and becomes destructive. Inflammation is a key element in the pathobiology of chronic pain, neurodegenerative diseases, stroke, spinal cord injury, and neuropsychiatric disorders. Glia, key players in such nervous system disorders, are not only capable of expressing a pro-inflammatory phenotype but respond also to inflammatory signals released from cells of immune origin such as mast cells. Chronic inflammatory processes may be counteracted by a program of resolution that includes the production of lipid mediators endowed with the capacity to switch off inflammation. These naturally occurring lipid signaling molecules include the N-acylethanolamines, N-arachidonoylethanolamine (an endocannabinoid), and its congener N-palmitoylethanolamine (palmitoylethanolamide or PEA). PEA may play a role in maintaining cellular homeostasis when faced with external stressors provoking, for example, inflammation. PEA is efficacious in mast cell-mediated models of neurogenic inflammation and neuropathic pain and is neuroprotective in models of stroke, spinal cord injury, traumatic brain injury, and Parkinson disease. PEA in micronized/ultramicronized form shows superior oral efficacy in inflammatory pain models when compared to naïve PEA. Intriguingly, while PEA has

no antioxidant effects per se, its co-ultramicronization with the flavonoid luteolin is more efficacious than either molecule alone. Inhibiting or modulating the enzymatic breakdown of PEA represents a complementary therapeutic approach to treat neuroinflammation. This review is intended to discuss the role of mast cells and glia in neuroinflammation and strategies to modulate their activation based on leveraging natural mechanisms with the capacity for self-defense against inflammation."

-Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Padua, Italy,
https://pubmed.ncbi.nlm.nih.gov/26055231/

Glia and mast cells as targets for palmitoylethanolamide, an anti-inflammatory and neuroprotective lipid mediator

"Glia are key players in a number of nervous system disorders. Besides releasing glial and neuronal signaling molecules directed to cellular homeostasis, glia respond also to pro-inflammatory signals released from immune-related cells, with the mast cell being of particular interest. A proposed mast cell-glia communication may open new perspectives for designing therapies to target neuroinflammation by differentially modulating activation of non-neuronal cells normally controlling neuronal sensitization-both peripherally and centrally. Mast cells and glia possess endogenous homeostatic mechanisms/molecules that can be upregulated as a result of tissue damage or stimulation of inflammatory responses. Such molecules include the N-acylethanolamines, whose principal family members are the endocannabinoid N-arachidonoylethanolamine (anandamide), and its congeners N-stearoylethanolamine, N-oleoylethanolamine, and N-palmitoylethanolamine (PEA). A key role of PEA may be to maintain cellular homeostasis when faced with external stressors provoking, for example, inflammation: PEA is produced and hydrolyzed by microglia, it downmodulates mast cell activation, it increases in glutamate-treated neocortical neurons ex vivo and in injured cortex, and PEA levels increase in the spinal cord of mice with chronic relapsing experimental allergic encephalomyelitis. Applied exogenously, PEA has proven efficacious in mast cell-mediated experimental models of acute and neurogenic inflammation. This fatty acid amide possesses also neuroprotective effects, for example, in a model of spinal cord trauma, in a delayed post-glutamate paradigm of excitotoxic death, and against amyloid β-peptide-induced learning and memory impairment in mice. These actions may be mediated by PEA acting through "receptor pleiotropism," i.e., both direct and indirect interactions of PEA with different receptor targets, e.g., cannabinoid CB2 and peroxisome proliferator-activated receptor-alpha."

-Dipartimento di Scienze del Farmaco, Università degli Studi di Padova, Padova, Italy,
https://pubmed.ncbi.nlm.nih.gov/23813098/

Mast cells, glia and neuroinflammation: partners in crime?

“Glia and microglia in particular elaborate pro-inflammatory molecules that play key roles in central nervous system (CNS) disorders from neuropathic pain and epilepsy to neurodegenerative diseases. Microglia respond also to pro-inflammatory signals released from other non-neuronal cells, mainly those of immune origin such as mast cells. The latter are found in most tissues, are CNS resident, and traverse the blood-spinal cord and blood-brain barriers when barrier compromise results from CNS pathology. Growing evidence of mast cell-glia communication opens new perspectives for the development of therapies targeting neuroinflammation by differentially modulating activation of non-neuronal cells that normally control neuronal sensitization - both peripherally and centrally. Mast cells and glia possess endogenous homeostatic mechanisms/molecules that can be up-regulated as a result of tissue damage or stimulation of inflammatory responses. Such molecules include the N-acylethanolamine family. One such member, N-palmitoylethanolamine is proposed to have a key role in maintenance of cellular homeostasis in the face of external stressors provoking, for example, inflammation. N-Palmitoylethanolamine has proven efficacious in mast-cell-mediated experimental models of acute and neurogenic inflammation. This review will provide an overview of recent progress relating to the pathobiology of neuroinflammation, the role of microglia, neuroimmune interactions involving mast cells and the possibility that mast cell-microglia cross-talk contributes to the exacerbation of acute symptoms of chronic neurodegenerative disease and accelerates disease progression, as well as promoting pain transmission pathways. We will conclude by considering the therapeutic potential of treating systemic inflammation or blockade of signalling pathways from the periphery to the brain in such settings.”…

“Inflammation is fundamentally a protective cellular response aimed at removing injurious stimuli and initiating the healing process. However, when prolonged, inflammation overrides the bounds of physiological control and eventually becomes destructive. Inflammation increasingly surfaces as a key element in the pathobiology of chronic pain, neurodegenerative diseases, stroke, spinal cord injury and perhaps even neuropsychiatric disorders.1–5 A plethora of pro-inflammatory cytokines, eicosanoids and other immune neurotoxins, have been found in cerebrospinal fluid and/or affected brain regions of patients with neurodegenerative disorders.6 Consider also that nuclear factor-κB, a requisite transcription factor for most pro-inflammatory molecules, is activated in the substantia nigra pars compacta of Parkinson's disease patients and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) -intoxicated mice and monkeys, and its selective inhibition protects dopaminergic neurons from MPTP toxicity.7 It is intriguing to note

that neuroinflammation may also raise the brain's sensitivity to stress.8 Indeed, a recently published study by Zhang et al.[9] reports that inflammation-activated signalling pathways in the brain's hypothalamus control the production of ageing-related hormones. This finding provides a link between inflammation, stress responses and ageing. Inflammation therefore constitutes an important target for neuronal protection in neurodegenerative disorders and neuropathic pain, the latter resulting from damage or disease affecting the somatosensory system.[10]"

"Recognition that there is extensive communication between the immune system and the central nervous system (CNS) is, no doubt, one of the more fundamental advances in neuroscience in recent times. Inflammatory cytokines occupy a key niche in this network, regulating host responses to infection, inflammation, stress and trauma. Glial cell activation has been implicated in the pathogenesis of Alzheimer's disease, Parkinson's disease, cerebral ischaemia, multiple sclerosis[2,7,11] and motor neuron disease,[12] and possibly schizophrenia and depression.[4,13] Microglia-mediated neuroinflammatory processes are also proposed to compromise healthy brain aging.[14] Found to accumulate at sites of injury or plaques in neurodegenerative CNS diseases,[11,15] microglia scavenge dead cells and secrete neuron survival factors; the latter may have beneficial effects in the recovery of injured CNS. However, inappropriate and prolonged activation of glia can cause autoimmune responses leading to brain injury and neuronal cell death.[2,11,15] Glia provide a link also between neuroinflammation and neuropathic pain;[16] microglia, in particular, show increased activity in multiple pain-processing pathways in response to peripheral injury.[17] Systemic inflammation gives rise to signals that communicate with the brain and leads to changes in metabolism and behaviour – including the expression of a pro-inflammatory phenotype by microglia.[18] It has been proposed that in multiple chronic disease states, and in ageing, microglia are primed by previous pathology, or by genetic predisposition, to respond more vigorously to subsequent inflammatory stimulation, so transforming an adaptive CNS inflammatory response to systemic inflammation, into one with deleterious consequences.[19] It therefore goes without saying that delineating the signalling pathways underlying glial cell activation is crucial in the design of agents capable of antagonizing such signalling steps – which may translate into therapeutic benefit for neurodegenerative disorders and neuropathic pain.

Although it is widely accepted that glial cell activation contributes to neuropathology, one must not forget that microglia and astrocytes also respond to pro-inflammatory signals released from other cells of immune origin. In this view, mast cells represent a potentially important (and underappreciated) peripheral immune signalling link to the brain in an inflammatory setting (Fig. (Fig.1).1)."

-Dipartimento di Scienze del Farmaco, Largo 'Egidio Meneghetti' 2, Università degli Studi di Padova, Padova, Italy.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3930370/

Nuclear Factor (NF-κB) Pathway

“The nuclear factor NF-κB pathway has long been considered a prototypical proinflammatory signaling pathway, largely based on the role of NF-κB in the expression of proinflammatory genes including cytokines, chemokines, and adhesion molecules. In this article, we describe how genetic evidence in mice has revealed complex roles for the NF-κB in inflammation that suggest both pro- and anti-inflammatory roles for this pathway. NF-κB has long been considered the “holy grail” as a target for new anti-inflammatory drugs; however, these recent studies suggest this pathway may prove a difficult target in the treatment of chronic disease. In this article, we discuss the role of NF-κB in inflammation in light of these recent studies.”

-Dr. Toby Lawrence Ph.D, Inflammation Biology Group, Centre d’Immunologie Marseille-Luminy, Parc Scientifique de Luminy, Marseille, France

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882124/

O

Obesity

…“A balanced omega-6/omega-3 [1:1] ratio is important for health and in the prevention and management of obesity."

-The Center for Genetics, Nutrition and Health, 4330 Klingle Street NW, Washington, DC , USA;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808858/

■■■

“Obesity is characterised by altered gut microbiota, low-grade inflammation and increased endocannabinoid (eCB) system tone; however, a clear connection between gut microbiota and eCB signalling has yet to be confirmed. Here, we report that gut microbiota modulate the intestinal eCB system tone, which in turn regulates gut permeability and plasma lipopolysaccharide (LPS) levels. The impact of the increased plasma LPS levels and eCB system

tone found in obesity on adipose tissue metabolism (e.g. differentiation and lipogenesis) remains unknown. By interfering with the eCB system using CB1 agonist and antagonist in lean and obese mouse models, we found that the eCB system controls gut permeability and adipogenesis. We also show that LPS acts as a master switch to control adipose tissue metabolism both in vivo and ex vivo by blocking cannabinoid-driven adipogenesis. These data indicate that gut microbiota determine adipose tissue physiology through LPS-eCB system regulatory loops and may have critical functions in adipose tissue plasticity during obesity."

-Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
-Bioanalysis and Pharmacology of Bioactive Lipids laboratory, Brussels, Belgium
-Metabolism and Nutrition research group, Brussels, Belgium
-Department of Molecular and Clinical Medicine, Sahlgrenska Center for Cardiovascular and Metabolic Research/Wallenberg Laboratory, University of Gothenburg, Gothenburg, Sweden
-Medicinal Chemistry, Brussels, Belgium
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2925525/

Cannabinoid signalling regulates inflammation and energy balance: the importance of the brain-gut axis.

"Energy balance is controlled by centres of the brain which receive important inputs from the gastrointestinal tract, liver, pancreas, adipose tissue and skeletal muscle, mediated by many different signalling molecules. Obesity occurs when control of energy intake is not matched by the degree of energy expenditure. Obesity is not only a state of disordered energy balance it is also characterized by systemic inflammation. Systemic inflammation is triggered by the leakage of bacterial lipopolysaccharide through changes in intestinal permeability. The endocannabinoid system, consisting of the cannabinoid receptors, endogenous cannabinoid ligands and their biosynthetic and degradative enzymes, plays vital roles in the control of energy balance, the control of intestinal permeability and immunity. In this review we will discuss how the endocannabinoid system, intestinal microbiota and the brain-gut axis are involved in the regulation of energy balance and the development of obesity-associated systemic inflammation. Through direct and indirect actions throughout the body, the endocannabinoid system controls the development of obesity and its inflammatory complications."

Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta, Canada.
http://www.ncbi.nlm.nih.gov/pubmed/22269477

Blockade of CB1 cannabinoid receptor alters gut microbiota and attenuates inflammation and diet-induced obesity.

"Obesity is characterized by chronic low-grade, systemic inflammation, altered gut microbiota, and gut barrier disruption. Additionally, obesity is associated with increased activity of endocannabinoid system (eCB). However, the clear connection between gut microbiota and the eCB system in the regulation of energy homeostasis and adipose tissue inflammation and metabolism, remains to be established."

-Department of Pathology, Microbiology, and Immunology, School of Medicine, Columbia, SC, USA.
-Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC, USA.
-Department of Pathology, Microbiology, and Immunology, School of Medicine, Columbia, SC, USA
https://www.ncbi.nlm.nih.gov/pubmed/29142285

An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity

"In the past three decades, total fat and saturated fat intake as a percentage of total calories has continuously decreased in Western diets, while the intake of omega-6 fatty acid increased and the omega-3 fatty acid decreased, resulting in a large increase in the omega-6/omega-3 ratio from 1:1 during evolution to 20:1 today or even higher. This change in the composition of fatty acids parallels a significant increase in the prevalence of overweight and obesity. Experimental studies have suggested that omega-6 and omega-3 fatty acids elicit divergent effects on body fat gain through mechanisms of adipogenesis, browning of adipose tissue, lipid homeostasis, brain-gut-adipose tissue axis, and most importantly systemic inflammation. Prospective studies clearly show an increase in the risk of obesity as the level of omega-6 fatty acids and the omega-6/omega-3 ratio increase in red blood cell (RBC) membrane phospholipids, whereas high omega-3 RBC membrane phospholipids decrease the risk of obesity. Recent studies in humans show that in addition to absolute amounts of omega-6 and omega-3 fatty acid intake, the omega-6/omega-3 ratio plays an important role in increasing the development of obesity via both AA eicosanoid metabolites and hyperactivity of the cannabinoid system, which can be reversed with increased intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A balanced omega-6/omega-3 ratio is important for health and in the prevention and management of obesity."

- Dr. Artemis P. Simopoulos M.D
-The Center for Genetics, Nutrition and Health, 4330 Klingle Street NW, 20016 Washington DC, United States
https://pubmed.ncbi.nlm.nih.gov/26950145

Omega-6 and omega-3 fatty acids: Endocannabinoids, genetics and obesity

"The tissue composition of polyunsaturated fatty acids (PUFA) is important to health and depends on both dietary intake and metabolism controlled by genetic polymorphisms that should be taken into consideration in the determination of nutritional requirements, obesity and chronic disease risk. Experimental and clinical intervention studies suggest that omega-6 and omega-3 fatty acids have opposing physiological and metabolic properties and elicit divergent effects on body fat gain through mechanisms of adipogenesis, browning of adipose tissue, lipid homeostasis, systemic inflammation and an increase in the tone of the endocannabinoid system. Overweight and obese individuals have higher levels of the arachidonic acid (AA) derived endocannabinoid N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) and an altered pattern of receptor expression. Since endocannabinoids are products of dietary fats, modification of the omega-6 and omega-3 fatty acid intake modulates the endocannabinoids, with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) displacing AA from cell membranes, reducing AEA and 2-AG production, resulting in decrease in appetite and food intake leading to weight loss. Polygenic risk scores reveal susceptibility and an increase risk for obesity. Therefore, persons at risk for obesity will have to lower omega-6 and increase their omega-3 fatty acid intake in order to have a balanced ratio for health. A process needs to be established to define when genomic discoveries such as gene-nutrient-disease associations are "ready" to be evaluated as potential tools for personalized nutrition to improve public health."

- Dr. Artemis P. Simopoulos M.D
-The Center for Genetics, Nutrition and Health, 4330 Klingle Street NW, 20016 Washington DC, United States
https://www.ocl-journal.org/articles/ocl/full_html/2020/01/ocl190046s/ocl190046s.html

Omega-3 fatty acids reduce obesity-induced tumor progression independent of GPR120 in a mouse model of postmenopausal breast cancer

"Obesity and inflammation are both risk factors for a variety of cancers, including breast cancer in postmenopausal women. Intake of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) decreases the risk of breast cancer, and also reduces obesity-associated inflammation and insulin resistance, but whether the two effects are related is currently unknown. We tested this hypothesis in a postmenopausal breast cancer model using ovariectomized, immune-competent female mice orthotopically injected with Py230 mammary tumor cells. Obesity, whether triggered genetically or by high-fat diet (HFD) feeding, increased inflammation in the mammary fat pad and promoted mammary tumorigenesis. The presence of tumor cells in the mammary fat pad further enhanced the local inflammatory milieu. Tumor necrosis factor-alpha (TNF-α) was the most highly upregulated cytokine in the obese mammary fat pad, and we observed that TNF-

α dose-dependently stimulated Py230 cell growth in vitro. An ω-3 PUFA-enriched HFD (referred to as fish oil diet, FOD) reduced inflammation in the obese mammary fat pad in the absence of tumor cells and inhibited Py230 tumor growth in vivo. Although some anti-inflammatory effects of ω-3 PUFAs were previously shown to be mediated by the G-protein-coupled receptor 120 (GPR120), the FOD reduced Py230 tumor burden in GPR120-deficient mice to a similar degree as observed in wild-type mice, indicating that the effect of FOD to reduce tumor growth does not require GPR120 in the host mouse. Instead, in vitro studies demonstrated that ω-3 PUFAs act directly on tumor cells to activate c-Jun N-terminal kinase, inhibit proliferation and induce apoptosis. **Our results show that obesity promotes mammary tumor progression in this model of postmenopausal breast cancer and that ω-3 PUFAs, independent of GPR120, inhibit mammary tumor progression in obese mice.**"

-Division of Endocrinology and Metabolism, Department of Medicine, University of California, La Jolla, CA, USA.

-Division of Endocrinology and Metabolism, Department of Medicine, University of California, La Jolla, CA, USA

- Biomedical Network Center for the study of Hepatic and Digestive Diseases (CIBERehd), Madrid, Spain.

-Department of Pathology, University of California at San Diego, La Jolla, CA, USA.

-Division of Endocrinology and Metabolism, Department of Medicine, University of California, La Jolla, CA, USA [2] Moores Cancer Center, University of California, La Jolla, CA, USA [3] San Diego VA Healthcare System, San Diego, CA, USA.

-Division of Endocrinology and Metabolism, Department of Medicine, University of California, La Jolla, CA, USA [2] Moores Cancer Center, University of California, La Jolla, CA, USA.

-Department of Pathology, University of California at San Diego, La Jolla, CA, USA [2] Moores Cancer Center, University of California, La Jolla, CA, USA.

https://pubmed.ncbi.nlm.nih.gov/25220417/

Omega-3 fatty acids and adipose tissue function in obesity and metabolic syndrome

"The n-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) have been reported to improve obesity-associated metabolic disorders including chronic inflammation, insulin resistance and dyslipidaemia. Growing evidence exits about adipose tissue as a target in mediating the beneficial effects of these marine n-3 PUFAs in adverse metabolic syndrome manifestations. Therefore, in this manuscript we focus in reviewing the current knowledge about effects of marine n-3 PUFAs on adipose tissue metabolism and secretory functions. This scope includes n-3 PUFAs actions on adipogenesis, lipogenesis and lipolysis as well as on fatty acid oxidation and mitochondrial biogenesis. The effects of n-3 PUFAs on adipose tissue glucose uptake and insulin signaling are also summarized. Moreover, the roles of peroxisome proliferator-activated receptor γ (PPARγ) and AMPK activation in mediating n-3 PUFAs actions on adipose tissue functions are discussed. Finally, the mechanisms underlying the

ability of n-3 PUFAs to prevent and/or ameliorate adipose tissue inflammation are also revised, focusing on the role of n-3 PUFAs-derived specialized proresolving lipid mediators such as resolvins, protectins and maresins."

-Department of Nutrition, Food Science and Physiology, School of Pharmacy, University of Navarra, Spain; Centre for Nutrition Research, School of Pharmacy, University of Navarra, Spain.

https://pubmed.ncbi.nlm.nih.gov/26219838/

Excessive intake of omega 6 and deficiencies in omega 3 induce obesity down the generations

"Chronic excess of linoleic acid (omega 6), coupled with a deficiency in alpha-linoleic acid (omega 3), can increase obesity down the generations. Researchers exposed several generations of male and female adult and young mice to a "Western-like" diet of this type, and then assessed the consequences of such a lipid environment in the human diet."

-ScienceDaily

-These findings are published on the website of the Journal of Lipid Research.

-Gérard Ailhaud (Université de Nice-Sophia Antipolis) working in collaboration with three CNRS laboratories and one INRA laboratory.

https://www.sciencedaily.com/releases/2010/07/100726221737.htm

Fat to treat fat: emerging relationship between dietary PUFA, endocannabinoids, and obesity

"Obesity incidence continues to escalate as a global nutrition and health problem. Scientists and clinicians are engaged in numerous research approaches that include behavior, education, applied nutrition studies and clinical therapies to prevent, control and reverse obesity. The common goal is to identify areas of basic and clinical research to understand aspects of human biology that contribute to obesity. In these approaches recent discoveries in biology and advancing technologies are tools employed to prevent and reverse obesity. The purpose of this review article is to present the current knowledge of key components of the endocannabinoid system that contribute to eating, influence systemic energy metabolism, and dietary factors that alter the responses of ligand binding and activation of cannabinoid receptors. Herein the objectives are to (1) describe the relationship between dietary polyunsaturated fatty acids (PUFA) and obesity, (2) explain the role of this signaling system in obesity, and (3) present areas of consequential future research with dietary long chain PUFA. There are several gaps in the knowledge of the role dietary PUFA play in the tone of the endocannabinoid signaling system

involving ligands and receptors. Elucidating the PUFA relationship to signaling tone may explain the presumed overstimulation of signaling believed to contribute to over eating, fat accretion and inflammation. Future research in this endeavor must be hypothesis driven utilizing appropriate models for investigations on dietary PUFA, endocannabinoids and obesity."

Lipid Chemistry and Molecular Biology Laboratory, Center on Aging, University of Connecticut, Storrs, CT 06269-4004, USA.

https://pubmed.ncbi.nlm.nih.gov/23466458/

Impaired Local Production of Proresolving Lipid Mediators in Obesity and 17-HDHA as a Potential Treatment for Obesity-Associated Inflammation

"Obesity-induced chronic low-grade inflammation originates from adipose tissue and is crucial for obesity-driven metabolic deterioration, including insulin resistance and type 2 diabetes. Chronic inflammation may be a consequence of a failure to actively resolve inflammation and could result from a lack of local specialized proresolving lipid mediators (SPMs), such as resolvins and protectins, which derive from the n-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). We assessed obesity-induced changes of n-3–derived SPMs in adipose tissue and the effects of dietary EPA/DHA thereon. Moreover, we treated obese mice with SPM precursors and investigated the effects on inflammation and metabolic dysregulation. Obesity significantly decreased DHA-derived 17-hydroxydocosahexaenoic acid (17-HDHA, resolvin D1 precursor) and protectin D1 (PD1) levels in murine adipose tissue. Dietary EPA/DHA treatment restored endogenous biosynthesis of n-3–derived lipid mediators in obesity while attenuating adipose tissue inflammation and improving insulin sensitivity. Notably, 17-HDHA treatment reduced adipose tissue expression of inflammatory cytokines, increased adiponectin expression, and improved glucose tolerance parallel to insulin sensitivity in obese mice. These findings indicate that impaired biosynthesis of certain SPM and SPM precursors, including 17-HDHA and PD1, contributes to adipose tissue inflammation in obesity and suggest 17-HDHA as a novel treatment option for obesity-associated complications."…

"The obesity-associated disturbance of 17-HDHA and PD1 biosynthesis may result from decreased substrate availability and/or altered enzyme activities. HF feeding has been shown to reduce n-3 PUFA availability by elevating the long-chain n-6–to–n-3 PUFA ratio in adipose tissue membranes compared with counterparts fed normal chow [(26)]. On one hand, we demonstrate an effect of HF diet on lipid mediator synthesis in adipose tissue, which is independent of obesity, because 17-HDHA and PD1 levels were affected also by short-term dietary treatment before the onset of obesity-induced adipose tissue inflammation [(Fig. 2)]."…

"In conclusion, we show for the first time that obesity significantly reduced the endogenous

production of 17-HDHA and PD1 in adipose tissue, which probably impairs resolution of adipose tissue inflammation. This lack of anti-inflammatory and proresolving lipid mediators could contribute to chronic adipose tissue inflammation and metabolic complications in obesity. Application of proresolving lipid mediators or 17-HDHA as a critical precursor reconstitutes endogenous resolution capacity and might thus provide a novel option for treatment and prevention of obesity-related diseases such as type 2 diabetes."

-Clinical Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, Austria

-Christian Doppler-Laboratory for Cardio-Metabolic Immunotherapy, Medical University of Vienna, Austria

-pharm-analyt Labor GmbH, Baden, Austria

-Department of Molecular Pathology and Innovative Therapies, University of Ancona (Politecnica delle Marche), Ancona, Italy

-Flanders Institute for Biotechnology and Katholieke Universiteit Leuven, Leuven, Belgium

-The Adipose Organ Laboratory, IRCCS San Raffele Pisana, Rome, Italy

-Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661630/

Endocannabinoids may mediate the ability of (n-3) fatty acids to reduce ectopic fat and inflammatory mediators in obese Zucker rats

"Dietary (n-3) long-chain PUFA [(n-3) LCPUFA] ameliorate several metabolic risk factors for cardiovascular diseases, although the mechanisms of these beneficial effects are not fully understood. In this study, we compared the effects of dietary (n-3) LCPUFA, in the form of either fish oil (FO) or krill oil (KO) balanced for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) content, with a control (C) diet containing no EPA and DHA and similar contents of oleic, linoleic, and alpha-linolenic acids, on ectopic fat and inflammation in Zucker rats, a model of obesity and related metabolic dysfunction. Diets were fed for 4 wk. Given the emerging evidence for an association between elevated endocannabinoid concentrations and metabolic syndrome, we also measured tissue endocannabinoid concentrations. In (n-3) LCPUFA-supplemented rats, liver triglycerides and the peritoneal macrophage response to an inflammatory stimulus were significantly lower than in rats fed the control diet, and heart triglycerides were lower, but only in KO-fed rats. These effects were associated with a lower concentration of the endocannabinoids, anandamide and 2-arachidonoylglycerol, in the visceral adipose tissue and of anandamide in the liver and heart, which, in turn, was associated with lower levels of arachidonic acid in membrane phospholipids, but not with higher activity of endocannabinoid-degrading enzymes. Our data suggest that the beneficial effects of a diet enriched with (n-3) LCPUFA are the result of changes in membrane fatty acid composition. The reduction of substrates for

inflammatory molecules and endocannabinoids may account for the dampened inflammatory response and the physiological reequilibration of body fat deposition in obese rats."

-Department of Biomedical Sciences and Technologies, University of Cagliari, Italy.
https://pubmed.ncbi.nlm.nih.gov/19549757/

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"The results of studies in animals in which the n-6/n-3 ratio is substantially reduced have been largely positive regarding insulin sensitivity and resolving inflammation. A particularly effective model for assessing the impact of n-6/n-3 ratios is the fat-1 transgenic mouse model which can endogenously synthesize omega-3 PUFAs from omega-6 PUFAs [44]. The ability to convert omega-6 fatty acids to omega-3 leads to an n-6/n-3 ratio of approximately 1. This model allows for the same diet to be used in all conditions and for the comparison of two significantly different n-6/n-3 ratios. It is, however, difficult to discern whether any effects are due to a reduction in the overall n-6/n-3 ratio or an increase in omega-3 PUFAs alone. Reductions in the n-6/n-3 ratio are associated with an improvement in whole body glucose tolerance, as well as preventing the age related decline in glucose tolerance [45,46]. Fat-1 mice were also protected from obesity related inflammatory activity and decrements in insulin sensitivity [47]. As well as improving glucose clearance, lowering the n-6/n-3 ratio also led to an increase in insulin secretion [48]. These studies demonstrate that a balance between omega-6 and omega-3 PUFAs within the lipid pool, may have a potential role in determining the metabolic effects of omega-3 PUFAs. Studies attempting to address this ratio in humans, however, would be difficult to adequately control. A human trial investigating a Mediterranean type diet which led to a reduction in the n-6/n-3 ratio observed that this reduction alongside other variables may confer some protection against metabolic dysfunction, providing some evidence that alterations in fatty acid content may have an effect on human health [15]."

-Health and Exercise Sciences Research Group, School of Sport, University of Stirling, Scotland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4663562/

Systemic low-grade inflammation is related to both circulating and adipose tissue TNFalpha, leptin and IL-6 levels in obese women

…"**Results**: We found a strong positive correlation between both circulating and adipose tissue levels of IL-6, TNFalpha and leptin and serum CRP [C-reactive protein] levels. All these adipose tissue adipocytokines were also positively correlated with serum AAG levels. These correlations disappeared when adjusted for fat mass, suggesting that the relationship observed was

dependent on fat amount."

…"Our results indicate a strong relationship between adipocytokines and inflammatory markers, and suggest that cytokines secreted by adipose tissue in obese subjects could play a role in increased inflammatory proteins secretion by the liver."…

-Service de Biochimie et Hormonologie, Hôpital Tenon, AP-HP, France.
https://pubmed.ncbi.nlm.nih.gov/15211360/

See also Caloric restriction (CR) , Fasting , Omega Ratio

Obsessive Compulsive Disorder (OCD)

The Endocannabinoid System: A New Treatment Target for Obsessive Compulsive Disorder?

"**Discussion:** A growing body of basic and clinical research has showed that the endocannabinoid system (ECS) plays a role in anxiety, fear, and repetitive behaviors. At the same time, some patients with OCD who smoke cannabis anecdotally report that it relieves their symptoms and mitigates anxiety, and several case reports describe patients whose OCD symptoms improved after they were treated with cannabinoids. Taken together, these findings suggest that the ECS could be a potential target for novel medications for OCD. In this study, we review evidence from both animal and human studies that suggests that the ECS may play a role in OCD and related disorders. We also describe findings from studies in which cannabinoid drugs were shown to impact symptoms of these conditions. **Conclusions:** An emerging body of evidence suggests that the ECS plays a role in OCD symptoms and may be a target for the development of novel medications."

-Department of Psychiatry, New York State Psychiatric Institute, Columbia University Vagelos College of Physicians and Surgeons, New York, New York.

-Department of Psychiatry, Weill Cornell Medical College, New York, New York.

https://www.researchgate.net/publication/333498177_The_Endocannabinoid_System_A_New_Treatment_Target_for_Obsessive_Compulsive_Disorder
http://bit.do/ecs-ocd

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…"These results suggest a potential role for drugs acting on the cannabinoid system in modulating compulsive behavior."

-Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo

https://www.ncbi.nlm.nih.gov/pubmed/21111767

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"Also, although no longer classified as an anxiety disorder, alterations in the immune system of patients with obsessive-compulsive disorder have also been reported [17, 18].
The activation and morphological changes of microglial cells associated with neuroinflammatory states have been recently found to depend on changes induced by stress, including the engagement of glucocorticoids and β-adrenergic receptors [19]."

-Department of Pharmacology, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil
-Center of Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Ribeirão Preto, Brazil
-Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA
-Edited by: Frank Kirchhoff, University of Saarland, Germany
-Reviewed by: Eng-Ang Ling, National University of Singapore, Singapore;
-Aviva Jane Symes
-Uniformed Services University of the Health Sciences, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4729885/

Endocannabinoid Modulation of Microglial Phenotypes in Neuropathology

"Microglia, the resident immune cells of the central nervous system, mediate brain homeostasis by controlling neuronal proliferation/differentiation and synaptic activity. In response to external signals from neuropathological conditions, homeostatic (M0) microglia can adopt one of two activation states: the classical (M1) activation state, which secretes mediators of the proinflammatory response, and the alternative (M2) activation state, which presumably mediates the resolution of neuroinflammation and tissue repair/remodeling. Since chronic inflammatory activation of microglia is correlated with several neurodegenerative diseases, functional modulation of microglial phenotypes has been considered as a potential therapeutic strategy. The endocannabinoid (eCB) system, composed of cannabinoid receptors and ligands and their metabolic/biosynthetic enzymes, has been shown to activate anti-inflammatory signaling pathways that modulate immune cell functions. Growing evidence has demonstrated that endogenous, synthetic, and plant-derived eCB agonists possess therapeutic effects on several neuropathologies; however, the molecular mechanisms that mediate the anti-inflammatory effects have not yet been identified. Over the last decade, it has been revealed

that the eCB system modulates microglial activation and population. In this review, we thoroughly examine recent studies on microglial phenotype modulation by eCB in neuroinflammatory and neurodegenerative disease conditions. We hypothesize that cannabinoid 2 receptor (CB2R) signaling shifts the balance of expression between neuroinflammatory (M1-type) genes, neuroprotective (M2-type) genes, and homeostatic (M0 type) genes toward the latter two gene expressions, by which microglia acquire therapeutic functionality."

-Department of Anatomy, Physiology and Genetics, Uniformed Services University Health Sciences, Bethesda, MD, USA

https://www.frontiersin.org/articles/10.3389/fneur.2020.00087/full

Oleoylethanolamide (OEA)

"Oleoylethanolamide (OEA) is a molecule [a fat-like lipid] produced in the body, usually found in the intestines. It is responsible for the feeling of satiety after meals. Further research is needed to determine if oral supplementation of OEA provides benefits for weight loss."

https://examine.com/supplements/oleoylethanolamide/

Oleoylethanolamide Supplementation Reduces Inflammation and Oxidative Stress in Obese People: A Clinical Trial

"The use of OEA as a complementary pharmacotherapy agent could be effective in improving inflammation and oxidative stress in obese people. Future studies are needed to confirm the obtained results."

-Talented Student Center, Student Research Committee, Nutrition Research Center, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran.

-Student Research Committee, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz

-Road Traffic Injury Research Center, Department of Statistics and Epidemiology, Faculty of Health, Tabriz University of Medical Sciences, Tabriz, Iran.

-Nutrition Research Center, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6156479/

Oligodendrocyte Dysfunction

"The emerging role of oligodendrocytes as key players that provide tropic support to neuronal axons has paved the way for a better understanding of the contribution of dysfunctional axon-oligodendrocyte coupling in neurodegenerative diseases. Here we have reviewed the growing evidence demonstrating that oligodendrocyte dysfunction plays an important role in several neurodegenerative diseases, including Alzheimer disease, amyotrophic lateral sclerosis, and multiple system atrophy. Given that aging is the single greatest risk factor for all of these diseases, age-related myelin deterioration could be an underlying neuropathological mechanism leading to neuronal dysfunction. Novel therapeutic approaches aimed at mimicking or increasing trophic support, ideally by restoring axon-oligodendrocyte coupling could be beneficial in a wide range of neurodegenerative diseases."

-Alexandra I. Mot, Department of Neurogenetics, Max Planck Institute of Experimental Medicine, Gottingen, Germany;

-Constanze Depp, MSc Constanze Depp, Department of Neurogenetics, Max Planck Institute of Experimental Medicine, Gottingen, Germany;

-Dr.Klaus-Armin Nave, PhD, Department of Neurogenetics, Max Planck Institute of Experimental Medicine, Gottingen, Germany;

https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC6436955

The Endocannabinoid System and Oligodendrocytes in Health and Disease

"Cannabinoid-based interventions are being explored for central nervous system (CNS) pathologies such as neurodegeneration, demyelination, epilepsy, stroke, and trauma. As these disease states involve dysregulation of myelin integrity and/or remyelination, it is important to consider effects of the endocannabinoid system on oligodendrocytes and their precursors. In this review, we examine research reports on the effects of the endocannabinoid system (ECS) components on oligodendrocytes and their precursors, with a focus on therapeutic implications. Cannabinoid ligands and modulators of the endocannabinoid system promote cell signaling in oligodendrocyte precursor survival, proliferation, migration and differentiation, and mature oligodendrocyte survival and myelination. Agonist stimulation of oligodendrocyte precursor cells (OPCs) at both CB1 and CB2 receptors counter apoptotic processes via Akt/PI3K, and promote proliferation via Akt/mTOR and ERK pathways. CB1 receptors in radial glia promote proliferation and conversion to progenitors fated to become oligodendroglia, whereas CB2 receptors promote OPC migration in neonatal development. OPCs produce 2-arachidonoylglycerol (2-AG), stimulating cannabinoid receptor-mediated ERK pathways responsible for differentiation to arborized, myelin basic protein (MBP)-producing oligodendrocytes. In cell culture models of excitotoxicity, increased reactive oxygen species, and depolarization-dependent calcium influx, CB1 agonists improved viability of oligodendrocytes. In transient and permanent middle cerebral artery occlusion models of anoxic stroke, WIN55212-2 increased OPC proliferation and maturation to oligodendroglia, thereby reducing cerebral tissue damage. In several models of rodent encephalomyelitis, chronic treatment with cannabinoid agonists ameliorated the damage by promoting OPC survival and oligodendrocyte function. Pharmacotherapeutic strategies based upon ECS and oligodendrocyte production and survival should be considered."

-Graduate Program in Neuroscience, Wake Forest School of Medicine, Winston Salem, NC, United States

-Department of Physiology and Pharmacology and Center for Research on Substance Use and Addiction, Wake Forest School of Medicine, Winston-Salem, NC, United States

-Department of Neurobiology and Anatomy, Wake Forest School of Medicine, Winston-Salem, NC, United States

-Department of Neurology and Comprehensive Multiple Sclerosis Center, Wake Forest School of Medicine, Winston-Salem, NC, United States

https://www.frontiersin.org/articles/10.3389/fnins.2018.00733/full

Olive Leaf & Oleuropein Extracts

…"Another interesting result of the present study is the correlation observed for the physiological stress response of the animal and plasma n-3 fatty acids. The well-being of the pigs at the time of slaughter was checked by measuring the cortisol level. It is important to note that the combination of dietary oleuropein and the other antioxidants significantly reduced cortisol levels as opposed to the unique administration of these antioxidants at lower doses. As far as we know, there is no information on the possible effects of oleuropein on the cortisol level under fasting and stressful conditions in pigs. It has been reported that oleuropein reduces anxiety responses in rats suffering from post-traumatic stress disorder [47]. Additionally, vitamin E (50 mg/kg) and Se (0.3 mg/kg) reduced cortisol in sheep under heat stress [48]. However, in pigs, following transport stress, the supplementation of 200 mg/kg of vitamin E was not enough to reduce cortisol, with supplementation with oregano essential oil having a greater effect. According to the results of the present study, the administration of higher doses of oleuropein together with the other antioxidants would be an interesting strategy to reduce stress before slaughter. The mode of action is still unclear. It has been suggested that oleuropein may alter catecholamine synthesis in the brain [47]. On the other hand, it has been reported that hydroxytyrosol, another antioxidant substance extracted from olive leaves, may affect the endocannabinoid system by inhibition of its receptors (CB1) [12]. The endocananabonoid system is not only involved in energy regulation in the organism as a metabolic signaling system, but also in the stress response [17]. Hence, it has been suggested that a higher PUFA n-6:n-3 ratio in neurons may produce over-activation of the endocannabinoid system in the limbic areas that control emotions [17]. Other studies show that n-3 fatty acids inhibit adrenal activation related to stress probably through effects on the central nervous system [49]. Plasma n-3 fatty acids are transported through the blood–brain barrier and represent the most important source for nerve cells [50]. Thus, the lower plasma n-3 fatty acids of the group supplemented with the higher dose of oleuropein would indicate a faster uptake for energy supply or biological functions such as those described in the brain for stress control in stressful situations."…

-Dpto. Producción Animal, Facultad de Veterinaria, Universidad Complutense de Madrid, Avda. Puerta de Hierro s/n., 28040 Madrid, Spain; moc.liamg@mced.aned

-Incarlopsa, Ctra. N-400 km. 95400, 16400 Tarancón, Cuenca, Spain; se.aspolracni@ovlacsiul

-Andres Pintaluba, S.A. Polígono Industrial Agro-Reus Prudenci Bertrana, 5, 43206 Reus, Spain;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7022758

“OLE [Oleuropein] interfered with Aβ42 [Alzheimer's peptides] and IAPP aggregation (Daccache et al., 2011; Rigacci et al., 2010, 2011). When this compound was used with Aβ42 and IAPP, OLE blocked their toxicity in cell culture assays (Rigacci et al., 2010, 2011). In the case of IAPP, addition of OLE to preformed fibrils did not induce the release of toxic oligomers (Rigacci et al., 2010), in addition polyphenol ability to drive the formation of stable Aβ42 protofibrils has been reported (Rigacci et al., 2011). NMR analysis revealed that oleuropein interacts with the Aβ40 region, Val12–Asn27, in a noncovalent manner (Galanakis et al., 2011). Recent data showed the ability of OLE to interfere with Aβ aggregation by inhibiting the formation of soluble toxic oligomers and amyloid fibrils in transgenic AD [Alzheimer's Disease], and inclusion body myositis C. elegans invertebrate models. In the inclusion body myositis worm model, oleuropein treatment reduced Aβ plaque deposition, decreased paralysis, and increased lifespan, while in the AD worm model, little protection was observed against paralysis when OLE was administered before the induction of transgene expression (Diomede et al., 2013).”….

-Neuroprotection in Alzheimer's Disease, 2017
https://www.sciencedirect.com/topics/neuroscience/oleuropein

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…“Oleuropein and oleocanthal have been reported to interfere with the amyloid aggregation of Aβ, amylin, and Tau (Fig. 1.4). The latter is a microtubule-associated protein found aggregated in several tauopathies, including AD [Alzheimer's Disease]. The data reported indicate that oleuropein36,37 and oleocanthal38,39 interfere with the aggregation path of these peptides/proteins upon binding to the aggregating molecules, skipping the appearance of toxic species and favoring the formation of nontoxic disordered aggregates.”...

-Role of the Mediterranean Diet in the Brain and Neurodegenerative Diseases, 2018
https://www.sciencedirect.com/topics/neuroscience/oleuropein

Omega-3

…"Currently, most clinicians do not assess omega-3 status, but it can be done by measuring individual omega-3s in plasma or serum phospholipids and expressing them as the percentage of total phospholipid fatty acids by weight [14-16]."…

-National Institute of Health (NIH) ~Referenced by
https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional

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"Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) are dietary factors involved in the prevention of cardiovascular, inflammatory, and neoplastic diseases."…

-Institute of General Pathology, Università Cattolica del Sacro Cuore, Roma, Italy
-Fondazione Policlinico Universitario A, Gemelli 00168 Roma, Italy
-Department of Pharmacy, Health and Nutritional Sciences, Università della Calabria, Cosenza, Italy

https://pubmed.ncbi.nlm.nih.gov/31114196/

Neoplastic diseases - are conditions that cause tumor growth — both benign and malignant. Benign tumors are noncancerous growths. They usually grow slowly and can't spread to other tissues. Malignant tumors are cancerous and can grow slowly or quickly.
-Healthline
https://www.healthline.com/health/neoplastic-disease

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…"The strongest evidence for a beneficial effect of ω-3 [omega-3] fats is mostly related to the heart.[78] Supplementation with ω-3 PUFAs has been reported to have several beneficial effects including reducing cardiovascular mortality[79,80], improved lipid profile[81,82], anti-inflammatory effects[83], reducing cardiac arrhythmias [82], vasodilatory mechanisms[84] and anti-platelet effects.[85] "…

-Department of Pharmacology, University of Michigan, Ann Arbor, MI
-Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6242736

Omega-3 PUFAs Lower the Propensity for Arachidonic Acid [omega-6] Cascade Overreactions

"A productive view of the benefits from omega-3 (n-3) nutrients is that the dietary essential omega-6 (n-6) linoleic acid has a very narrow therapeutic window which is widened by n-3 nutrients. The benefit from moderate physiological actions of the arachidonic acid cascade can easily shift to harm from excessive pathophysiological actions. Recognizing the factors that predispose the cascade to an unwanted overactivity gives a rational approach for arranging beneficial interactions between the n-3 and n-6 essential nutrients that are initial components of the cascade. Much detailed evidence for harmful cascade actions was collected by pharmaceutical companies as they developed drugs to decrease those actions. A remaining

challenge is to understand the factors that predispose the cascade toward unwanted outcomes and create the need for therapeutic interventions. Such understanding involves recognizing the similar dynamics for dietary n-3 and n-6 nutrients in forming the immediate precursors of the cascade plus the more vigorous actions of the n-6 precursor, arachidonic acid, in forming potent mediators that amplify unwanted cascade outcomes. Tools have been developed to aid deliberate day-to-day quantitative management of the propensity for cascade overactivity in ways that can decrease the need for drug treatments."

- Professor Bill Lands (Professor of Biochemistry)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537720

Effects of supplemental fish oil on resting metabolic rate, body composition, and salivary cortisol in healthy adults

…"One possibility lies in the well-documented ability of dietary omega 3 fatty acids to reduce inflammatory cytokines [40], since inflammatory cytokines have the ability to increase protein degradation mainly by activating the ATP-ubiquitin-dependent pathway [41-45]. It is possible then, that dietary fish oil is simply decreasing the breakdown of protein tissue caused by inflammatory cytokines, and this results in an increased accretion of protein over time."

-Department of Health Sciences, Gettysburg College, Gettysburg Pennsylvania, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2958879/

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..."Levels of EPA and DHA in Western diets are often inadequate,[7] and lifestyle factors can impair in vivo HUFA synthesis from its essential precursors. High dietary intake of saturated fats, deficiency of vitamin and mineral cofactors (notably zinc deficiency), smoking, and excessive consumption of alcohol or coffee might result in EPA and DHA depletion. Impairment of HUFA synthesis might also be due to diabetes, eczema, asthma, or other allergic conditions.[4] In the case of dyslexia, contributory genetic factors might include mild abnormalities of fatty acid metabolism that act to increase the usual dietary requirements for these essential nutrients.[9]

Fatty acid deficiency presents with excessive thirst, frequent urination, rough and dry patches on the skin, dry hair, dandruff, and fraying fingernails.[4,10] In one study, these signs were considerably more common among 135 adults with dyslexia compared with 71 adults without dyslexia. The severity of fatty acid deficiency correlated with the individuals' scores on the dyslexia screening checklist. Moreover, fatty acid deficiency was found to be associated with other dyslexia-related

features, including impaired visual perception and auditory and language confusion.[11] The results suggest that dietary supplementation with fatty acids might be of benefit for patients with dyslexia."…

-Michal Zelcer, MSc
-Ran D. Goldman, MD FRCPC
-Canadian Family Physician
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4569108/

Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA

..."Thus, DHA is quantitatively the most important omega-3 PUFA in the brain."…

-Faculty of Health and Social Sciences, Bournemouth University, Bournemouth, UK
-Edited by: Fernanda Laezza, University of Texas Medical Branch, USA
-Reviewed by: Valentina Echeverria Moran, Bay Pines VA Medical Center, USA; Vicent Balanzá-Martínez, University of -Valencia Medical School, Spain
https://www.frontiersin.org/articles/10.3389/fnagi.2015.00052/full

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"Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have received attention for their potential beneficial effects in a vast number of diseases including dermatitis, rheumatoid arthritis, osteoarthritis, neoplasia, cardiovascular diseases, and inflammatory bowel disease (Dumlao et al., 2012; Shek et al., 2012). The prominent feature of n-3 PUFAs in these diseases is their anti-inflammatory effects. A diet rich in n-6 PUFAs (e.g., AA) has been linked to the development and persistence of various diseases (Shek et al., 2012)."

-Department of Veterinary Pathobiology, University of Missouri, Columbia, MO, USA
-Edited by: Tanja Petnicki-Ocwieja, Tufts University School of Medicine and Tufts Medical Center, USA
-Reviewed by: Margaret E. Bauer, Indiana University School of Medicine, USA,
Ashu Sharma, University at Buffalo, State University of New York, USA; Dakshina Jandhyala, Tufts Medical Center, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4036060/

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"Inflammation is the normal host response to infection or injury that mediates immune elimination of pathogens and tissue repair [1]. Inflammatory processes include increased production of cytokines, chemokines, nitric oxide and eicosanoids by the innate immune system

in conjunction with altered leukocyte homing, all of which can greatly impact acquired immunity. Aberrant inflammatory responses not only evoke acute injury, as exemplified by endotoxic shock, but contribute significantly to chronic autoimmune diseases. The capacity of dietary n-3 [omega-3] polyunsaturated fatty acids (PUFAs) found in fish oil to suppress inflammation-associated processes has made them attractive candidates for both the prevention and amelioration of a variety of organ-specific and systemic diseases [2,3]. This review specifically discusses pre-clinical and clinical studies of the efficacy of n-3 PUFAs in prevention and treatment of autoimmune-mediated kidney diseases."

-James J. Pestka, Department of Food Science and Human Nutrition, Department of Microbiology
-Molecular Genetics, Center for Integrative Toxicology, Michigan State University, East Lansing, MI, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2885141/

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"N-3 Polyunsaturated fatty acids have been shown to have potential beneficial effects for chronic diseases including cancer, insulin resistance and cardiovascular disease. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in particular have been studied extensively, whereas substantive evidence for a biological role for the precursor, alpha-linolenic acid (ALA), is lacking. It is not enough to assume that ALA exerts effects through conversion to EPA and DHA, as the process is highly inefficient in humans. Thus, clarification of ALA's involvement in health and disease is essential, as it is the principle n-3 polyunsaturated fatty acid consumed in the North American diet and intakes of EPA and DHA are typically very low. There is evidence suggesting that ALA, EPA and DHA have specific and potentially independent effects on chronic disease. Therefore, this review will assess our current understanding of the differential effects of ALA, EPA and DHA on cancer, insulin resistance, and cardiovascular disease. Potential mechanisms of action will also be reviewed. Overall, a better understanding of the individual role for ALA, EPA and DHA is needed in order to make appropriate dietary recommendations regarding n-3 polyunsaturated fatty acid consumption."…

Sources and Metabolism

"Polyunsaturated fatty acids are hydrocarbon chains with two or more double bonds situated along the length of the carbon chain. Depending on the location of the first double bond relative to the methyl terminus, they can be classified as either n-6 or n-3. Linoleic acid (LA; 18:2n-6), the parent fatty acid of the n-6 PUFA family is an essential fatty acid and cannot be endogenously synthesized by mammals. LA is found in vegetable oils, seeds and nuts. ALA (18:3n-3), the parent fatty acid of the n-3 PUFA family, must be consumed through the diet. ALA is found in leafy vegetables, walnuts, soybeans, flaxseed, and seed and vegetable oils. Both LA and ALA can be

further metabolized to long chain PUFA through a series of desaturation and elongation steps. LA is metabolized to arachidonic acid (AA, 20:4n-6), while ALA can be metabolized to EPA; (20:5n-3) and ultimately DHA (22:6n-3). Alternatively, AA can be obtained from animal fat sources and EPA and DHA can be consumed directly from marine sources.

The average per capita intake of DHA plus EPA is approximately 0.1–0.2 g per day in North America and the average per capita intake of ALA in North America is ~1.4 g daily [1]. As mentioned, ALA can be endogenously converted to EPA and DHA, however this is not an efficient process. Assessment of apparent conversion efficiency of dietary ALA to EPA and DHA is typically done by measuring the net rise in circulating EPA and DHA after increasing ALA intake. Early studies in this area found that while some moderate net rise in the level of EPA resulted with higher levels of ALA, no net rise in the level of circulating DHA occurred [2,3]. For example, feeding 10.7 g/d of ALA from flaxseed oil for 4 weeks failed to increase low DHA levels in breast milk of lactating women [4]. Some estimate that only 5–10% and 2–5% of ALA in healthy adults is converted to EPA and DHA, respectively [5], while others suggest that humans convert less than 5% of ALA to EPA or DHA [6]. The International Society for the Study of Fatty Acids and Lipids (ISSFAL) recently released an official statement on the conversion efficiency of ALA to DHA. They concluded that the conversion of ALA to DHA is on the order of 1% in infants, and considerably lower in adults [7]. Given the demonstrated benefits of DHA on visual acuity [8,9] and in the developing mammalian brain [10,11], poor conversion of ALA to DHA is a concern, particularly for vegetarians and for individuals who do not eat fatty fish.

Given the poor conversion efficiency of ALA to its longer-chain counterparts, ALA levels in the blood and tissue of humans approximate dietary intakes. Since n-3 PUFA in a typical North American diet is comprised mainly of ALA, it is pertinent to elucidate the specific effects this fatty acid. EPA and DHA intake is also low in some European countries as reviewed [12] and in India [13], making ALA the principle n-3 PUFA consumed in these regions. The prevalence of CVD [14], IR [15], and some types of cancers [16] in these countries is elevated, in contrast to countries with high fatty fish intake like Japan [17]. If conversion efficiency is the main criteria, then the epidemiological evidence above would suggest that ALA may not confer the same health benefits as its longer chain counter-parts, EPA and DHA.”…

-Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3224740

A synaptogenic amide N-docosahexaenoylethanolamide promotes hippocampal development

“Docosahexaenoic acid (DHA), the n-3 essential fatty acid that is highly enriched in the brain, increases neurite growth and synaptogenesis in cultured mouse fetal hippocampal neurons. These cellular effects may underlie the DHA-induced enhancement of hippocampus-dependent learning and memory functions. We found that N-docsahexaenoylethanolamide (DEA), an ethanolamide derivative of DHA, is a potent mediator for these actions. This is supported by the observation that DHA is converted to DEA by fetal mouse hippocampal neuron cultures and a hippocampal homogenate, and DEA is present endogenously in the mouse hippocampus. Furthermore, DEA stimulates neurite growth and synaptogenesis at substantially lower concentrations than DHA, and it enhances glutamatergic synaptic activities with concomitant increases in synapsin and glutamate receptor subunit expression in the hippocampal neurons. These findings suggest that DEA, an ethanolamide derivative of DHA, is a synaptogenic factor, and therefore we suggest utilizing the term ‘synaptamide’. This brief review summarizes the neuronal production and actions of synaptamide and describes other N-docosahexaenoyl amides that are present in the brain.”

-Laboratory of Molecular Signaling, National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, United States

https://www.sciencedirect.com/science/article/abs/pii/S1098882311000633

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…“Polyunsaturated fatty acids (PUFAS) are unsaturated fatty acids whose carbon chain has more than one double bond per molecule. Of those, omega-3 (n-3) and omega-6 (n-6) are known as "essential" fatty acids, as humans are unable to synthesize them.

The n-3 series are derived from alpha-linolenic acid (ALA) and the n-6 series, from linoleic acid (LA). The main ALA derivates are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Gamma linolenic acid (GLA), dihomogamma linolenic acid (DGLA) and arachidonic acid (AA) are the main LA products. GLA is produced from LA by the enzyme delta-6-desaturase and is further metabolized to DGLA. A small amount of DGLA can also be converted to AA by the enzyme delta-5-desaturase. Human conversion of ALA and LA to their derivates is limited, and the existence of them depends on the ingestion of certain food sources.

PUFAS are key components to the brain and count up to 15-20% of its dry mass [1]. Other relevant roles of PUFAS are the influence over fluidity of neuronal membranes and acting as second messengers in neurotransmitter systems [2]. According to Naliwaiko, et al. [3], changes in cell membrane fatty acid composition occurs in the central nervous system (CNS) depending on

PUFAS dietary intake [4,5]. Therefore it has been postulated that adequate supplementation of omega-3 and omega-6 would have beneficial effects on brain functions, although the ratio between them has not yet been established [6].”…

-Psychobiology Department, Federal University of São Paulo, Edifício de Ciências Biomédicas, Rua Botucatu 862 - 1° Andar, São Paulo, Brasil

-Laboratory of Physical Activity and Aging of Rio Claro Biosciences Institute - Universidade Paulista Júlio de Mesquita Filho, Rio Claro, São Paulo, Brasil and Centro de Matemática, Computação e Cognição da UFABC, Santo Andrá, São Paulo, Brasil

-Psychobiology Department, Federal University of São Paulo, Edifício de Ciências Biomédicas, Rua Botucatu 862 - 1° Andar, São Paulo, Brasil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3162484/

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…“Omega-3 FAs are a class of polyunsaturated fatty acids derived from the double bond in third position, starting the count from the terminal carbon of the chain. The three most important physiological omega-3 FAs are described: EPA, alpha-linolenic acid (ALA), and DHA. FAs are precursors for neuronal components membranes, fluidity of cell membranes, signalling, neurotransmission and modulation of enzymatic activities [72,73].”…

-IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy;

-Department of Physiopathology and Transplants, University of Milano, Milan, Italy

-Department of Biology and Biotechnology, University of Pavia, Pavia, Italy;

-Istituto per lo Studio e la Cura del Diabete [ISCD], Casagiove, Caserta, Italy;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164598/

Dietary omega-3 fatty acids aid in the modulation of inflammation and metabolic health

“This article focuses on the role of omega-3 fatty acids as precursors for lipid signaling molecules known as oxylipins. Although omega-3 fatty acids are beneficial in autoimmune disorders, inflammatory diseases and heart disease, they are generally underrepresented in the American diet. A literature review confirms that the consumption of omega-3 fatty acids — whether in food sources such as walnuts, flax seeds and fatty fish (including salmon and sardines), or in supplements — is associated with decreased morbidity and mortality. This growing body of evidence, including the results of a recent study of patients with kidney disease, highlights the need to measure omega-3 fatty acids and their oxylipin products as markers of metabolic health and biomarkers of disease. In addition, there is substantial evidence of the need to increase the

omega-3 fatty acid content of American diets to optimize metabolic health.
Many of the most significant U.S. health concerns today are modulated by omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids are associated with the prevention or reduction in severity of a multitude of diseases, from metabolic diseases such as heart disease, diabetes and kidney disease to neurodegenerative diseases such as Alzheimer's to an array of other inflammatory diseases including osteoarthritis.

EPA and DHA attenuate the development of atherosclerosis, or arterial plaques, by reducing concentrations of inflammatory signaling molecules called cytokines and adhesion molecules at the arterial wall where plaque forms (De Caterina et al. 2004). EPA and DHA have also been shown to stabilize atherosclerotic plaques, thereby reducing the likelihood of fatal and nonfatal cardiovascular events (Thies et al. 2003). EPA and DHA additionally reduce the synthesis of triglycerides (fat molecules) and secretion from the liver, and increase the size of low-density lipoproteins, which contribute to the reduction of cardiovascular disease risk (Griffin et al. 2006). EPA and DHA improve liver health by reducing steatosis (accumulation of fat in the liver) in patients with nonalcoholic fatty liver disease (Capanni et al. 2006). They also improve kidney health by attenuating or even reversing the loss of kidney function and reducing hypertension in kidney diseases involving the glomerulus, the main filtering part of the kidney (Donadio et al. 1994). Omega-3 fatty acids affect the joints and are used as analgesics or pain reducers in rheumatoid arthritis (Goldberg and Katz 2007).

The omega-3s even play a role in brain health: high blood plasma levels of omega-3 fatty acids are associated with a reduced risk of neurodegenerative diseases such as Alzheimer's disease (Schaefer et al. 2006) and mental disorders such as schizophrenia (McNamara et al. 2007) and depression (Sanchez-Villegas et al. 2007). Taken in supplement or food form, omega-3 fatty acids have been found to reverse the progression of a number of inflammatory diseases, from inflammatory bowel disease to diseases of the skin and joints, to other autoimmune diseases such as lupus and multiple sclerosis (Simopoulos 2002). This review focuses on the basic biology of omega-3 fatty acids as nutritional modulators of inflammation and presents preliminary results of a study of oxylipin biomarkers in kidney disease patients."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

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…"Ultimately, n-3 PUFAs may protect against CVD through several mechanisms, including acting as an antiatherogenic agent [1,17]; lowering serum triglycerides [1]; slightly lowering blood pressure

[17,19]; improving endothelial function [17]; reducing inflammatory responses [17]; inhibiting platelet aggregation and thombosis [1,17]; and decreasing the incidence of arrhythmias [1,17]."…

-National Centre for Agri-Food Research in Medicine and the Division of Stroke and Vascular Disease, St Boniface Hospital Research Centre

-Department of Physiology, Faculties of Medicine and Pharmacy, University of Manitoba, Winnipeg, Manitoba

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719153/

Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence

"The present review aims to illustrate current knowledge about the efficacy of omega-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) in treating/preventing several metabolic pathologies. We reviewed systematically the published evidence on the effectiveness of n-3 LC-PUFAs fish consumption or n-3 LC-PUFAs supplementation on prevention/treatment of obesity, metabolic syndrome, and cardiovascular diseases. Most of the reviewed studies were randomized-controlled interventional trials, although some relevant prospective and cross-sectional studies as well as some meta-analysis were also reviewed. Supplementation with n-3 LC-PUFAs might improve some obesity-associated metabolic syndrome features such as insulin resistance, hypertension and dyslipidemia by decreasing plasma triglycerides. Moreover, the blood pressure-lowering and anti-inflammatory properties of these fatty acids and their benefits in vascular function might confer cardioprotection. However, the efficacy of n-3 LC-PUFA on reducing myocardial infarction, arrhythmia, cardiac and sudden death, or stroke is controversial. Due to the beneficial actions of n-3 LC-PUFAs, several worldwide government and health organizations have established some recommendations of n-3 LC-PUFAs intake for groups of population. In general, the recommended levels for diseases prevention are lower than those advised for particular treatments. However, more clinical trials are necessary to recommend the most effective dosages and formulas (type of n-3 LC-PUFA, EPA/DHA ratio) for specific pathologies."

-Department of Nutrition, Food Science and Physiology, University of Navarra, Pamplona, Spain.

https://pubmed.ncbi.nlm.nih.gov/23794360/

Dietary supplementation with eicosapentaenoic acid, but not with other long-chain n-3 or n-6 polyunsaturated fatty acids, decreases natural killer cell activity in healthy subjects aged >55 y

"**Background:** Animal studies showed that dietary flaxseed oil [rich in the n-3 polyunsaturated

fatty acid alpha-linolenic acid (ALA)], evening primrose oil [rich in the n-6 polyunsaturated fatty acid gamma-linolenic acid (GLA)], and fish oil [rich in the long-chain n-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] can decrease natural killer (NK) cell activity. There have been no studies of the effect on NK cell activity of adding these oils to the diet of humans."…

"**Results:** The fatty acid composition of plasma phospholipids changed significantly in the GLA, AA, DHA, and fish oil groups. NK cell activity was not significantly affected by the placebo, ALA, GLA, AA, or DHA treatment. Fish oil caused a significant reduction (mean decline: 48%) in NK cell activity that was fully reversed by 4 wk after supplementation had ceased.

Conclusion: A moderate amount of EPA but not of other n-6 or n-3 polyunsaturated fatty acids can decrease NK cell activity in healthy subjects."

-Department of Biochemistry, University of Oxford, Oxford, United Kingdom.

https://pubmed.ncbi.nlm.nih.gov/11237929/

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…"Omega-3 fatty acids are known for their multiple effects on health and disease. Omega-3 fatty acids have been shown to protect against cardiovascular disease,[1] playing a role in the secondary prevention of myocardial infarction,[2] having an anti-arrhythmic action[3] and reducing inflammation.[4,5] Omega-3 fatty acids play a role in the treatment of inflammatory bowel disease, and, if taken, may have a beneficial effect.[6] Omega-3 fatty acids are tested for their therapeutic potential in multiple sclerosis.[7–9]"…

-Department of Endocrinology, Asclepeion Hospital, Voula, Athens, Greece
-First Department of Medicine, Asclepeion Hospital, Voula, Athens, Greece
-Department of Rheumatology, St. Paul's Hospital, Thessaloniki, Greece
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7362115

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"Omega-3 (n-3) long-chain polyunsaturated fatty acids (LCPUFA), particularly eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), can offer many health benefits when regularly consumed in sufficient quantities. Health benefits of n-3 LCPUFA include reduction of preterm birth, decreased risk for low birth weight in infants, improved visual acuity in infants, facilitation of early childhood neurodevelopment, inflammation modulation such as with chronic disease or cancer-related complications, risk reduction of cardiovascular disease (CVD), prevention of

dementia and cognitive decline, and a decreased risk for developing age-related macular degeneration [1,2,3,4,5,6,7,8,9,10,11,12,13].

There are currently no Recommended Dietary Allowances or Dietary Reference Intakes set for EPA or DHA. Other government and public health agencies have offered recommendations, but these vary widely and are based primarily on age or gender [14,15,16]. Although symptomatic polyunsaturated fatty acid deficiency, which presents with scaly skin and dermatitis, is very rare in the United States (US), the Western diet typically includes lower amounts of n-3 LCPUFA than those recommended for age and gender groups by the National Institutes of Health and the World Health Organization [14,17,18,19,20] (Table 1).”...

“Adequate Intakes for omega-3 (n-3) long-chain polyunsaturated fatty acids (LCPUFA).

World Health Organization [14]	**Age**	**AI (Adequate Intake; per day)**
DHA	12–24 months	10–12 mg/kg
EPA+DHA	2–4 years	100–150 mg
	4–6 years	150–200 mg
	6–10 years	200–250 mg
	Adults	200–250 mg
National Institutes of Health [18]	**Age**	**Male/Female (per day)**
EPA+DHA	1–3 years	70 mg/70 mg
	4–8 years	90 mg/90 mg
	9–13 years	120 mg/100 mg
	14–18 years	160 mg/110 mg
	19–50 years	160 mg/110 mg
	51 years	160 mg/110 mg

mg = milligrams, kg = kilograms.”

-Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE 68198, USA; (M.T.)
-College of Public Health, University of Nebraska Medical Center, Omaha, NE 68198, USA;
-Department of Nutritional Sciences, University of Arizona, Tucson, AZ 85721, USA;
-Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA 16802, USA;
-Division of Biomedical Sciences, School of Medicine, University of California Riverside, Riverside, CA 92521, USA

-College of Allied Health Professions, University of Nebraska Medical Center, Omaha, NE 68198, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7400855/

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"Omega-3 fatty acids are a subset of polyunsaturated fatty acids found in marine sources as eicosapentaenoic acid and docosahexaenoic acid and in some leafy vegetables, nuts, and oils as alpha-linolenic acid (ALA). The metabolism of omega-3's may explain the cardioprotective effects observed in epidemiologic and experimental studies. Although most data for cardioprotective effects come from studies of marine sources, vegetable sources of omega-3 fatty acids (alpha-linolenic acid) may have similar effects through in vivo conversion to eicosapentaenoic acid and docosahexaenoic acid. This document will provide an overview of omega-3 fatty acids with a focus on specific sources, metabolism, safety issues, and their potential indication for cardiovascular prevention."

-Division of General Medicine, Emory University School of Medicine, Atlanta, GA, USA.
https://pubmed.ncbi.nlm.nih.gov/16504616/

See also Antitumorigenic

Omega-3s & Addiction

Dietary Supplementation with Omega-3 Polyunsaturated Fatty Acids Reduces Opioid-Seeking Behaviors and Alters the Gut Microbiome

"Opioids are highly addictive substances with a relapse rate of over 90%. While preclinical models of chronic opioid exposure exist for studying opioid dependence, none recapitulate the relapses observed in human opioid addiction. The mechanisms associated with opioid dependence, the accompanying withdrawal symptoms, and the relapses that are often observed months or years after opioid dependence are poorly understood. Therefore, we developed a novel model of chronic opioid exposure whereby the level of administration is self-directed with periods of behavior acquisition, maintenance, and then extinction alternating with reinstatement. This profile arguably mirrors that seen in humans, with initial opioid use followed by alternating periods of abstinence and relapse. Recent evidence suggests that dietary interventions that reduce inflammation, including omega-3 polyunsaturated fatty acids (n-3 PUFAs), may reduce substance misuse liability. Using the self-directed intake model, we characterize the observed

profile of opioid use and demonstrate that an n-3-PUFA-enriched diet ameliorates oxycodone-seeking behaviors in the absence of drug availability and reduces anxiety. Guided by the major role gut microbiota have on brain function, neuropathology, and anxiety, we profile the microbiome composition and the effects of chronic opioid exposure and n-3 PUFA supplementation. We demonstrate that the withdrawal of opioids led to a significant depletion in specific microbiota genera, whereas n-3 PUFA supplementation increased microbial richness, phylogenetic diversity, and evenness. Lastly, we examined the activation state of microglia in the striatum and found that n-3 PUFA supplementation reduced the basal activation state of microglia. These preclinical data suggest that a diet enriched in n-3 PUFAs could be used as a treatment to alleviate anxiety induced opioid-seeking behavior and relapse in human opioid addiction."

-Department of Psychiatry and Biobehavioral Sciences, Hatos Center for the Study of Opioids Receptors and Drugs of Abuse, UCLA Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine,

-The Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA

-UCLA Microbiome Center, David Geffen School of Medicine at UCLA

-Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas at Austin

-ZS Associates, San Mateo, CA

-Division of Gastroenterology, Hepatology and Parenteral Nutrition, VA Greater Los Angeles Healthcare System

-UCLA Brain Research Institute, UCLA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723154/

Effects of Sex, Drinking History, and Omega-3 and Omega-6 Fatty Acids Dysregulation on the Onset of Liver Injury in Very Heavy Drinking Alcohol-Dependent Patients

"Heavy alcohol consumption frequently causes liver inflammation/injury, and certain fatty acids (FAs) may be involved in this liver pathology. In this study, we evaluated the association of heavy drinking and the changes in the FA levels involved in the ω-6 (pro-inflammatory) and ω-3 (anti-inflammatory) state in alcohol-dependent (AD) patients who had no clinical manifestations of liver injury. We aimed to identify sex-based differences in patients with mild or no biochemical evidence of liver injury induced by heavy drinking."

…"Measures of heavy drinking, TD90 and HDD90, predicted changes in liver injury. Changes in the ω-3 and ω-6 FA levels and the ω-6:ω-3 ratio showed a pro-inflammatory shift in patients with biochemical liver injury with a significant effect in females. Changes in FAs involved in the inflammatory state may represent one mechanism for liver inflammation/injury in response to heavy alcohol drinking."

-Department of Medicine (VV, MS, MCC, SSB, CJM), University of Louisville School of Medicine, Louisville, Kentucky;
-Robley Rex Veterans Affairs Medical Center (VV, MCC, CJM), Louisville, Kentucky; Laboratory of Clinical and Translational Studies (VV, MLS, DTG, VAR)
- National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland;
-Department of Pharmacology and Toxicology (MCC, SSB, CJM), University of Louisville School of Medicine, Louisville, Kentucky
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5367046/

The relationship between omega-3 and smoking habit: a cross-sectional study

"Omega3 polyunsaturated fatty acids (PUFAs) are related to several diseases, including smoking. The aim of this study was to evaluate the relationship between omega-3 intake and tobacco smoking, taking into account the qualitative differences in dietary intake between smokers and non-smokers, the amount of the ingested PUFA and their red blood (RBC) contents. We also looked for an association between omega-3 RBC content and smoking, and also between omega3 intake and the level of nicotine dependence."

…"After adjusting for confounding factors, non-smokers showed higher consumption of PUFAs, especially salmon: 800 g (0–7.740) than smokers 430 g (0–2.150) $P<0.001$. They also had higher DHA levels compared to smokers: 4.81 % (2.79–10.21) and 4.13 % (2.33–7.73), respectively, $p<0.05$. The other PUFAs showed no significant differences between the two groups."

"Smokers ate less fish rich in omega3 fatty acids than non-smokers, showing and inverse and significant relationship between omega3 intake and smoking. Smokers had lower levels of DHA and EPA, a not previously reported finding. Considering that PUFAs probably interfere in smoking habit, the increase in omega-3 consumption may become a perspective in prevention or treatment of smoking. However, this inference must be evaluated through specific studies."

-Pontifícia Universidade Catolica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil
-Asthma & Airway Centre, University Health Network, Toronto, Canada
-Asthma and Airways Centre, McMaster University, Toronto, Canada
-Department of Family and Community Medicine and Psychiatry, University of Toronto, Toronto, Canada
-Department of Medicine, Toronto General Hospital, University of Toronto, Toronto, Canada
-Department of Medicine, Division of Respiratory Diseases, University of Toronto, Toronto, Canada
-Hospital São Lucas da PUCRS – Centro Clínico, 6690 Ipiranga Ave, Porto Alegre, RS 90610000 Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4804563/

Omega-3 decreases D1 and D2 receptors expression in the prefrontal cortex and prevents amphetamine-induced conditioned place preference in rats.

"Amphetamine (AMPH) abuse is a serious public health problem due to the high addictive potential of this drug, whose use is related to severe brain neurotoxicity and memory impairments. So far, therapies for psychostimulant addiction have had limited efficacy. Omega-3 polyunsaturated fatty acids (n-3 PUFA) have shown beneficial influences on the prevention and treatment of several diseases that affect the central nervous system. Here, we assessed the influence of fish oil (FO), which is rich in n-3 PUFA, on withdrawal and relapse symptoms following re-exposure to AMPH. Male Wistar rats received d,l-AMPH or vehicle in the conditioned place preference (CPP) paradigm for 14 days. Then, half of each experimental group was treated with FO (3 g/kg, p.o.) for 14 days. Subsequently, animals were re-exposed to AMPH-CPP for three additional days, in order to assess relapse behavior. Our findings have evidenced that FO prevented relapse induced by AMPH reconditioning. While FO prevented AMPH-induced oxidative damages in the prefrontal cortex, molecular assays allowed us to observe that it was also able to modulate dopaminergic cascade markers (DAT, TH, VMAT-2, D1R and D2R) in the same brain area, thus preventing AMPH-induced molecular changes. **To the most of our knowledge, this is the first study to show a natural alternative tool which is able to prevent psychostimulant relapse following drug withdrawal. This non-invasive and healthy nutraceutical may be considered as an adjuvant treatment in detoxification clinics.**" [sic]

-Programa de Pós-Graduação em Farmacologia-Universidade Federal de Santa Maria, RS, Brazil.

-Programa de Pós-Graduação em Bioquímica Toxicológica - Universidade Federal de Santa Maria, RS, Brazil.

-Programa de Pós-Graduação em Ciência e Tecnologia dos Alimentos-Universidade Federal de Santa Maria, RS, Brazil.

-Departamento de Tecnologia e Ciências dos Alimentos - Universidade Federal de Santa Maria, RS, Brazil.

-Programa de Pós-Graduação em Farmacologia-Universidade Federal de Santa Maria, RS, Brazil. Electronic address: marilise.burger@ufsm.br.

-Programa de Pós-Graduação em Farmacologia-Universidade Federal de Santa Maria, RS, Brazil; Universidade Federal do Pampa, Campus Uruguaiana, RS, Brazil.

https://www.ncbi.nlm.nih.gov/pubmed/30951972

Dietary supplementation with fish oil prevents high fat diet-induced enhancement of sensitivity to the locomotor stimulating effects of cocaine in adolescent female rats.

"Eating a diet high in fat can lead to obesity, chronic metabolic disease, and increased inflammation in both the central and peripheral nervous systems. Dietary supplements that are high in omega-3 polyunsaturated fatty acids can reduce or prevent these negative health consequences in rats. Eating high fat chow also increases the sensitivity of rats to behavioral

effects of drugs acting on dopamine systems (e.g., cocaine), and this effect is greatest in adolescent females."

…"These results demonstrate that dietary supplementation with fish oil can prevent high fat diet-induced sensitization to cocaine, but they fail to support the view that these effects are due to changes in proinflammatory cytokines. These data add to a growing literature on the relationship between diet and drug abuse and extend the potential health benefits of fish oil to stimulant drug abuse prevention."

-Departments of Pharmacology and Psychiatry, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX, USA.

-Departments of Pharmacology and Psychiatry, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX, USA.

-Departments of Pharmacology and Psychiatry, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX, USA.

https://www.ncbi.nlm.nih.gov/pubmed/27242289

Polyunsaturated fatty acid status and relapse vulnerability in cocaine addicts.

"There is mounting evidence that low levels of some polyunsaturated fatty acids (PUFAs) play a role in the pathophysiology of depressive and aggressive disorders, including homicides. There is also evidence derived mostly from the animal literature that PUFAs could play a role in the abuse of substances through their action on central serotonergic and dopaminergic systems that are both known to play a role in reward mechanisms. In this study, we explored the possibility that the relapse rates of cocaine addicts discharged after a period of detoxification on an inpatient unit would be associated with their PUFA status. Thirty-eight patients were enrolled in the study. PUFA status was assessed only at baseline, shortly after admission. Resumption of substance use was assessed 3 months, 6 months and 1 year following discharge. Thirty-two patients remained available for follow-up for the duration of the study. Subjects who relapsed at 3 months had significantly lower baseline levels of total n-6 [omega-6] PUFAs, linoleic acid (LA, 18:2n-6), arachidonic acid (AA, 20:4n-6) and total n-3 [omega-3] PUFAs when compared to non-relapsers by ANCOVAs with age and weight as covariates. Lower baseline total n-6 PUFAs, LA and AA continued to predict relapse 6 months and 12 months following discharge. Age, marital status, educational level, cocaine use parameters or psychopathology did not differ between relapsers and non-relapsers. In conclusion, low PUFA status at baseline was a better predictor of relapse than cocaine use, sociodemographic or clinical parameters. These data suggest, but do not prove, the existence of a causal relationship between n-6 or n-3 status and relapse vulnerability in cocaine addicts, and provide a rationale for the exploration of possible relationships between relapse to addictive disorders and PUFA status in observational and interventional trials."

-Department of Psychiatry, State University of New York-Health Science Center at Brooklyn

-Veterans Affairs New York Harbor Healthcare System, Brooklyn Campus (11S/BK), 800 Poly Place, Brooklyn, NY, USA.
https://www.ncbi.nlm.nih.gov/pubmed/14500111/

Long chain n-3 [omega-3] polyunsaturated fatty acids decrease feelings of anger in substance abusers

"It has been suggested that low levels of n-3 [omega-3] polyunsaturated fatty acids (PUFAs) play a role in the pathophysiology of some psychiatric disorders. In light of the existence of strong associations between high-frequency and high-severity aggressive behaviors and substance use disorders and of our observation that substance abusers have poor dietary habits, the possibility that the administration of supplements of n-3 PUFAs would decrease their anger levels was explored. A life long history of aggressive behaviors and problems with the law was obtained in 24 patients. Thirteen patients received on a daily basis capsules containing 3 g of n-3 PUFAs (EPA+DHA). Eleven patients received placebo capsules. The trial was double-blind, randomized, and lasted 3 months. An anger scale was administered at baseline and every month thereafter. Six PUFA group patients and eight placebo group patients were followed for an additional 3 months after treatment discontinuation. Four patients in each group had a history of assaultive behavior. The baseline fish and n-3 PUFA intakes of these 8 patients were significantly lower than those of the non-aggressive patients. When given for 3 months, n-3 PUFAs were superior to placebo in diminishing anger scores. These scores remained decreased for 3 months following treatment discontinuation. These data provide further support to emerging evidence indicating that supplementation with long-chain n-3 PUFAs could be beneficial in the treatment of some individuals with aggressive tendencies."

-VA New York Harbor Healthcare System – Brooklyn Campus, 800 Poly Place, Brooklyn, NY, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225526/

Omega-3s in Children

…"Essential fatty acids are a fundamental and necessary nutritional contribution to the healthy development of the organism and, of all of them, omega-3 long chain polyunsaturated fatty acids (LC-PUFA) are those that have presented the healthiest effects. Several reports have shown that the contribution of O3 through diet can have cardioprotective effects, reducing the incidence of acute myocardial infarction, act as an antihypertensive, have anti-inflammatory effects, and intervene in the process of inhibiting the growth of some tumor cells in the adult population, among other benefits [1,2,3,4,5]. In children, an adequate O3 intake prevents obesity-

related chronic diseases [6], and lowers the risk of allergies [7], increased visual acuity [1,8] and improved cognitive ability [5,9,10,11], in particular O3 in the form of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA). EPA and DHA are part of the organism's cell membrane phospholipids, but DHA has the highest presence, up to 50%, in the organ-specific membrane phospholipids such as in the retina and the cerebral cortex [12,13]. This determines the importance of O3 LC-PUFA for the correct functioning and development of these organs, as well as in the deterioration of some functions when these substances are deficient, such as impairment of brain function, lack of growth, skin lesions, loss of muscle tone and degenerative changes in some organs [2,14,15,16,17]."…

-Frailty and Cognitive Impairment Organized Group (FROG), University of Valencia, Spain-Department of Nursing, University of Valencia, Spain

-Department of Biomedical Sciences, Cardenal Herrera University CEU, Avenida Seminario, s/n, Valencia, Spain;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7697719/

Omega-3, Omega-6 Anti-Inflammatory & Pro-Inflammatory Actions

Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance.

"Inflammation is a condition which contributes to a range of human diseases. It involves a multitude of cell types, chemical mediators, and interactions. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 (n-3) fatty acids found in oily fish and fish oil supplements. These fatty acids are able to partly inhibit a number of aspects of inflammation including leukocyte chemotaxis, adhesion molecule expression and leukocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid, production of inflammatory cytokines, and T-helper 1 lymphocyte reactivity. In addition, EPA gives rise to eicosanoids that often have lower biological potency than those produced from arachidonic acid and EPA and DHA give rise to anti-inflammatory and inflammation resolving mediators called resolvins, protectins and maresins. Mechanisms underlying the anti-inflammatory actions of marine n-3 fatty acids include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B so reducing expression of inflammatory genes, activation of the anti-inflammatory transcription factor peroxisome proliferator activated receptor γ and binding to the G protein coupled receptor GPR120. These mechanisms are

interlinked, although the full extent of this is not yet elucidated. Animal experiments demonstrate benefit from marine n-3 fatty acids in models of rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and asthma. Clinical trials of fish oil in RA demonstrate benefit, but clinical trials of fish oil in IBD and asthma are inconsistent with no overall clear evidence of efficacy."

-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK
-NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK
-Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia.
https://www.ncbi.nlm.nih.gov/pubmed/25149823

Essential fatty acids and lipid mediators. Endocannabinoids

"In 1929 Burr and Burr discovered the essential fatty acids omega-6 and omega-3. Since then, researchers have shown a growing interest in polyunsaturated fatty acids (PUFA) as precursors of "lipid mediator" molecules, often with opposing effects, prostaglandins, prostacyclins, thromboxanes, leukotrienes, lipossines, resolvines, protectines, maresins that regulate immunity, platelet aggregation, inflammation, etc. They showed that the balance between omega-3 and omega-6 acids has a profound influence on all the body's inflammatory responses and a raised level of PUFA omega-3 in tissue correlate with a reduced incidence of degenerative cardiovascular disease, some mental illnesses such as depression, and neuro-degenerative diseases such as Alzheimer's. The CYP-catalyzed epoxidation and hydroxylation of arachidonic acid (AA) were established recently as the so-called third branch of AGE cascade. Cytochrome P450 (CYP) epoxygenases convert AA to four epoxyeicosatrienoic acid (EET) regioisomers, that produce vascular relaxation anti-inflammatory effects on blood vessels and in the kidney, promote angiogenesis, and protect ischemic myocardium and brain. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are accessible to CYP enzymes in the same way as AA. Metabolites derived from EPA include epoxye-icosatetraenoic acids (EETR) and hydroxyeicosapentaenoic acids (19- and 20-HEPE), whereas DHA include epoxydocosapentaenoic acids (EDPs) hydroxydocosahexaenoic acids (21- and 22-HDoHE). For many of the CYP isoforms, the n-3 PUFAs are the preferred substrates and the available data suggest that some of the vasculo- and cardioprotective effects attributed to dietary n-3 PUFAs may be mediated by CYP-dependent metabolites of EPA and DHA. From AA derives also endocannabinoids like anandamide (N-arachidonoylethanolamine) and 2-arachidonoylglycerol, capable of mimicking the pharmacological actions of the active principle of Cannabis sativa preparations such as hashish and marijuana (-)-Delta9-tetrahydrocannabinol. They act as true 'endogenous cannabinoids' by binding and functionally activating one or both cannabinoid

receptor present on nervous and peripheral cell membranes. Enzymes that carry out anandamide oxidation are the same fatty acid oxygenases that are known to act on endogenous arachidonic acid namely, the members of the COX, LOX, and P450 families of enzymes. Recent advances in the biochemistry and pharmacology of the endocannabinoid system, also for its central and peripheral roles in regulating food intake, will offer the development of novel therapeutic agents."

-Primary Emeritus of Pediatrics and Neonatology, Specialized Maternal at Child Hospital G. Salesi
https://www.ncbi.nlm.nih.gov/pubmed/22730630

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…"Omega-3 fatty acids have anti-inflammatory action. Eicosanoids are synthesized from omega-6 and omega-3 fatty acids. Arachidonic acid and eicosapentaenoic acid compete for the cyclo-oxygenase and lipoxygenase enzymes for conversion into eicosanoids. Those derived from arachidonic acid are pro-inflammatory and pro-aggregatory, whereas those derived from omega-3 fatty acids are anti-inflammatory and inhibit platelet aggregation. The beneficial effects of omega-3 fatty acids are mediated by themselves as well as their metabolites, namely resolvins, protectins and maresins. The most studied omega-3 metabolites are resolvins, which are classified into two classes. Class D resolvins are products of docosahexaenoic acid and class E resolvins are products of eicosapentaenoic acid.16–18 These metabolites of omega-3 fatty acids compete with those of omega-6 to promote the resolution of the inflammatory cycle.19,20 They are thought to play a significant role in the attenuation of inflammation and regulation of autoimmunity.[19,20]"…

-Department of Endocrinology, Asclepeion Hospital, Voula, Athens, Greece
-First Department of Medicine, Asclepeion Hospital, Voula, Athens, Greece
-Department of Rheumatology, St. Paul's Hospital, Thessaloniki, Greece
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7362115/

Omega-3 fatty acids and inflammatory processes: from molecules to man.

"Inappropriate, excessive or uncontrolled inflammation contributes to a range of human diseases. Inflammation involves a multitude of cell types, chemical mediators and interactions. The present article will describe nutritional and metabolic aspects of omega-6 (n-6) and omega-3 (n-3) fatty acids and explain the roles of bioactive members of those fatty acid families in inflammatory processes. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are n-3 fatty acids found in oily fish and fish oil supplements. These fatty acids are capable of partly inhibiting many aspects of inflammation including leucocyte chemotaxis, adhesion molecule

expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid and production of pro-inflammatory cytokines. In addition, EPA gives rise to eicosanoids that often have lower biological potency than those produced from arachidonic acid, and EPA and DHA give rise to anti-inflammatory and inflammation resolving mediators called resolvins, protectins and maresins. Mechanisms underlying the anti-inflammatory actions of EPA and DHA include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor κB so reducing expression of inflammatory genes and activation of the anti-inflammatory transcription factor peroxisome proliferator-activated receptor γ. Animal experiments demonstrate benefit from EPA and DHA in a range of models of inflammatory conditions. Human trials demonstrate benefit of oral n-3 fatty acids in rheumatoid arthritis and in stabilizing advanced atherosclerotic plaques. Intravenous n-3 fatty acids may have benefits in critically ill patients through reduced inflammation. The anti-inflammatory and inflammation resolving actions of EPA, DHA and their derivatives are of clinical relevance."

-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, IDS Building, MP887 Southampton General Hospital, Tremona Road, Southampton, U.K..

-NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, U.K.

https://www.ncbi.nlm.nih.gov/pubmed/28900017

Polyunsaturated fatty acids and inflammation

"The n-6 polyunsaturated fatty acid, arachidonic acid, is a precursor of prostaglandins, leukotrienes and related compounds that have important roles as mediators and regulators of inflammation. Consuming increased amounts of long chain n-3 polyunsaturated fatty acids (found in oily fish and fish oils) results in a partial replacement of the arachidonic acid in cell membranes by eicosapentaenoic and docosahexaenoic acids. This leads to decreased production of arachidonic acid-derived mediators. This alone is a potentially beneficial anti-inflammatory effect of n-3 fatty acids. However, n-3 fatty acids have a number of other effects that might occur downstream of altered eicosanoid production or are independent of this. For example, they result in suppressed production of pro-inflammatory cytokines and can modulate adhesion molecule expression. These effects occur at the level of altered gene expression."

-Institute of Human Nutrition, School of Medicine, University of Southampton, Bassett Crescent East, Southampton

https://pubmed.ncbi.nlm.nih.gov/15787620/

The Heart and Medicine: Recent advanced in Fatty Acid Metabolism

…"As we consider the biology of the endothelial layer, the role of lipids remains a significant one and indeed an evolving one. Close attention still needs to be made to the concentrations of low-density lipoprotein (LDL), high-density lipoprotein (HDL) and the very low density lipoprotein fractions. Yet, fatty acids are more than just building blocks for obstructive plaque. Fatty acids play integral roles in inflammatory processes and cell signaling. It has been demonstrated in the GISSI study that low dose fish oil significantly reduced the cumulative rate of all-cause death, nonfatal MI, and nonfatal stoke.[8] The individual components of fish oil docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have been evaluated for their individual properties. DHA is the principal omega-3 fatty acid in fish and fish oils responsible for their blood pressure and heart rate lowering effects in humans.[9] EPA and DHA seem to be equally effective in lowering triglycerides with the caveat that while DHA leads to significant increases in HDL cholesterol, it may also lead to increases in LDL cholesterol not seen with EPA containing supplements.[10] Traditionally, supplementation of omega-3 fatty acids was conducted to restore balance between the pro-inflammatory omega-6 prostaglandins and the antiinflammatory omega-3 prostaglandins. Recent research demonstrates additional pathways for modulation of physiology by omega-3 fatty acids as it has been shown that DHA, by modulating MAP kinases, regulates the expression of transcription factors involved in t-cell differentiation in disease and health.[11] Beyond this regulatory kinase role, omega-3 fatty acids bind to the G-coupled protein receptors (GPCR) 120 and 140. When upregulated, these receptors increase insulin sensitivity by increasing glucose-dependent, glucose-like, peptide-1 secretion and by regulating adipocyte differentiation while down regulating inflammation.[12,13] GPR-120 functions as a receptor for unsaturated long chain fatty acids and plays a critical role in modulating adipogensis and regulation of appetite and food preferences. Ichimura et al[14] have shown that GPR-120 deficient mice fed a high fat diet developed many of the signs and symptoms we associate with cardiometabolic syndrome, including obesity, glucose intolerance and fatty liver disease. And it has been found that intravenous infusion of free fatty acids influences proliferation of the beta cell in type 2 diabetic subjects.[15]"…

-Dr Joseph Lamb, M.D
- Director of Intramural Clinical Research, Metagenics
-Anti-Aging Medical News - The Future of Medicine Today (2014)
https://www.a4m.com/assets/pdf/medical-news/medical-news-winter-2014.pdf

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…"Both omega-6 and omega-3 fatty acids are important structural components of cell

membranes, serve as precursors to bioactive lipid mediators, and provide a source of energy. Long-chain omega-3 polyunsaturated fatty acids (PUFA in particular exert anti-inflammatory effects; it is recommended to increase their presence in the diet."…

- *Oregon State University*
https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids#metabolism-bioavailability

Omega-3 fatty acids and inflammatory processes: from molecules to man.

"Inappropriate, excessive or uncontrolled inflammation contributes to a range of human diseases. Inflammation involves a multitude of cell types, chemical mediators and interactions. The present article will describe nutritional and metabolic aspects of omega-6 (n-6) and omega-3 (n-3) fatty acids and explain the roles of bioactive members of those fatty acid families in inflammatory processes. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are n-3 fatty acids found in oily fish and fish oil supplements. These fatty acids are capable of partly inhibiting many aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid and production of pro-inflammatory cytokines. In addition, EPA gives rise to eicosanoids that often have lower biological potency than those produced from arachidonic acid, and EPA and DHA give rise to anti-inflammatory and inflammation resolving mediators called resolvins, protectins and maresins. Mechanisms underlying the anti-inflammatory actions of EPA and DHA include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor κB so reducing expression of inflammatory genes and activation of the anti-inflammatory transcription factor peroxisome proliferator-activated receptor γ. Animal experiments demonstrate benefit from EPA and DHA in a range of models of inflammatory conditions. Human trials demonstrate benefit of oral n-3 fatty acids in rheumatoid arthritis and in stabilizing advanced atherosclerotic plaques. Intravenous n-3 fatty acids may have benefits in critically ill patients through reduced inflammation. The anti-inflammatory and inflammation resolving actions of EPA, DHA and their derivatives are of clinical relevance."

-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, IDS Building, MP887 Southampton General Hospital, Tremona Road, Southampton, U.K.

-NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton SO16 6YD, U.K.

https://www.ncbi.nlm.nih.gov/pubmed/28900017

N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic.

“The immune system is involved in host defense against infectious agents, tumor cells, and environmental insults. Inflammation is an important component of the early immunologic response. Inappropriate or dysfunctional immune responses underlie acute and chronic inflammatory diseases. The n-6 PUFA arachidonic acid (AA) is the precursor of prostaglandins, leukotrienes, and related compounds that have important roles in inflammation and in the regulation of immunity. Feeding fish oil results in partial replacement of AA in cell membranes by EPA. This leads to decreased production of AA-derived mediators, through several mechanisms, including decreased availability of AA, competition for cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, and decreased expression of COX-2 and 5-LOX. This alone is a potentially beneficial anti-inflammatory effect of n-3 FA. However, n-3 FA have a number of other effects that might occur downstream of altered eicosanoid production or might be independent of this effect. For example, dietary fish oil results in suppressed production of proinflammatory cytokines and can modulate adhesion molecule expression. These effects occur at the level of altered gene expression. Fish oil feeding has been shown to ameliorate the symptoms of some animal models of autoimmune disease and to protect against the effects of endotoxin. Clinical studies have reported that oral fish oil supplementation has beneficial effects in rheumatoid arthritis and among some asthmatics, supporting the idea that the n-3 FA in fish oil are anti-inflammatory. There are indications that the inclusion of fish oil in enteral and parenteral formulae is beneficial to patients.”

-Institute of Human Nutrition, School of Medicine, University of Southampton, Bassett Crescent East, Southampton SO16 7PX, United Kingdom.

https://www.ncbi.nlm.nih.gov/pubmed/12848278

Differential effects of prostaglandin derived from ω-6 and ω-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion

“Omega-6 (ω-6) polyunsaturated fatty acids (PUFA), abundant in the Western diet, are precursors for a number of key mediators of inflammation including the 2-series of prostaglandins (PG). PGE2, a cyclooxygenase (COX) metabolite of arachidonic acid, a ω-6 PUFA, is a potent mediator of inflammation and cell proliferation. Dietary supplements rich in ω-3 PUFA reduce the concentrations of 2-series PG and increase the synthesis of 3-series PG (e.g., PGE3), which are believed to be less inflammatory. “….

“We further show that increasing the ω-3 [omega-3] content of membrane phospholipid results in a decrease in mitogen-induced PGE2 synthesis. Taken together, our data suggest that

successful replacement of ω-6 PUFA with ω-3 PUFA in cell membranes can result in a decreased cellular response to mitogenic and inflammatory stimuli."

-Divisions of Hematology–Oncology and †Gynecologic Oncology, Department of Obstetrics and Gynecology, Division of Cardiology, Department of Medicine, and Department of Molecular and Medical Pharmacology, University of California, Los Angeles, CA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC149905/

Polyunsaturated fatty acids, inflammation, and immunity.

"The fatty acid composition of inflammatory and immune cells is sensitive to change according to the fatty acid composition of the diet. In particular, the proportion of different types of polyunsaturated fatty acids (PUFA) in these cells is readily changed, and this provides a link between dietary PUFA intake, inflammation, and immunity. The n-6 PUFA arachidonic acid (AA) is the precursor of prostaglandins, leukotrienes, and related compounds, which have important roles in inflammation and in the regulation of immunity. Fish oil contains the n-3 PUFA eicosapentaenoic acid (EPA). Feeding fish oil results in partial replacement of AA in cell membranes by EPA. This leads to decreased production of AA-derived mediators. In addition, EPA is a substrate for cyclooxygenase and lipoxygenase and gives rise to mediators that often have different biological actions or potencies than those formed from AA. Animal studies have shown that dietary fish oil results in altered lymphocyte function and in suppressed production of proinflammatory cytokines by macrophages. Supplementation of the diet of healthy human volunteers with fish oil-derived n-3 PUFA results in decreased monocyte and neutrophil chemotaxis and decreased production of proinflammatory cytokines. Fish oil feeding has been shown to ameliorate the symptoms of some animal models of autoimmune disease. Clinical studies have reported that fish oil supplementation has beneficial effects in rheumatoid arthritis, inflammatory bowel disease, and among some asthmatics, supporting the idea that the n-3 PUFA in fish oil are anti-inflammatory and immunomodulatory."

-Institute of Human Nutrition, University of Southampton, Southampton, UK

https://www.ncbi.nlm.nih.gov/pubmed/11724453

Modulation of inflammatory cytokines by omega-3 fatty acids

"Many human diseases have been linked to inflammation, which is mediated by a number of chemical molecules including lipid mediators and cytokines. Polyunsaturated fatty acids (omega-6 and omega-3 fatty acids) are the precursors of the lipid mediators and play an important role in regulation of inflammation. Generally, omega-6 fatty acids (e.g. arachidonic acid) promote

inflammation whereas omega-3 fatty acids (e.g. eicosapentaenoic acid and docosahexaenoic acid) have anti-inflammatory properties. Omega-3 fatty acids dampen inflammation through multiple pathways. On the one hand, omega-3 fatty acids inhibit the formation of omega-6 fatty acids-derived pro-inflammatory eicosanoids (e.g. PGE2 and LTB4), and on the other hand these fatty acids can form several potent anti-inflammatory lipid mediators (e.g. resolvins and protectins). These together directly or indirectly suppress the activity of nuclear transcription factors, such as NFkappaB, and reduce the production of pro-inflammatory enzymes and cytokines, including COX-2, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-1beta. This chapter focuses on the evidence from recent studies using new experimental models."

-Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA
https://pubmed.ncbi.nlm.nih.gov/18751910/

Polyunsaturated fatty acids and inflammation

"The n-6 polyunsaturated fatty acid arachidonic acid gives rise to the eicosanoid family of mediators (prostaglandins, thromboxanes, leukotrienes and related metabolites). These have inflammatory actions in their own right and also regulate the production of other mediators including inflammatory cytokines. Consumption of long chain n-3 polyunsaturated fatty acids decreases the amount of arachidonic acid in cell membranes and so available for eicosanoid production. Thus, n-3 polyunsaturated fatty acids decrease production of arachidonic acid-derived eicosanoids. These fatty acids also decrease the production of the classic inflammatory cytokines tumour necrosis factor, interleukin-1, and interleukin-6 and the expression of adhesion molecules involved in inflammatory interactions between leukocytes and endothelial cells. These latter effects may occur by eicosanoid-independent mechanisms including modulation of the activation of transcription factors involved in inflammatory processes. The anti-inflammatory actions of long chain n-3 fatty acid-induced effects may be of therapeutic use in conditions with an acute or chronic inflammatory component."

-Institute of Human Nutrition, School of Medicine, University of Southampton, UK
https://pubmed.ncbi.nlm.nih.gov/16828270/

Modulation of pro-inflammatory cytokine biology by unsaturated fatty acids

"The production of pro-inflammatory cytokines, such as interleukins 1 and 6 and tumour necrosis factors, occurs rapidly following trauma or invasion of the body by pathogenic organisms. The cytokines mediate the wide range of symptoms associated with trauma and infection, such as fever, anorexia, tissue wasting, acute phase protein production and

immunomodulation. In part, the symptoms result from a co-ordinated response, in which the immune system is activated and nutrients released, from endogenous sources, to provide substrate for the immune system. Although the cytokine mediated response is an essential part of the response to trauma and infection, excessive production of pro-inflammatory cytokines, or production of cytokines in the wrong biological context, are associated with mortality and pathology in a wide range of diseases, such as malaria, sepsis, rheumatoid arthritis, inflammatory bowel disease, cancer and AIDS. Cytokine biology can be modulated by antiinflammatory drugs, recombinant cytokine receptor antagonists and nutrients. Among the nutrients, fats have a large potential for modulating cytokine biology. A number of trials have demonstrated the anti-inflammatory effects of fish oils, which are rich in n-3 polyunsaturated fatty acids, in rheumatoid arthritis, inflammatory bowel disease, psoriasis and asthma. Animal studies, conducted by ourselves and others, indicate that a range of fats can modulate pro-inflammatory cytokine production and actions. In summary fats rich in n-6 polyunsaturated fatty acids enhance IL1 production and tissue responsiveness to cytokines, fats rich in n-3 polyunsaturated fatty acids have the opposite effect, monounsaturated fatty acids decrease tissue responsiveness to cytokines and IL6 production is enhanced by total unsaturated fatty acid intake. There are a large number of potential cellular mechanisms which may mediate the effects observed. The majority relate to the ability of fats to alter the composition of membrane phospholipids. As a consequence of alterations in phospholipid composition, membrane fluidity may change, altering binding of cytokines to receptors and G protein activity. The nature of substrate for various signalling pathways associated with cytokine production and actions may also be changed. Consequently, alterations in eicosanoid production and activation of protein kinase C may occur. We have examined a number of these potential mechanisms in peritoneal macrophages of rats fed fats with a wide range of fatty acid composition. We have found that the total C18:2 and 20:4 diacyl species of phosphatidylethanolamine in peritoneal macrophages relates in a positive curvilinear fashion with dietary linoleic acid intake; that TNF induced IL1 and IL6 production relate in a positive curvilinear fashion to linoleic acid intake; that leukotriene B4 production relates positively with dietary linoleic acid intake over a range of moderate intakes and is suppressed at high intakes, while PGE2 production is enhanced. There was no clear relationship between linoleic acid intake and membrane fluidity, however fluidity was influenced in a complex manner by the type of fat in the diet, the period over which the fat was fed and the presence of absence of TNF stimulation. None of the proposed mechanisms, acting alone, can explain the positive effect of dietary linoleic acid intake on pro-inflammatory cytokine production. However each may be involved, in part, in the modulatory effects observed."

-Department of Human Nutrition, University of Southhampton, United Kingdom.
https://pubmed.ncbi.nlm.nih.gov/9558730

Polyunsaturated fatty acids and inflammatory processes: New twists in an old tale

“The n-6 fatty acid arachidonic acid (AA; 20:4n-6) gives rise to eicosanoid mediators that have established roles in inflammation and AA metabolism is a long recognised target for commonly used anti-inflammatory therapies. It has generally been assumed that all AA-derived eicosanoids are pro-inflammatory. However this is an over-simplification since some actions of eicosanoids are anti-inflammatory (e.g. prostaglandin (PG) E(2) inhibits production of some inflammatory cytokines) and it has been discovered quite recently that PGE(2) inhibits production of inflammatory leukotrienes and induces production of inflammation resolving lipoxin A(4). The n-3 fatty acids from oily fish and "fish oils", eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), are incorporated into inflammatory cell phospholipids in a time- and dose-dependent manner. They are incorporated partly at the expense of AA, but also of other n-6 fatty acids. EPA and DHA inhibit AA metabolism. Thus production of AA-derived eicosanoids is decreased by these n-3 fatty acids; this occurs in a dose-dependent manner. EPA gives rise to an alternative family of eicosanoids (e.g. PGE(3)), which frequently, but not always, have lower potency than those produced from AA. Recently a new family of EPA- and DHA-derived lipid mediators called resolvins (E- and D-series) has been described. These have potent anti-inflammatory and inflammation resolving properties in model systems. It seems likely that these mediators will explain many of the antiinflammatory actions of n-3 fatty acids that have been described. In addition to modifying the profile of lipid-derived mediators, fatty acids can also influence peptide mediator (i.e. cytokine) production. To a certain extent this action may be due to the altered profile of regulatory eicosanoids, but it seems likely that eicosanoid-independent actions are a more important mechanism. Indeed effects on transcription factors that regulate inflammatory gene expression (e.g. nuclear factor kappaB) seem to be important.”

-Institute of Human Nutrition, University of Southampton, Southampton General Hospital, UK.
https://pubmed.ncbi.nlm.nih.gov/19455748

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“Both ALA and LA are converted to their respective long chain metabolites by the same set of enzymes, however the metabolic products of each pathway are structurally and functionally distinct. EPA and AA are substrates for the synthesis of a group of inflammatory mediators including thromboxanes (TX), leukotrienes (LT), and prostaglandins (PG), collectively referred to as eicosanoids. Because the typical Western diet contains a much greater proportion of n-6

PUFA to n-3 PUFA, the membranes of most cells contain large quantities of AA, thus, it is typically the principle precursor for eicosanoid production [18]. AA metabolism yields 2-series PGs and 4-series LTs, highly active agents of inflammation, whereas EPA metabolism results in 3-series PGs and 5-series LTs, far less potent prostanoids by comparison [19].

Cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) are enzymes required for PG and LT synthesis, respectively. Competition between n-6 and n-3 PUFA for enzymatic metabolism occurs for both PG and LT synthesis. Competition by EPA results in decreased production of TXA2 and LTB4, and PGE2 metabolites, which ultimately reduces platelet aggregation, vasoconstriction, and leukocyte chemotaxis and adherence [20]. In addition, metabolism of EPA gives rise to less potent eicosanoids [19]. A concurrent rise in TXA3, prostacyclin PGI3, and LTB5 results, inhibiting platelet aggregation and vasoconstriction and promoting vasodilation [20]. It is not difficult to associate these metabolic products and their corresponding effects with beneficial outcomes related to CVD. A decrease in platelet aggregation reduces the development of atherosclerotic plaques by making blood less viscous and decreases the likelihood of thrombus formation. Increased vasodilation promotes blood flow with reduced resistance, thus decreasing the likelihood of endothelial damage and plaque initiation.

Recent studies have identified several new groups of mediators that exert anti-inflammatory actions, via derivation from COX-2; Lipoxins (LXs) from AA, E-series resolvins from EPA [21-23] and D-series resolvins, docosatrienes and neuroprotectins from DHA [24-26]. LXs and resolvins act as anti-inflammatory mediators by assisting in the resolution of inflammatory events and assisting with the clearance of cellular debris from the site of inflammation [27]. They also suppress IL-1, IL-2, IL-6 and TNF-alpha production by T cells [28-31], thus functioning as endogenous anti-inflammatory agents. Neuroprotectin D1 possesses anti-inflammatory and neuroprotective characteristics [32,33] and has been shown to promote wound healing [34] and brain cell survival [35,36]. While this area of research requires more detailed investigation, these novel classes of inflammatory mediators may be implicated in a variety of health-related conditions.

While the conversion of ALA to its long-chain derivatives is important, human and animal studies reveal that a major metabolic fate of ALA metabolism is β-oxidation. Over a 24 hour period, 20% of palmitic, stearic, and arachidonic acids orally administered to rats were expired as CO2, compared to 60% for labelled ALA [37]. In humans, the values are slightly less, with 16–20% of ALA being expired as CO2 over 12 hours [6,38]. This corresponds with a recent tracer study in men consuming a control meal that included 700 mg of labelled ALA, which demonstrated that ~34% of the labelled ALA was recovered as CO2 over 24 hours [39]. In a subsequent study using test diets with elevated levels of ALA (10 g/d) or EPA+DHA (1.5 g/d) consumed for 8 weeks, it was observed that the amount of expired label in the second tracer study was not affected by

increasing either ALA or EPA+DHA intakes [39]. In addition, a separate study in humans determined that ALA was the most highly oxidized fatty acid when compared to other 18 carbon fatty acids including linoleate, elaidate, oleate, and stearate [40]. Other metabolic routes of ALA include carbon recycling for de novo lipogenesis in the brain and other tissues [41].

Interestingly, whole-body ALA conversion to DHA in rats has been found to be higher than originally predicted [42,43]. In fact, in one study, the hepatic (representative of whole-body) DHA synthesis rate in rats intravenously infused with labelled ALA was approximately 30 times higher as compared to previously published rat brain DHA consumption rates [42]. Another study found hepatic DHA synthesis from ALA was only 5–10 fold higher than brain DHA consumption rates [43]. While there is discrepancy in ALA conversion rates in rats, these studies imply that dietary ALA could sufficiently supply the brain with DHA in the absence of exogenous DHA intake. It is important to note that the hepatic DHA synthesis rates observed for rats do not extend to humans [44]. The higher rates reflect a more efficient ALA elongation process in mice and rats, therefore results using these experimental models should be carefully considered when extrapolating effects in humans."

-Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3224740

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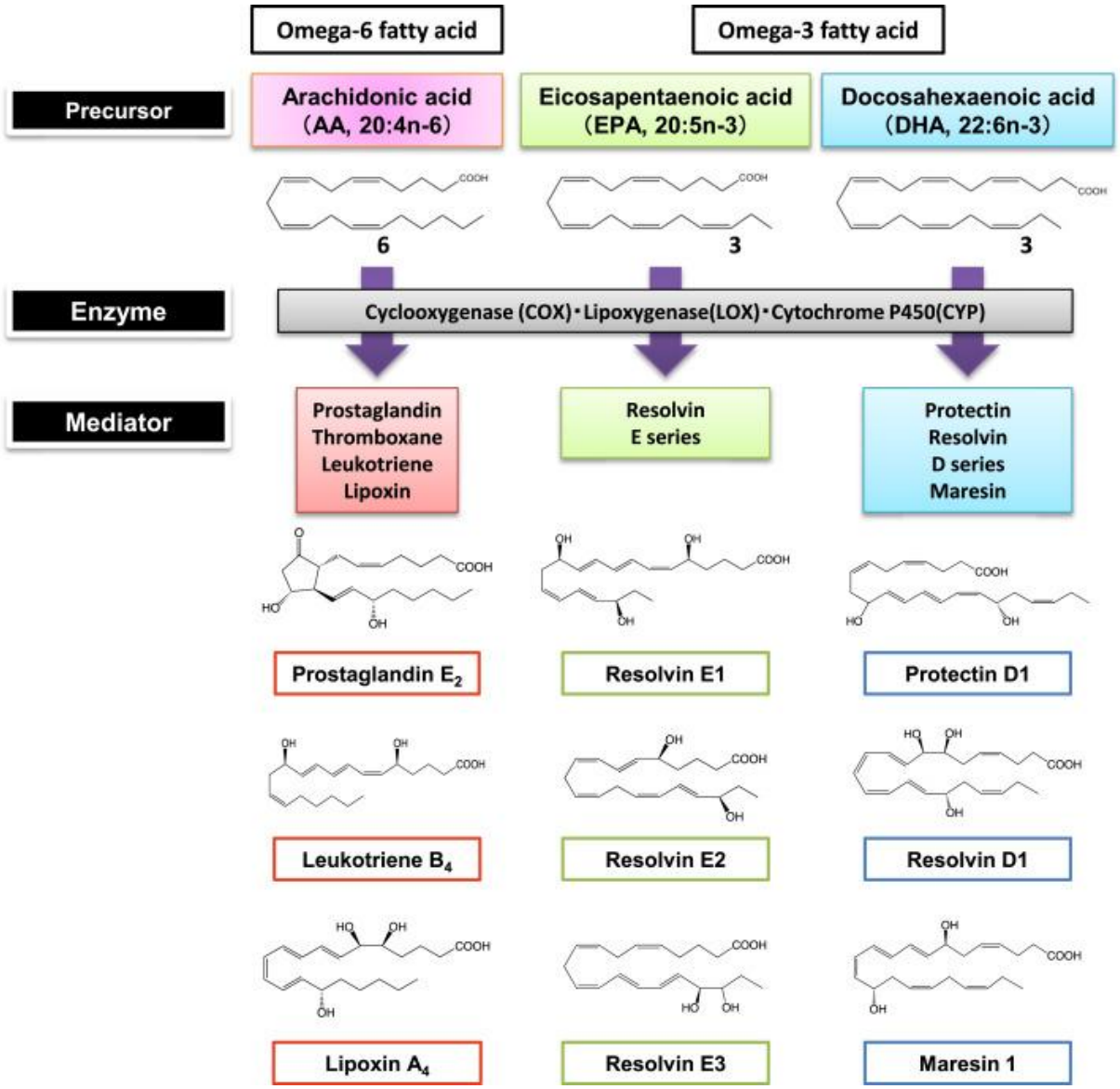
…"This invention relates to the provision of polyunsaturated fatty acids (PUFAs) in the diet of humans and animals. More specifically it relates to the provision of polyunsaturated fatty acids of the n-6 and the n-3 families, and in particular the n-6 fatty acid arachidonic acid (ARA) and the n-3 fatty acid docosahexaenoic acid (DHA), and ratios thereof in balanced amounts.

The invention is in part based on the finding that an optimal balance of the n-6 and n-3 families can play a significant role in health and the prevention of chronic diseases. The main reason for this is that the two families compete for the same enzyme(s) for the formation of the long-chain members from their C18 precursors. As a consequence, and this occurs in prior art compositions, a surplus of member(s) of one family tends to depress the amount of the other family. Moreover, the members of the two families can in some circumstances have adverse effects on essential functions in the body, such as blood clotting and the immune response."….

-DSM N.V., is a Dutch multinational corporation active in the fields of health, nutrition and materials.
-Inventor:Isabel Antonia Maria Van Waterschoot, Hugo Streekstra
https://patents.google.com/patent/WO2000021524A1/en

Pro-resolving lipid mediator (Protectins Resolvins Maresins)



…“Polyunsaturated fatty acid-derived lipid mediators. Arachidonic acid is a metabolic precursor to eicosanoids (i.e. prostaglandins and leukotrienes) that have distinct roles as pro-inflammatory mediators. In contrast, omega-3 fatty acids are converted to bioactive metabolites such as resolvins and protectins with anti-inflammatory and pro-resolving properties.”…

-Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan
-Graduate School of Medical Life Science, Yokohama City University, Kanagawa, Japan
https://www.sciencedirect.com/science/article/pii/S1323893014000100

Omega-3, Omega-6, Brain protection & Repair

Interplay Between n-3 [omega-3] and n-6 [omega-6] Long-Chain Polyunsaturated Fatty Acids and the Endocannabinoid System in Brain Protection and Repair

"The brain is enriched in arachidonic acid (ARA) and docosahexaenoic acid (DHA), long-chain polyunsaturated fatty acids (LCPUFAs) of the n-6 and n-3 series, respectively. Both are essential for optimal brain development and function. Dietary enrichment with DHA and other long-chain n-3 PUFA, such as eicosapentaenoic acid (EPA), has shown beneficial effects on learning and memory, neuroinflammatory processes, and synaptic plasticity and neurogenesis. ARA, DHA and EPA are precursors to a diverse repertoire of bioactive lipid mediators, including endocannabinoids. The endocannabinoid system comprises cannabinoid receptors, their endogenous ligands, the endocannabinoids, and their biosynthetic and degradation enzymes. Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the most widely studied endocannabinoids and are both derived from phospholipid-bound ARA. The endocannabinoid system also has well-established roles in neuroinflammation, synaptic plasticity and neurogenesis, suggesting an overlap in the neuroprotective effects observed with these different classes of lipids. Indeed, growing evidence suggests a complex interplay between n-3 and n-6 LCPUFA and the endocannabinoid system. For example, long-term DHA and EPA supplementation reduces AEA and 2-AG levels, with reciprocal increases in levels of the analogous endocannabinoid-like DHA and EPA-derived molecules. This review summarises current evidence of this interplay and discusses the therapeutic potential for brain protection and repair."

"N-6 and n-3 long-chain polyunsaturated fatty acids (LCPUFA) are essential components of membrane phospholipids and also precursors to a large and ever expanding repertoire of bioactive lipid mediators. The brain is highly enriched in the n-6 PUFA, arachidonic acid (ARA), and the n-3 PUFA, docosahexaenoic acid (DHA), with both essential for optimum brain development and function [1]. Elevated dietary intake of DHA and eicosapentaenoic acid (EPA), another n-3 LCPUFA, has beneficial effects on learning and memory, decreases neuroinflammatory processes and enhances synaptic plasticity and neurogenesis [2]."

Simon C. Dyall PhD - Faculty of Health and Social Sciences, Bournemouth University, Dorset, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5656721/

Neurological benefits of omega-3 fatty acids.

"The central nervous system is highly enriched in long-chain polyunsaturated fatty acid (PUFA) of the omega-6 and omega-3 series. The presence of these fatty acids as structural components of neuronal membranes influences cellular function both directly, through effects on membrane properties, and also by acting as a precursor pool for lipid-derived messengers. An adequate intake of omega-3 PUFA is essential for optimal visual function and neural development. Furthermore, there is increasing evidence that increased intake of the long-chain omega-3 PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may confer benefits in a variety of psychiatric and neurological disorders, and in particular neurodegenerative conditions. However, the mechanisms underlying these beneficial effects are still poorly understood. Recent evidence also indicates that in addition to the positive effects seen in chronic neurodegenerative conditions, omega-3 PUFA may also have significant neuroprotective potential in acute neurological injury. Thus, these compounds offer an intriguing prospect as potentially new therapeutic approaches in both chronic and acute conditions. The purpose of this article is to review the current evidence of the neurological benefits of omega-3 PUFA, looking specifically at neurodegenerative conditions and acute neurological injury."

-British College of Osteopathic Medicine, Lief House, 120-122 Finchley Road, NW5 5HR, London, UK.
https://www.ncbi.nlm.nih.gov/pubmed/18543124

Repetitive and Prolonged Omega-3 Fatty Acid Treatment after Traumatic Brain Injury Enhances Long-Term Tissue Restoration and Cognitive Recovery

"Traumatic brain injury (TBI) is one of the most disabling clinical conditions that could lead to neurocognitive disorders in survivors. Our group and others previously reported that prophylactic enrichment of dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs) markedly ameliorate cognitive deficits after TBI. However, it remains unclear whether a clinically relevant therapeutic regimen with n-3 PUFAs administered after TBI would still offer significant improvement of long-term cognitive recovery. In the present study, we employed the decline of spatial cognitive function as a main outcome after TBI to investigate the therapeutic efficacy of post-TBI n-3 PUFA treatment and the underlying mechanisms. Mice were subjected to sham operation or controlled cortical impact, followed by random assignment to receive the following four treatments: (1) vehicle control; (2) daily intraperitoneal injections of n-3 PUFAs for 2 weeks, beginning 2 h after TBI; (3) fish oil dietary supplementation throughout the study, beginning 1 day after TBI; or (4) combination of treatments (2) and (3). Spatial cognitive deficits and chronic brain tissue loss, as well as endogenous brain repair processes such as neurogenesis, angiogenesis, and oligodendrogenesis, were evaluated up to 35 days after TBI. The results revealed prominent

spatial cognitive deficits and massive tissue loss caused by TBI. Among all mice receiving post-TBI n-3 PUFA treatments, the combined treatment of fish oil dietary supplement and n-3 PUFA injections demonstrated a reproducible beneficial effect in attenuating cognitive deficits although without reducing gross tissue loss. Mechanistically, the combined treatment promoted post-TBI restorative processes in the brain, including generation of immature neurons, microvessels, and oligodendrocytes, each of which was significantly correlated with the improved cognitive recovery. These results indicated that repetitive and prolonged n-3 PUFA treatments after TBI are capable of enhancing brain remodeling and could be developed as a potential therapy to treat TBI victims in the clinic."…

"Numerous preclinical studies by our and other groups have suggested omega-3 polyunsaturated fatty acid (n-3 PUFA) as an emerging candidate for TBI therapy[12,15]. **The most important n-3 PUFAs for human health, that is, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), must be acquired through dietary intake, with the primary sources being fish and fish oil**[16,17]. **n-3 PUFAs exist abundantly in the brain and play a crucial role in essential neuronal functions, such as axonal guidance, synapse and dendrite formation, neurotransmission, etc.**[16,18]. Following experimental TBI, n-3 PUFAs exert potent protective effects through multifaceted actions, for example, amelioration of oxidative stress[19], mitigation of endoplasmic reticulum stress[20], modulation of microglial activation[21], and improvement of white matter integrity[15]. The use of n-3 PUFAs to treat TBI has not hitherto been translated to the clinic, although there are sporadic case studies using n-3 PUFAs acutely after human TBI[22,23]. A large portion of the preclinical studies on n-3 PUFAs employed a pre-TBI treatment paradigm, achieved through prophylactic dietary supplement or genetic engineering[12,15,19], which provided limited information when considering translating this treatment from bench to bedside. While some studies delivered invaluable mechanistic insights of post-TBI n-3 PUFA treatment[14,20], concerns still remain over the short delivery time window or the lack of long-term functional evaluation. To facilitate future investigations on n-3 PUFAs toward patient use, we aim to develop a clinically feasible treatment regimen using manageable delivery routes and time window, hoping to validate the use of n-3 PUFAs post-TBI and potentially benefit the TBI victims."…

-Department of Neurosurgery, General Hospital of PLA, China

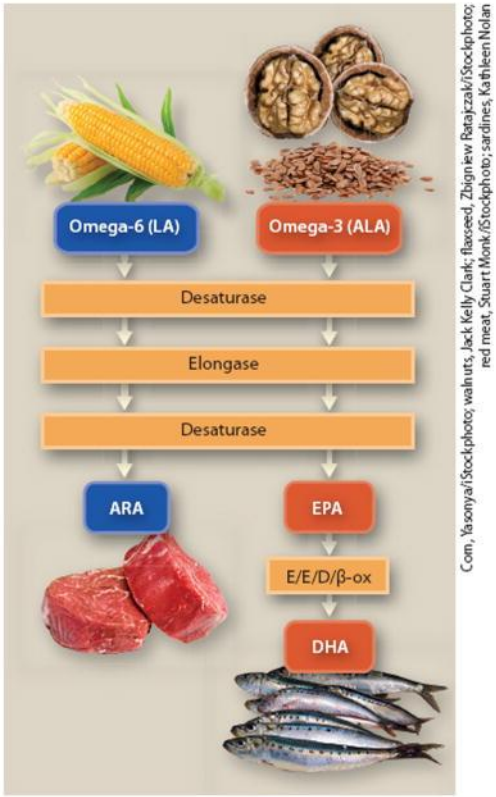
-Pittsburgh Institute of Brain Disorders and Recovery and Department of Neurology, University of Pittsburgh, Pittsburgh, USA

-State Key Laboratory of Medical Neurobiology and Institute of Brain Sciences, Fudan University, Shanghai, P.R. China

-Pittsburgh Institute of Brain Disorders and Recovery, University of Pittsburgh, S507 Biomedical Science Tower, Pittsburgh, PA, USA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5531869

Omega-3 & Omega-6 Conversion



…"Dietary sources and enzymatic conversion pathways of omega-3 and omega-6 fatty acid precursors. The omega-3 precursor alpha-linolenic acid (ALA) is found in walnuts and flax seeds, and the omega-6 precursor linoleic acid (LA) is found in corn and vegetable oils. Both are converted by desaturase and elongase enzymes into their long-chain derivatives: ALA is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); and LA is converted to arachidonic acid (ARA [or AA]). ARA is found in animal products, such as beef, and EPA and DHA are found in fatty fish, such as sardines."

"However, since omega-3 and omega-6 fatty acids compete for the same enzymes, the relative dietary proportions of precursor fatty acids determine the net rate of conversion to their respective long-chain derivatives (Goyens et al. 2006; Liou et al. 2007). Linoleic acid is readily converted to its long-chain metabolite arachidonic acid, and this conversion is driven by the amount of linoleic acid ingested. However, most humans convert a smaller proportion of ingested alpha-linolenic

acid into EPA and even less into DHA (Pawlosky et al. 2003). Most studies agree on estimates of about 5% conversion to EPA and less than 1% conversion to DHA (Burdge and Calder 2006). Due to this low rate of conversion of alpha-linolenic acid to EPA and DHA, and a generally low consumption of preformed dietary long-chain omega-3 fatty acids, many Americans are likely deficient in EPA or DHA.

Omega-6 fatty acids are abundant in the Western diet and are found in high proportions in most cooking oils, grains and grain-fed animal products. On the other hand, omega-3 fatty acids are generally deficient in the foods typically consumed by Americans. Certain foods — including leafy greens, walnuts, canola oil, flax-fed chicken eggs and fatty fish (e.g., wild salmon, anchovies, mackerel and tuna) — have relatively large concentrations of omega-3. Historically, humans consumed diets with much higher relative proportions of omega-3, with ratios of omega-6 to omega-3 of 1-to-1 or 2-to-1, in contrast to modern diets with ratios as high as 15-to-1 to 25-to-1 (Simopoulos 2008). The disproportionate consumption of omega-6 as compared to omega-3 fatty acids is the result of common U.S. dietary patterns. Foods such as salmon, walnuts, kale and eggs from chickens fed flax have higher omega-3 fatty acid content than do more common American foods, like corn oil, beef and potatoes (USDA 2011). For example, raw pink salmon has 419 milligrams of EPA and 586 milligrams of DHA per 100 grams, whereas raw ground beef contains none. Walnuts contain 3,800 milligrams of linoleic acid and 9,080 milligrams of alpha-linolenic acid per 100 grams. On the other hand, peanuts contain 15,600 milligrams of linoleic and only 3 milligrams of alpha-linolenic acid per 100 grams. These ratios mean that the typical American diet is deficient in omega-3 fatty acids, especially when considered in relation to omega-6 fatty acids (Kris-Etherton et al. 2000).

Because of the increasing levels of contaminants, like mercury and dioxins, in both domestic and imported fish (Stahl et al. 2009; Sunderland 2007), the consumption of fish as a main source of long-chain omega-3 fatty acids is problematic, and some types of fish are not recommended for consumption by pregnant women and small children (Jedrychowski et al. 2007). Since terrestrial plants contain only the short-chain omega-3 precursor alpha-linolenic acid, and since alpha-linolenic acid is poorly converted into its long-chain metabolites EPA and DHA, it is likely that the American diet will continue to be relatively deficient in these important molecules unless significant dietary changes are made."…

-Dr. Angela M. Zivkovic Ph.D, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645

Omega-3 Deficiency

…"Inadequate dietary intake of n-3s [omega-3s] could be a health-risk factor for military personnel. Indeed, n-3 status is lower in military personnel compared to the general U.S. population (Lewis et al. 2011). "…

-Military Nutrition Division, U.S. Army Research Institute of Environmental Medicine, Kansas Street, Building 42, Natick, Massachusetts

-Performance Optimization Research Team, Combat Feeding Directorate, Natick Soldier, Research and Engineering Center, Kansas Street, Building 36, Natick, Massachusetts

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431787/

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"Omega-3 is an essential polyunsaturated fatty acid (PUFA) that most animals need to acquire in their diet. Mammalian brains are rich in docosahexaenoic acid (DHA), a long-chain form of omega-3, whose deficiency, coupled with a high omega-6:3 ratio, leads to numerous cognitive disorders and mental diseases."…

-B. Triwaks Bee Research Center, Department of Entomology, Robert H. Smith Faculty of Agriculture, Food & Environment, The Hebrew University of Jerusalem, Rehovot 76100, Israel;

-Gilat Research Center, Institute of Plant Sciences, Agricultural Research Organization, Mobile Post Negev 85280, Israel

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4697434/

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…"Elevated dietary intake of DHA and eicosapentaenoic acid (EPA), another n-3 LCPUFA, has beneficial effects on learning and memory, decreases neuroinflammatory processes and enhances synaptic plasticity and neurogenesis [2]. Similarly, inverse relationships are typically observed between fish intake or blood DHA levels and age-related cognitive decline [3]. However, recent estimates indicate that worldwide many populations are currently consuming DHA and EPA at levels well below the recommendations issued by many international authorities [4–6]"…

Simon C. Dyall PhD - Faculty of Health and Social Sciences, Bournemouth University, Dorset, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5656721/

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…"Several studies have warned against health and disease outcomes that could result from radical increases of dietary LA in the MWD in such a short period of time [26,78,79]. Given the shared enzymatic steps involved in the processing of LA and ALA, these n-6 and n-3 18C-PUFAs

and their metabolic intermediates compete with each other in the liver and other tissues as substrates for synthetic enzymatic reactions that produce LC-PUFAs [80,81]. Additionally, there is an overall limited capacity of 18C-PUFAs that can be converted to LC-PUFAs [53]. As discussed in detail below, this biosynthetic limit in capacity is highly impacted at an individual level by genetic variation in the LC-PUFA biosynthetic pathway. Consequently, a dramatic increase in LA in the MWD observed over the past 75 years together with competition between n-6 and n-3 substrates within the pathway has been shown in animal models and humans to shift the pathway toward the biosynthesis of high levels n-6 LC-PUFAs and away from n-3 LC-PUFAs [53,82,83,84,85,86,87]. In 1992, Lands and colleagues described non-linear interactions between LA and ALA in forming LC-PUFAs utilizing a hyperbolic equation that fit for rats, mice and humans [53]. The equation points out the limitation of generating n-3 LC-PUFAs when n-3 ALA is ingested together with several-fold greater amounts of n-6 LA as is the case with the MWD. Wood and colleagues reviewed human studies that examined the effect of altering LA and ALA on n-6 and n-3 LC-PUFA biosynthesis and concluded that it is possible to increase n-3 LC-PUFAs by reducing LA or increasing ALA intake in humans [82]. However, LA levels need to be reduced to <2.5% energy before levels of DHA can be increased. Again, typical LA levels in the MWD reside between 6–8% energy; consequently, high levels of LA in the MWD would be predicted to markedly reduce, not increase DHA. In fact, it has been estimated that LA concentrations in the MWD have decreased the omega-3 index by 41%, from 6.51 to 3.84 [1].

A 1997 paper by Okuyama and colleagues made a compelling case that excess LA and the increase in the LA/ALA ratio as a result of moving away from traditional diets led to ‘Omega-3 Deficiency Syndrome’ in the elderly in Japan [84]. The paper summarized the “evidence which indicates that increased dietary LA and relative n-3 deficiency are major risk factors for western-type cancers, cardiovascular and cerebrovascular diseases and also for allergic hyper-reactivity.” They also suggest that n-3 LC-PUFAs deficiency created by excess LA and LA/ALA ratios in the MWD affects human behavior patterns in industrialized countries. Certainly these assertions are supported by a large body of scientific literature in both animal models and human studies discussed throughout this review.”…

-Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, USA
-Department of Urology, Wake Forest School of Medicine, Winston-Salem, USA;
-Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, USA;
-Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, NC, USA;
-GeneSTAR Research Program, General Internal Medicine, Johns Hopkins University School of Medicine, USA;
-Department of Internal Medicine, Section on Molecular Medicine, Wake Forest School of Medicine, Winston-Salem, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707637/

N-3 [omega-3] fatty acid deficiency in the rat pineal gland: effects on phospholipid molecular species composition and endogenous levels of melatonin and lipoxygenase products.

"N-3 [omega-3] essential fatty acid deficiency affects a number of biological and physiological processes. In this study, we investigated the effect of n-3 essential fatty acid status on two key pineal biochemical functions, melatonin production and lipoxygenation, using pineal glands from rats given an n-3-adequate or n-3-deficient diet. The pineal total lipid profile and phospholipid molecular species distribution altered by n-3 deficiency were evaluated in parallel."

…."Concomitantly, the endogenous 12-HETE level decreased by 35% in deficient pineals. In contrast, n-3 deficiency led to a more than 60% increase in the daytime pineal melatonin level. In conclusion, n-3 fatty acid deficiency not only has profound effects on pineal lipid profiles but also on pineal biochemical activities. These results suggest that n-3 fatty acids may play a critical role in regulating pineal function."

-Section of Mass Spectrometry, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, MD, USA.

https://www.ncbi.nlm.nih.gov/pubmed/9684742

Omega-3 fatty acid biochemistry: perspectives from human nutrition.

"The possibility that western diets poor in omega-3 and rich in omega-6 fatty acids contribute to the increasing burden of chronic diseases including neurological problems is becoming recognized. Modern, westernized diets provide 80 to 90% of polyunsaturated fatty acids as omega-6 linoleic acid (LA) and are depleted in omega-3 fatty acids, giving a distorted balance of LA to α-linoleic acid, and to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). LA intakes exceed Δ-6 desaturase needs for maximal activity. LA accumulates in blood and tissue lipids with increasing intake, and this exacerbates competition between LA and limited omega-3 fatty acids for metabolism and acylation into tissue lipids. Increasing EPA and DHA intake decreases tissue omega-6 fatty acids while also providing EPA and DHA. However, strategies for EPA and DHA supplementation do not address potential underlying problems of omega-6 and omega-3 fatty acid imbalance in the food supply."

-Nutrition Research Program, Child and Family Research Institute, Department of Paediatrics, University of British Columbia, Vancouver, British Columbia, Canada.

https://www.ncbi.nlm.nih.gov/pubmed/25373090

Novel CB1-ligands maintain homeostasis of the endocannabinoid system in 3- and 6-long-chain-PUFA deficiency

“Mammalian ω3- and ω6-PUFAs are synthesized from essential fatty acids (EFAs) or supplied by the diet. PUFAs are constitutive elements of membrane architecture and precursors of lipid signaling molecules. EFAs and long-chain (LC)-PUFAs are precursors in the synthesis of endocannabinoid ligands of Gi/o protein-coupled cannabinoid receptor (CB)1 and CB2 in the endocannabinoid system, which critically regulate energy homeostasis as the metabolic signaling system in hypothalamic neuronal circuits and behavioral parameters. “….

“Conservation of the multifaceted structures of ω3- and ω6-PUFAs during evolution, their high reactivity for multi-purpose biological activities, high energy-demanding biosynthesis, and tissue- and subcellular membrane-specific distribution put PUFAs down to essential entities for mammalian homeostasis. Numerous nutritional studies suggest essential physiological and pathogenetic implications of dietary ω3- and ω6-PUFA supply and their ratio in current Western diet in the development of metabolic, cardiovascular, and neurodegenerative disorders awaiting molecular understanding [(1–4)]. Molecular insight into the majority of their pleiotropic structures and functions has remained elusive [(5, 6)].

PUFAs are essential constituents of membrane phospholipid bilayers and lipoproteins, and precursors of several lipid signaling molecules, including two endocannabinoid families, N-acyl-ethanolamides (NAEs) and 2-monoacyl-glycerols (2-MAGs). N-arachidonoyl-ethanolamide (AEA) and 2-arachidonoyl-glycerol (2-AG) are the most dominant ligands of cannabinoid receptor (CB)1 and CB2. The endocannabinoid system (ECS) [(7–10)] consists of endocannabinoids, receptors CB1 and CB2, and associated anabolic and catabolic enzymes [(11–13)], and modulates the orexinergic inputs into the neuronal network in selective regions of the CNS, sensing nutrient availability for maintaining body energy homeostasis [(14)]. Unlike the intensively studied structure-function relationship of CB1 and CB2 in the ECS of the CNS [for review see (15)], the role of the dietary supply of PUFAs and their transformation to lipophilic CB1 ligands has remained elusive.

Biosynthesis from essential fatty acids (EFAs) and dietary supply maintain homeostasis of the cellular pool of long-chain (LC)-PUFAs in mammals. “….

-Center of Molecular Medicine (CMMC), Laboratory of Molecular Neurosciences, Institute of Biochemistry, University of Cologne, Cologne, Germany.

-Cluster of Excellence, Cellular Stress Response in Aging Related Diseases (CECAD) University of Cologne, Cologne, Germany.

-Institute of Biochemistry Deutsche Sporthochschule (DSHS) Cologne, Cologne, Germany.

-Institute of Vegetative Physiology, Center of Physiology and Pathophysiology, University of Cologne, Cologne, Germany.

-Center of Molecular Medicine (CMMC), Laboratory of Molecular Neurosciences, Institute of Biochemistry, University of Cologne, 50931 Cologne, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6672042/

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…"Children with low fish and seafood intakes and a high use of vegetable oils that are rich in n-6 fatty acids (FAs) are at risk of inadequate n-3 FA intakes [2]. Both iron and n-3 FAs are essential nutrients to ensure optimal growth and brain development [3]. Iron is required for neuronal growth and differentiation [4] and is a cofactor for enzymes involved in cell division as well as in the synthesis of neurotransmitters, myelin, and brain eicosanoids [5–8]. In contrast, the long-chain PUFAs DHA (22:6n-3) and EPA (20:5n-3) play important roles in neuronal growth and differentiation as well as in myelination, monoaminergic neurotransmission, and eicosanoid synthesis [9–12]. The deficiencies in iron and n-3 FAs may interact directly via iron-dependent hepatic desaturases involved in the conversion of essential fatty acids into long-chain PUFAs [13]."…

-Laboratory of Human Nutrition, Institute of Food, Nutrition and Health, Swiss Federal Institute of Technology Zürich, Switzerland.

https://academic.oup.com/ajcn/article/96/6/1327/4571461

Omega-3 Long-Chain Polyunsaturated Fatty Acids Intake by Ethnicity, Income, and Education Level in the United States: NHANES 2003–2014

"Although there are many recognized health benefits for the consumption of omega-3 (n-3) long-chain polyunsaturated fatty acids (LCPUFA), intake in the United States remains below recommended amounts. This analysis was designed to provide an updated assessment of fish and n-3 LCPUFA intake (eicosapentaenoic (EPA), docosahexaenoic acid (DHA), and EPA+DHA) in the United States adult population, based on education, income, and race/ethnicity, using data from the 2003–2014 National Health and Nutrition Examination Survey (NHANES) (n = 44,585). Over this survey period, participants with less education and lower income had significantly lower n-3 LCPUFA intakes and fish intakes ($p < 0.001$ for all between group comparisons). N-3 LCPUFA intake differed significantly according to ethnicity ($p < 0.001$), with the highest intake of n-3 LCPUFA and fish in individuals in the "Other" category (including Asian Americans). Supplement use increased EPA + DHA intake, but only 7.4% of individuals consistently took supplements. Overall, n-3 LCPUFA intake in this study population was low, but our findings indicate that individuals with lower educational attainment and income are at even higher risk of lower n-3 LCPUFA and fish intake."…

-Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE 68198, USA; (M.T.)
-College of Public Health, University of Nebraska Medical Center, Omaha, NE 68198, USA;

-Department of Nutritional Sciences, University of Arizona, Tucson, AZ 85721, USA;
-Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA 16802, USA;
-Division of Biomedical Sciences, School of Medicine, University of California Riverside, Riverside, CA 92521, USA
-College of Allied Health Professions, University of Nebraska Medical Center, Omaha, NE 68198, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7400855/

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….“Current dietary intakes of EPA/DHA in North America and elsewhere are well below those recommended by the American Heart Association for the management of patients with coronary heart disease.”

-Department of Psychiatry and Behavioural Neurosciences, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada.
https://pubmed.ncbi.nlm.nih.gov/15524182

Dietary Repletion with ω3 Fatty Acid or with COX Inhibition Reverses Cognitive Effects in F3 ω3 Fatty-Acid–Deficient Mice

“Dietary deficiency of ω3 fatty acid during development leads to impaired cognitive function. However, the effects of multiple generations of ω3 fatty-acid deficiency on cognitive impairment remain unclear. In addition, we sought to test the hypothesis that the cognitive impairments of ω3 fatty-acid–deficient mice are mediated through the arachidonic acid–cyclooxygenase (COX) pathway. To address these issues, C57BL/6J mice were bred for 3 generations and fed diets either deficient (DEF) or sufficient (SUF) in ω3 fatty acids. At postnatal day 21, the F3 offspring remained on the dam's diet or were switched to the opposite diet, creating 4 groups. In addition, 2 groups that remained on the dam's diet were treated with a COX inhibitor. At 19 wk of age, spatial-recognition memory was tested on a Y-maze. Results showed that 16 wk of SUF diet reversed the cognitive impairment of F3 DEF mice. However, 16 wk of ω3 fatty-acid–deficient diet impaired the cognitive performance of the F3 SUF mice, which did not differ from that of the F3 DEF mice. These findings suggest that the cognitive deficits after multigenerational maintenance on ω3 fatty-acid–deficient diet are not any greater than are those after deficiency during a single generation. In addition, treatment with a COX inhibitor prevented spatial-recognition deficits in F3 DEF mice. Therefore, cognitive impairment due to dietary ω3 fatty-acid deficiency appears to be mediated by the arachidonic acid–COX pathway and can be prevented by 16 wk of dietary repletion with ω3 fatty acids or COX inhibition.”….

“Previous studies have been shown that the cognitive and memory deficits of a transgenic mouse model are due to increased prostaglandin activity from formation of cyclooxygenase

(COX).[13] Dietary ω3 fatty acid deficiency has been suggested to increase prostaglandin activity in animals.[16] Therefore, the administration of a COX inhibitor may protect against cognitive impairment in the elevated plus-maze task by inhibiting the synthesis of prostaglandin.[11] Treatment with a COX inhibitor improved open-field exploration in mice by inhibiting the synthesis of prostaglandin.[23] Similarly, COX inhibitors such as celecoxib inhibit prostaglandin E2 levels and consequently improve cognitive performance in rats as assessed by the elevated plus-maze test.[5] In addition, the administration of naproxen, another COX inhibitor, was protective against motor and cognitive impairment in rats by decreasing oxidative stress.[14] Moreover, naproxen reduced oxidative stress levels and prevented neurologic disorders, especially memory deficits, in an animal model of excitotoxic neuronal injury.[20] Clearly, these findings suggest that COX inhibitors may protect against cognitive and memory deficits in animals by inhibiting prostaglandin activity."

-School of Psychological Science

-School of Life Sciences, La Trobe University, Victoria, Australia

-School of Exercise and Nutrition Sciences, Deakin University, Victoria, Australia

-Department of Veterinary Preclinical Sciences, Faculty of Veterinary Medicine, University Putra Malaysia, Serdang, Selangor Malaysia

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3997287/

See also Aging

Omega-3s & Cancer

n-3 [omega-3] Polyunsaturated Fatty Acids and their Role in Cancer Chemoprevention

"Polyunsaturated fatty acids (PUFAs), including omega-3 (n-3) and omega-6 (n-6) PUFAs, are essential for human health. Recent research shows n-3 PUFAs and their mediators can inhibit inflammation, angiogenesis and cancer via multiple mechanisms, including reduced release of n-6 fatty acid arachidonic acid from cell membranes, inhibition of enzymatic activities, and direct competition with arachidonic acid for enzymatic conversions. In this review, we discuss inflammation-related cancer, anti-inflammatory effects of n-3 PUFA lipid mediators, antineoplastic activities of n-3 PUFA in vitro and in vivo, and present an update on recent human trials."

"The beneficial effects of omega-3 polyunsaturated fatty acids (n-3 PUFAs) on human health have been known for a long time. The idea that dietary PUFAs may be beneficial in preventing disease has first been suggested in the 1970's [1–3]. Studies continue to demonstrate the health

benefits of n-3 PUFAs, and in particular, preclinical and clinical studies accumulated more data on the effects of n-3 PUFAs on cancer prevention and suppression [4–10].”…

-State Key Laboratory of Food Science and Technology, School of Food Science and Technology, Jiangnan University, Wuxi 214122, P.R. China

-The Synergistic Innovation Center for Food Safety and Nutrition, Wuxi 214122, P.R. China

-Department of Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, NC USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4596534/

Omega-3 polyunsaturated fatty acids as adjuvant therapy of colorectal cancer

..“Evidence is also accumulating that O3FAs [omega-3 fatty acids] may have anti-colorectal cancer (CRC) properties.”…

“Multiple mechanisms of actions and molecular targets have been described to explain the anti-inflammatory and anti-cancer activity of O3FAs. These have been reviewed extensively elsewhere [7, 10, 11]. “…

Leeds Institute of Biomedical and Clinical Sciences, St James’s University Hospital, University of Leeds, Leeds, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6133177/

Protective Effects of Omega-3 Fatty Acids in Cancer-Related Complications

“Omega-3 polyunsaturated fatty acids (PUFAs) are considered immunonutrients and are commonly used in the nutritional therapy of cancer patients due to their ample biological effects. Omega-3 PUFAs play essential roles in cell signaling and in the cell structure and fluidity of membranes. They participate in the resolution of inflammation and have anti-inflammatory and antinociceptive effects. Additionally, they can act as agonists of G protein-coupled receptors, namely, GPR40/FFA1 and GPR120/FFA4. Cancer patients undergo complications, such as anorexia-cachexia syndrome, pain, depression, and paraneoplastic syndromes. Interestingly, the 2017 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for cancer patients only discuss the use of omega-3 PUFAs for cancer-cachexia treatment, leaving aside other cancer-related complications that could potentially be managed by omega-3 PUFA supplementation. This critical review aimed to discuss the effects and the possible underlying mechanisms of omega-3 PUFA supplementation in cancer-related complications. Data compilation in this critical review indicates that further investigation is still required to assess the factual benefits of omega-3 PUFA supplementation in cancer-associated illnesses. Nevertheless, preclinical evidence reveals that omega-3 PUFAs and their metabolites might modulate pivotal

pathways underlying complications secondary to cancer, indicating that this is a promising field of knowledge to be explored."…

"Omega-3 PUFAs are essential fatty acids, containing between 18 and 22 carbons, with the first double bond on the third carbon, counting from the omega end. Omega-3 PUFAs comprise three different active molecules: (i) α-linolenic acid (ALA; 18:3n-3), (ii) eicosapentaenoic acid (EPA; 20:5n-3), and (iii) docosahexaenoic acid (DHA; 22:6n-3). ALA is synthesized in plants and can be found in seeds, nuts, and plant oils. EPA and DHA are not synthesized by the organism and can only be found in the flesh of cold-water fish [30]. Interestingly, ALA can be converted to EPA and DHA by several reactions of elongation and desaturation, but these conversions produce small amounts of EPA and DHA in the organism [31].

The omega-6 arachidonic acid (AA; 20:4n-6) and linoleic acid (LA; 18:2n-6) are also essential fatty acids. Notably, both became major components of the cell membrane due to the increase of Western diets, rich in cereals and vegetable oils, containing excessive omega-6 PUFAs and leading to an undesired omega-6/omega-3 ratio of 20:1 [32]. The metabolic pathways of AA and LA share the same enzymes that convert ALA to EPA and DHA, indicating that there is competition between the pathways. In inflammatory processes, membrane phospholipids are cleaved by phospholipase A2 (PLA2) to release AA to the cytoplasm and initiate the production of highly inflammatory eicosanoids (such as prostaglandin E2 and leukotriene B4) by the action of cyclooxygenases and lipoxygenases. The membrane lipid composition modification from an omega-6 PUFA to omega-3 PUFA profile is very important because it increases the production of omega-3-derived mediators, such as thromboxane A3 and prostacyclin I3, which are weaker inducers of inflammation [33]. Supporting this mechanism, a systematic review and meta-analysis demonstrated that omega-3 PUFAs were able to reduce thromboxane B2 blood levels in subjects with a high risk of cardiovascular diseases, along with a decrease of leukotriene B4 in the neutrophils of unhealthy patients [34]. Regarding lymphocyte membranes, an in vitro and pilot clinical study evaluated the fatty acid composition of CD4+T cell membranes after EPA and DHA supplementation. The in vitro analysis showed that EPA or DHA incubation increased the membrane contents of omega-3 PUFAs. Additionally, the pilot clinical study from the same article evaluated the membrane composition of lymphocytes in elderly individuals after six weeks of omega-3 PUFA supplementation and observed a similar omega-3 PUFA-rich membrane [35]. Additionally, a review article demonstrated that EPA and DHA supplementation are often employed in the nutritional therapy of cancer patients and promotes beneficial effects during cancer treatment due to a membrane modulation [36]. On the other hand, an analysis of the fatty acid composition of the red blood cells of cancer patients showed that there was no difference between the omega-3 PUFAs contents in the membrane of cancer patients and

healthy subjects, irrespective of their diet. Interestingly, the same cancer patients showed higher omega-6 PUFA contents and an increased desaturation activity, demonstrating a higher inflammatory profile [37].

The notion that an omega-3 PUFA-enriched membrane could be favorable for disease management was corroborated by the discovery of pro-resolution mediators of inflammation, derived from omega-3 PUFAs. Over the past decade, the identification of resolvins, protectins/neuroprotectins, and maresins was a milestone—currently, it is well-recognized that solving, rather than inhibiting, inflammation is quite an interesting approach for the treatment of a series of chronic illnesses such as cancer."....

-Toxicology and Pharmacology Research Center, School of Health Sciences, PUCRS, Brazil;
-Postgraduate Program in Medicine and Health Sciences, School of Medicine, PUCRS, Brazil
- Postgraduate Program in Dentistry, School of Health Sciences, PUCRS, Porto Alegre, Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6566772/

Omega-3 Fatty Acids and Cancer Cell Cytotoxicity: Implications for Multi-Targeted Cancer Therapy

-Department of Molecular Medicine, Istituto Pasteur-Fondazione Cenci Bolognetti, Sapienza University of Rome, 00161 Rome, Italy;
-Department of Ecological and Biological Sciences (DEB), La Tuscia University, Largo dell'Università, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4773771/

See also Omega Ratio

Omega-3s & Endocannabinoids

Omega-3 fatty acids fight inflammation via cannabinoids

..."Some cannabinoids, such as THC in marijuana or endocannabinoids can bind to these receptors and elicit anti-inflammatory and anti-pain action," she said.

Our team discovered an enzymatic pathway that converts omega-3-derived endocannabinoids into more potent anti-inflammatory molecules that predominantly bind to the receptors found in the immune system," Das said. "This finding demonstrates how omega-3 fatty acids can produce some of the same medicinal qualities as marijuana, but without a psychotropic effect."

-Science Daily

-University of Illinois at Urbana-Champaign
https://www.sciencedaily.com/releases/2017/07/170718142909.htm

Emerging Class of Omega-3 Fatty Acid Endocannabinoids & Their Derivatives

"Cannabinoid receptor activation is involved in homeostatic regulation of the body. These receptors are activated by cannabinoids, that include the active constituents of Cannabis sativa as well as endocannabinoids (eCBs). The eCBs are endogenously synthesized from the omega-6 and omega-3 polyunsaturated fatty acids (PUFAs). The consumption of omega-3 fatty acids shifts the balance towards a higher proportion of omega-3 eCBs, whose physiological functions warrants further investigation. Herein, we review the discovery of omega-3 fatty acid derived eCBs that are generated from long chain omega-3 PUFAs - docosahexaenoyl ethanolamide (DHA-EA or synaptamide), docosahexanoyl-glycerol (DHG), eicosapentaenoyl ethanolamide (EPA-EA), eicosapentanoylglycerol (EPG). Furthermore, we outline the lesser known omega-3 eCB-like molecules that arise from the conjugation of the omega-3 fatty acids with neurotransmitters serotonin and dopamine - DHA-serotonin (DHA-5HT), EPA-serotonin (EPA-5HT), DHA-dopamine (DHA-DA) and EPA-dopamine (EPA-DA). Additionally, we describe the role of these omega-3 eCBs and their derivatives in different disease states such as pain, inflammation and cancer. Moreover, we detail the formation and potential physiological roles of the oxidative metabolites that arise from the metabolism of omega-3 eCBs by eicosanoid synthesizing enzymes - cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 epoxygenase (CYP450). In summary, we outline the novel findings regarding a growing class of signaling molecules, omega-3 eCBs, that can control the physiological and pathophysiological processes in the body."…

-Department of Comparative Biosciences, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Department of Biochemistry, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Division of Nutritional Sciences, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Beckman Institute for Advanced Science, Neuroscience Program, Center for Biophysics and Quantitative Biology, Department of Bioengineering, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6685292

Dietary Omega-6/Omega-3 and Endocannabinoids: Implications for Brain Health and Diseases

"Omega-3 (ω-3) and omega-6 (ω-6) are polyunsaturated fatty acids (PUFAs) that play critical role in human health and have to be provided by food. In the brain, PUFAs are also precursors of endocannabinoids. The aim of this chapter is to review the existing literature on how dietary PUFAs impact on the endocannabinoid system in the brain and what are the consequences for brain function and dysfunction. In this chapter, we will first describe how PUFAs enter the brain,

what are their metabolism processes and roles in brain function. We will describe the pathways from PUFAs to endocannabinoid production. Then, we will review the literature on how dietary ω-6/ω-3 ratio impacts the endocannabinoid system, in terms of endocannabinoid levels, proteins and endocannabinoid-dependent synaptic plasticity. In the next part, we will describe what we know about the interactions between PUFAs and endocannabinoids in neurological and neuropsychiatric disorders. Finally, we will conclude on the possible implications of the interactions between dietary PUFAs and endocannabinoids in the normal and pathological brain. In particular, we will discuss how dietary PUFAs, as homeostatic regulators of endocannabinoids, can constitute interesting therapeutic strategies for the prevention and/or treatment of neurological disorders with endocannabinoids impairment."…

- INTECH / Clémentine Bosch-Bouju and Sophie Layé

https://www.intechopen.com/books/cannabinoids-in-health-and-disease/dietary-omega-6-omega-3-and-endocannabinoids-implications-for-brain-health-and-diseases
https://pdfs.semanticscholar.org/3207/a9f78c2eda6ad0c94120a1bfe777f7824f98.pdf

The role of n-3 PUFA-derived fatty acid derivatives and their oxygenated metabolites in the modulation of inflammation

"Notwithstanding the ongoing debate on their full potential in health and disease, there is general consensus that n-3 PUFAs play important physiological roles. Increasing dietary n-3 PUFA intake results in increased DHA and EPA content in cell membranes as well as an increase in n-3 derived oxylipin and -endocannabinoid concentrations, like fatty acid amides and glycerol-esters. These shifts are believed to (partly) explain the pharmacological and anti-inflammatory effects of n-3 PUFAs. Recent studies discovered that n-3 PUFA-derived endocannabinoids can be further metabolized by the oxidative enzymes CYP-450, LOX and COX, similar to the n-6 derived endocannabinoids. Interestingly, these oxidized n-3 PUFA derived endocannabinoids of eicosapentaenoyl ethanolamide (EPEA) and docosahexaenoyl ethanolamide (DHEA) have higher anti-inflammatory and anti-proliferative potential than their precursors. In this review, an overview of recently discovered n-3 PUFA derived endocannabinoids and their metabolites is provided. In addition, the use of chemical probes will be presented as a promising technique to study the n-3 PUFA and n-3 PUFA metabolism within the field of lipid biochemistry."

-Nutrition and Pharmacology Group, Division of Human Nutrition, Wageningen University & Research, Wageningen, the Netherlands;

-Laboratory of Organic Chemistry, Wageningen University & Research, the Netherlands.

-School of Pharmaceutical Sciences and Technology, Tianjin University, PR China

-Department of Chemical and Materials Engineering, King Abdulaziz University, Jeddah, Saudi Arabia.

https://pubmed.ncbi.nlm.nih.gov/31260750/

Omega-3, Omega-6 & Pain

…"High Omega-6 (n-6) PUFAs are associated with inflammation, nociception, and psychological distress."…

-Department of Aging & Geriatric Research, University of Florida, Gainesville, FL, USA
-Pain Research & Intervention Center of Excellence, University of Florida
-Department of Anesthesia, Cincinnati Children's Hospital, Cincinnati, OH, USA
-Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL, USA
-Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, FL, USA
-Department of Biostatistics, University of Florida, Gainesville, Florida, USA
-Department of Psychology, University of Alabama at Birmingham, AL, USA
-Department of Medicine/ Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, AL, USA
-College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, USA
-Center of Excellence for Stress and Mental Health (CESAMH)
-VA San Diego Healthcare System
-University of California, San Diego, CA, USA
-Department of Medicine, University of Florida, Gainesville, FL, USA
-Biostatistics Department, School of Public Health University of Alabama at Birmingham, AL, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5701880

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…"Omega-6 (n-6) and omega-3 (n-3) fatty acids regulate multiple pain-related biochemical pathways. As major components of vascular, immune, myelin, glial, and neuronal cell membranes [46], n-6 and n-3 fatty acids can be converted to lipid mediators with pro- or antinociceptive properties (eg, endovanilloids, eicosanoids, endocannabinoids, resolvins) [1,20,34–36,48,58,60]. In general, and with a few notable exceptions [52], lipid mediators derived from n-6 fatty acids have pronociceptive properties [1,2,19,20,22,35,36,56], while mediators derived from n-3 fatty acids have antinociceptive properties [32,34,48,58]. Therefore, dietary interventions with targeted alterations in n-6 and n-3 fatty acids may be able to reduce pain (Fig. 1)."…

-Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA
-Department of Physical Medicine and Rehabilitation, Program on Integrative Medicine, University of North Carolina-Chapel Hill, NC, USA
-Department of Biostatistics, School of Public Health, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA
-Nutrition Research and Metabolism Core, North Carolina Translational Clinical Sciences Institute, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

-Department of Pediatric Gastroenterology, Hepatology and Nutrition, University of California, San Diego, San Diego, CA, USA
-School of Medicine and Pharmacology, Royal Perth Hospital, The University of Western Australia, Perth, Australia
-Division of Gastroenterology and Hepatology, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA
-School of Dentistry, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA
-Department of Neurology, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3850757

pronociceptive - preceding or leading to nociception (pain), the perception of pain.
antinociceptive - inhibiting the sensation of pain

■■■

…"N-6 [omega-6] and n-3 [omega-3] fatty acids regulate multiple inflammation and pain-related biochemical pathways as major components of meninges, myelin, glia, skeletal muscle, and neuronal cell membranes [16]. N-6 and n-3 fatty acids can be converted to lipid mediators with pro- and anti-nociceptive properties (e.g. prostanoids [17], octadecanoids [18–20], endocannabinoids [21], n-3 monoepoxides [22], and resolvins [23–25]). With a few notable exceptions (e.g. lipoxins and epoxyeicosatrienoic acids), lipid mediators derived from n-6 fatty acids have pro-nociceptive properties, while mediators derived from n-3 fatty acids have anti-nociceptive and pro-resolvin properties [17–24]."…

-Department of Neurology, UNC, 2133 Physicians Office Bld, 170 Manning Drive, Chapel Hill, NC, United States
-Department of Physical Medicine and Rehabilitation, UNC School of Medicine, Chapel Hill, NC, United States
-UNC Healthcare Department of Nutrition & Food Services - Metabolic & Nutrition Research Core, Chapel Hill, NC, United States
-Department of Medicine, 4111 Bioinformatics Building, Chapel Hill, NC, United States
-Department of Biostatistics, Gillings School of Global Public Health, Chapel Hill, NC, United States
-Department of Physical Medicine and Rehabilitation, UNC School of Medicine, Chapel Hill, NC, United States
-North Carolina Department of Agriculture and Consumer Services,Raleigh, NC, United States
-Lipid Mediators, Inflammation, and Pain Unit, Laboratory of Clinical Investigation, National Institute on Aging, NIH, Baltimore, MD, United States
-UNC Cytokine Analysis Facility, North Carolina Oral Health Institute, Chapel Hill, NC, United States
-Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, NIH, Rockville, MD, United States
-Intramural Program of the National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD, United States
-Department of Physical Medicine and Rehabilitation, UNC School of Medicine, Chapel Hill, NC , United States
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6269096

Omega Ratio

…"Eicosanoids (prostaglandins, thromboxanes, leucotrienes) derived from AA [arachidonic acid / omega-6] on the one hand, and EPA and DHA on the other hand, have a different physiological effect on man (vonShacky, 2001). Proinflammatory and proaggregatory AA derived eicosanoids increase the risk of cardiovascular and autoimmune diseases (Adam, 2003). On the other hand, anti-inflammatory, antithrombotic, antiarrhythmic and immunomodulating properties of EPA and DHA can be helpful in the prevention of atherosclerosis, coronary heart diseases, hypertension, inflammatory and autoimmune disorders, cancers and diabetes. From the above-mentioned follows the demand to keep the proper n-6/n-3 PUFA ratio in the diet, preferably 2 or below (Okuyama et al., 1997)."…

-Department of Food Technology & Department of Animal Nutrition, Faculty of Agriculture, Mendel University of Agriculture and Forestry Brno, Czech Republic
https://www.cabi.org/Uploads/animal-science/worlds-poultry-science-association/WPSA-italy-2006/10103.pdf

The use of n-3 PUFAs (fish oil) in enteral nutrition

"Severely ill patients in need of enteral nutrition support must obtain all essential nutrients in at least the amounts recommended for daily intake (RDA) by healthy populations. Until recently essential fatty acids have been entirely omitted from enteral solutions or included only in the form of n-6 PUFAs which are structurally important for cell membranes and play a significant role as precursors (esp. arachidonic acid, AA) of eicosanoids (prostaglandins, thromboxanes, leukotrienes). However, in the absence of n-3 PUFAs, these eicosanoids may produce exaggerated effects in acute stress responses causing immunosuppression, platelet aggregation and excessive or chronic inflammation. n-3 PUFAs act as precursors of complementary eicosanoids which counteract the exaggerated responses of AA-derived eicosanoids. Therefore, n-3 PUFAs should be part of any optimally balanced diet and must be included also in enteral solutions. Since the transformation of the n-3 parent fatty acid, alpha-linolenic acid, to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is slow and unreliable, it is necessary to provide them as preformed nutrients as they occur in fish oil. The British Nutrition Foundation recommends a daily intake of EPA and DHA in amounts corresponding to the intake of 3 to 4g standardized fish oil. The requirements can also be covered by the weekly consumption of 2 to 3 portions of fatty fish. Preliminary clinical trials have shown certain beneficial effects of fish oil intakes in diseases associated with inflammatory reactions such as rheumatoid arthritis or inflammatory bowel disease, in conditions with impaired immune

competence such as burns, post-operative situations and cyclosporine treatment after renal transplants, and in conditions with enhanced platelet aggregation such as after coronary angioplasty. While these findings must be verified in strictly controlled trials, the intake of fish oil n-3 PUFAs in a balanced ratio to n-6 PUFAs can be recommended for all patients including those in need of enteral nutrition support."

-Vitamin Research Department, F. Hoffmann-La Roche Ltd, Basel, Switzerland.
https://pubmed.ncbi.nlm.nih.gov/7657477/

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…"It is worthwhile to mention that the prevalence of CVD [cardiovascular disease] is closely associated with diet.[94] Anthropological and epidemiological studies as well as studies at the molecular level indicate that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of ~1, whereas in Western diets the ratio is anywhere between 15/1 and 16.7/1.[95] Some studies suggest that this alteration of the ratio of ω-6 to ω-3 essential fatty acids in Western diets promotes the pathogenesis of many diseases including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of ω −3 PUFA (a lower ω-6/ω-3 ratio), exert suppressive effects.[49, 50] "…

-Department of Pharmacology, University of Michigan, Ann Arbor, MI
-Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6242736

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…"The fatty acid composition of the modern Western diet has changed dramatically the last century, and these changes are thought to be related to increases in inflammatory-related diseases (Hallahan and Garland, 2005; Weber and Leaf, 1991). For example, the early hunter-gatherer diet had an n-6:n-3 [omega-6:omega-3] PUFA ratio of 2:1 to 3:1 (Cordain et al., 2005). However, during the early 1900s, the typical Western diet underwent fundamental alterations with the enormous growth in refined vegetable oil use, a central n-6 source that replaced n-3 PUFAs from fish, wild game, and leaves (Cordain et al., 2005; van West and Maes, 2003), leading to the contemporary North American n-6:n-3 ratio of 15:1 to 17:1 (Hibbeln et al., 1997; Simopoulos, 2002). It has been suggested that these dramatic shifts in the modern Western diet's fatty acid composition are related to the increases in depression and cardiovascular disease (Hallahan and Garland, 2005; Hibbeln, 1998; van West and Maes, 2003; Wall et al., 2010)."…

-Institute for Behavioral Medicine Research, Ohio State University College of Medicine, USA
-Department of Psychiatry, Ohio State University College of Medicine, USA
-Department of Human Nutrition, Ohio State University
-Division of Biostatistics, College of Public Health, Ohio State University

-Department of Internal Medicine, Ohio State University College of Medicine, USA
-Department of Molecular Virology, Immunology, and Medical Genetics, Ohio State University College of Medicine, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191260

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"The proinflammatory effects of the AA-derived [arachidonic acid / omega-6] prostanoids and leukotrienes have been described [37]. A mechanism has been proposed whereby a coordinated program for resolution initiates in the first few hours after the inflammatory response. A switch occurs whereby the AA-derived prostanoids and leukotrienes, which have set the inflammatory response to begin, undergo further metabolism to become another generation of eicosanoids derived from AA termed lipoxins and hence terminate inflammation at the local contained sites [55]. Since these lipoxins are involved in the resolution of the acute inflammation that occurs as a result of the overproduction of the proinflammatory eicosanoids derived from AA, they are said to have "pro-resolving" and anti-inflammatory functions. These events coincide with the biosynthesis of resolvins and protectins from n-3 [omega-3] fatty acids, which act to shorten the period of neutrophil infiltration [55]. However, while the initial response of the AA-derived eicosanoids to promote inflammation is beneficial in one respect, for example, in the control of blood flow and vessel dilation, the increase in the ratio of n-6:n-3 PUFA leads to an overall increase in the production of proinflammatory cytokines and an unnecessary over reactive inflammatory response leading to the pathogenesis of inflammatory diseases. In addition, the decrease in consumption of n-3 PUFA which leads to an overall decrease in resolvin and protectin production is detrimental to the inflammatory response as these products, which have the ability to dominate the resolution phase of inflammation, can no longer exert this potential; thus, the inflammatory response cannot be terminated effectively."…

"Increases in the ratio of n-6:n-3 PUFA, characteristic of the Western diet, could potentiate inflammatory processes and consequently predispose to or exacerbate many inflammatory diseases. The change in ratio and increase in n-6 PUFA consumption change the production of important mediators and regulators of inflammation and immune responses towards a proinflammatory profile. Chronic conditions such as CVD, diabetes, obesity, rheumatoid arthritis, and IBD are all associated with increased production of PGE2, LTB4, TXA2, IL-1β, IL-6, and TNF-α, whereby the production of these factors increases with increased dietary intake of n-6 PUFA and decreased dietary intake of n-3 PUFA. In conclusion, the unbalanced dietary consumption of n-6:n-3 PUFA is detrimental to human health, and so the impact of dietary supplementation with n-3 PUFA upon the alleviation of inflammatory diseases, more specifically, NAFLD needs to be more thoroughly investigated."

-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland
-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

Health Implications of High Dietary Omega-6 Polyunsaturated Fatty Acids

"Omega-6 (n-6) polyunsaturated fatty acids (PUFA) (e.g., arachidonic acid (AA)) and omega-3 (n-3) PUFA (e.g., eicosapentaenoic acid (EPA)) are precursors to potent lipid mediator signalling molecules, termed "eicosanoids," which have important roles in the regulation of inflammation. In general, eicosanoids derived from n-6 PUFA are proinflammatory while eicosanoids derived from n-3 PUFA are anti-inflammatory. Dietary changes over the past few decades in the intake of n-6 and n-3 PUFA show striking increases in the (n-6) to (n-3) ratio (~15:1), which are associated with greater metabolism of the n-6 PUFA compared with n-3 PUFA. Coinciding with this increase in the ratio of (n-6):(n-3) PUFA are increases in chronic inflammatory diseases such as nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, obesity, inflammatory bowel disease (IBD), rheumatoid arthritis, and Alzheimer's disease (AD). By increasing the ratio of (n-3):(n-6) PUFA in the Western diet, reductions may be achieved in the incidence of these chronic inflammatory diseases."….

"Over the last few decades, extreme qualitative nutritional changes have taken place with increased levels of fatty acid consumption [4]. Today, industrialised societies are characterised by an increase in saturated fat, omega 6 PUFA, and trans fatty acid intake, as well as an overall decrease in omega-3 PUFA intake [5]. Fatty acids now represent 28–42% of total energy consumed by European populations [4, 6], whereas, in ancestral nutrition, fatty acid consumption was only approximately 20–30% of total energy [4, 7, 8]. As a result of the increased consumption of LA-rich vegetable oils associated with the Western diet, n-6 PUFA consumption has become progressively much higher than that of n-3 PUFA [9]. Optimal dietary intakes of the n-6:n-3 ratio should be around 1–4:1. However, according to the nutritional changes described above in the Western diet, this ratio has now increased to be within the range of 10:1 to 20:1 [4]. In parallel, there are coinciding increases in the incidence of diseases involving inflammatory processes such as cardiovascular disease, obesity, IBD, rheumatoid arthritis, and cancer. Neurodegenerative and psychiatric illnesses such as AD and depression are other examples [10]. A study carried out by Hassan and Hanachi, involving 984 Iranian women, suggested that a good dietary pattern rich in fruits, legumes, vegetables, cereals, and fish, rich in n-3 PUFA, can decrease the likelihood of developing the Metabolic Syndrome [11]. Another study performed in France, involving 912 men, concluded that a low consumption of fish rich in n-3 PUFA is associated with a higher probability

of developing the Metabolic Syndrome [12]. Thus, high intake of n-6 PUFA, along with low intakes of n-3 PUFA, shifts the physiological state to one that is proinflammatory and prothrombotic with increases in vasospasm, vasoconstriction, and blood viscosity and the development of diseases associated with these conditions."

-Alimentary Pharmabiotic Centre, Biosciences Institute, Ireland
-Teagasc Food Research Centre, Biosciences Department, Ireland
-Department of Microbiology, University College Cork, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257/

Dietary fat and health: the evidence and the politics of prevention: careful use of dietary fats can improve life and prevent disease.

"Every year, more young people start the slow progressive injury that eventually becomes cardiovascular disease and death. It could be prevented with nutrition education, but medical efforts focus more on treatments for older people than on preventing primary causes of disease in young people. Two avoidable risks are prevented by simple dietary interventions: (1) Eat more omega-3 and less omega-6 fats, so tissues have less intense n-6 eicosanoid action, and (2) eat less food per meal to lower vascular postprandial oxidant stress. An empirical diet-tissue relationship was developed and put into an interactive personalized software program to aid informed food choices."

-College Park MD 20740 USA
https://www.ncbi.nlm.nih.gov/pubmed/16387724

Importance of maintaining a low omega–6/omega–3 ratio for reducing inflammation

"The consumption of seed oils high in the omega-6 polyunsaturated fat (PUFA) linoleic acid (LA) contributes to low-grade inflammation, oxidative stress, endothelial dysfunction and atherosclerosis.[1] Moreover, dietary LA significantly increases cyclooxygenase-2 (COX-2) expression in the aorta,[2] converting arachidonic acid (AA) to proinflammatory eicosanoids."…

-Saint Luke's Mid America Heart Institute, Kansas, Missouri, USA
-Dr James J DiNicolantonio & James H O'Keefe
https://openheart.bmj.com/content/openhrt/5/2/e000946.full.pdf

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…"Up until about 100 years ago, the omega-6/3 ratio had been around 4:1 or less.[2] However, the

typical Western diet now provides an omega-6/3 ratio approximately 20-fold higher in favor of omega-6.[2] While foods such as nuts, seeds, and eggs are high in omega-6, the increase in the omega-6/3 ratio is primarily due to an increase in the intake of industrial seed oils (soybean, corn, safflower, cottonseed, and canola). Additionally, there has been a reduction in the intake of long-chain omega-3s, which can primarily be found in fatty fish and shellfish. A high omega-6/3 ratio predisposes to supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation.[3] The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of EPA and DHA, has been proposed to put the population in a pro-inflammatory and pro-thrombotic state.[3, 4]"...

-MSMA member since 2003, Saint Luke's Mid America Heart Institute, Kansas City, Missouri.
-Dr James J. DiNicolantonio
-Dr. James O'Keefe, MD
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7721408

An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity.

"In the past three decades, total fat and saturated fat intake as a percentage of total calories has continuously decreased in Western diets, while the intake of omega-6 fatty acid increased and the omega-3 fatty acid decreased, resulting in a large increase in the omega-6/omega-3 ratio from 1:1 during evolution to 20:1 today or even higher. This change in the composition of fatty acids parallels a significant increase in the prevalence of overweight and obesity. Experimental studies have suggested that omega-6 and omega-3 fatty acids elicit divergent effects on body fat gain through mechanisms of adipogenesis, browning of adipose tissue, lipid homeostasis, brain-gut-adipose tissue axis, and most importantly systemic inflammation. Prospective studies clearly show an increase in the risk of obesity as the level of omega-6 fatty acids and the omega-6/omega-3 ratio increase in red blood cell (RBC) membrane phospholipids, whereas high omega-3 RBC membrane phospholipids decrease the risk of obesity. Recent studies in humans show that in addition to absolute amounts of omega-6 and omega-3 fatty acid intake, the omega-6/omega-3 ratio plays an important role in increasing the development of obesity via both AA eicosanoid metabolites and hyperactivity of the cannabinoid system, which can be reversed with increased intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A balanced omega-6/omega-3 ratio is important for health and in the prevention and management of obesity."

-The Center for Genetics, Nutrition and Health, Klingle Street NW, Washington, DC

https://www.ncbi.nlm.nih.gov/pubmed/26950145

…"The dietary imbalance between omega-6 and omega-3 fatty acids can result in inappropriately elevated or sustained immuno-stimulatory responses to injury or inappropriately diminished immuno-suppressing responses after an injury has been repaired. It has been suggested that the increasing incidence of hypertensive and inflammatory conditions corresponds to the proportional increase in omega-6 fatty acids and decrease in omega-3 fatty acids in the American diet [Simopoulos 2002]."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

High Dietary ω-6:ω-3 PUFA Ratio Is Positively Associated with Excessive Adiposity and Waist Circumference

"This study suggests that high dietary ω-6:ω-3 PUFA ratio is positively associated with excessive adiposity and worse metabolic profile."

-Medical Molecular Biology Service, "Fray Antonio Alcalde" Civil Hospital of Guadalajara, Department of Molecular Biology and Genomics, University Center of Health Sciences, University of Guadalajara, Guadalajara, Mexico

-Department of Microbiology and Parasitology, University Center of Health Sciences, University of Guadalajara, Guadalajara, Mexico

-Office of Disease Prevention, National Institutes of Health, Bethesda, MD, USA

-Department of Human Reproduction and Child Growth and Development, University Center of Health Sciences, University of Guadalajara, Guadalajara, Mexico

-Erika Martinez-Lopez, PhD, Medical Molecular Biology, 'Fray Antonio Alcalde' Civil Hospital of Guadalajara, Guadalajara, Jalisco, Mexico

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6189529/

"Omega-3 is an essential polyunsaturated fatty acid (PUFA) that most animals need to acquire in their diet. Mammalian brains are rich in docosahexaenoic acid (DHA), a long-chain form of omega-3, whose deficiency, coupled with a high omega-6:3 ratio, leads to numerous cognitive disorders and mental diseases."

…"Long-chain omega-3 PUFAs are major constituents of mammalian brain, and deficiency in these PUFAs, coupled with a high omega-6:3 ratio, is associated with many diseases and neurological disorders [2, 3]. "…

-B. Triwaks Bee Research Center, Department of Entomology, Robert H. Smith Faculty of Agriculture, Food & Environment, The Hebrew University of Jerusalem, Rehovot, Israel;

-Gilat Research Center, Institute of Plant Sciences, Agricultural Research Organization, Mobile Post Negev, Israel

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4697434/

The Importance of the Ratio of Omega-6/Omega-3 Essential Fatty Acids.

"Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of approximately 1 whereas in Western diets the ratio is 15/1-16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a low omega-6/omega-3 ratio) exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2-3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries, that are being exported to the rest of the world."

-Dr. Artemis P. Simopoulos M.D

-The Center for Genetics, Nutrition and Health, Washington

https://www.ncbi.nlm.nih.gov/pubmed/12442909

https://www.karger.com/Article/Pdf/73789

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"A lower dietary omega-6/omega-3 (n-6/n-3) fatty acid ratio (< 4) has been shown to be

beneficial in preventing a number of chronic illnesses."…

-Department of Physical Sciences, Thompson Rivers University, Kamloops, British Columbia, Canada.
https://www.ncbi.nlm.nih.gov/pubmed/23943402

Lifelong imbalanced LA/ALA intake impairs emotional and cognitive behavior via changes in brain endocannabinoid system

"Imbalanced dietary n-3 and n-6 PUFA content has been associated with a number of neurological conditions. Endocannabinoids are n-6 PUFA derivatives, whose brain concentrations are sensitive to modifications of fatty acid composition of the diet and play a central role in the regulation of mood and cognition. As such, the endocannabinoid system appears to be an ideal candidate for mediating the effects of dietary fatty acids on mood and cognition. Lifelong administration of isocaloric α-linolenic acid (ALA)-deficient and -enriched diets induced short-term memory deficits, whereas only dietary ALA enrichment altered emotional reactivity in adult male rats compared with animals fed a standard diet that was balanced in ALA/linoleic acid (LA) ratio. In the prefrontal cortex, both diets reduced 2-AG levels and increased MAG lipase expression, whereas only the enriched diet reduced AEA levels, simultaneously increasing FAAH expression. In the hippocampus, an ALA-enriched diet decreased AEA content and NAPE-PLD expression, and reduced 2-AG content while increasing MAG lipase expression. These findings highlight the importance of a diet balanced in fatty acid content for normal brain functions and to support a link between dietary ALA, the brain endocannabinoid system, and behavior, which indicates that dietary ALA intake is a sufficient condition for altering the endocannabinoid system in brain regions modulating mood and cognition."

..."Over the last decades, the ratio of n-6 to n-3 fatty acid intake in the overall population, including children and adolescents, has dramatically shifted in the Western diet. In the eating habits of Western industrial countries, food tends to be rich in n-6 fatty acids and low in long-chain n-3 fatty acids [3, 4]. This dysregulation can affect the equilibrium of several organs and particularly of the brain that is highly enriched in LCPUFAs. Brain's LCPUFAs are involved in the maturation of neuronal structures and are essential throughout the entire lifespan for maintaining normal brain activities [5, 6]. Consequently, it is unsurprising that a lack of n-3 LCPUFAs or an imbalance in the n-3 and n-6 ratio has been associated with a number of neurological and psychiatric disorders, including depression, anxiety, schizophrenia, and attention deficit hyperactivity disorder in both children and adults [7–12]."

…"Despite the growing body of evidence suggesting a link between n-3 LCPUFA dysregulation and neuropsychiatric diseases, how dietary fatty acids can actually affect the brain and behavior

is still poorly understood.

The endocannabinoid system appears to be an ideal candidate for mediating the effects of dietary fatty acids on mood and cognition. Indeed, endocannabinoids are local neuromodulators that are metabolic derivatives of the n-6 LCPUFA, AA, and their concentrations in the brain are sensitive to modifications of the fatty acid composition of the diet [13, 14]. Furthermore, the endocannabinoid system plays a role in the regulation of mood and cognition under physiological conditions, and its dysregulation is believed to contribute to the development of several neuropsychiatric pathologies [15].

[SEE URL BELOW FOR THIS IMAGE / CAPTION:]

Schematic representation of n-6 and n-3 metabolism.

"In this context, endocannabinoids shape neuronal architecture [16], and recent preclinical studies comparing the effects of lifelong n-3-deficient to regular diets have pointed out that long-term ALA dietary insufficiency impairs endocannabinoid-mediated long-term synaptic depression in brain areas associated with the development of anxiety- and depressive-like behaviors [17, 18], suggesting that lifelong deficiency in n-3 PUFAs may influence cerebral areas controlling mood through alteration of the endocannabinoid system functionality. However, the above-cited studies investigated the consequences of diets deficient in ALA and without comparing the effects of such dietary imbalances to those present after administration of a healthy diet balanced in n-3 and n-6 fatty acid content."….

*-Department of Biotechnology and Life Sciences (DBSV),*University of Insubria, Busto Arsizio (VA), Italy*

-Endocannabinoid Research Group,†Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Pozzuoli, Naples, Italy

-Department of Physiology and Pharmacology,§Sapienza University of Rome, Rome, Italy

*-Department of Biomedical Sciences,**University of Cagliari, Cagliari, Italy*

-Department of Medicine,††Campus Bio-Medico University of Rome, Rome, Italy

-European Center for Brain Research/IRCCS Santa Lucia Foundation,§§ Rome, Italy

*-Zardi Gori Foundation,*** Milan, Italy*

-T. Rubino and D. Parolaro are senior co-authors.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5282947/

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…"An increased intake of omega-3 PUFA, especially the long-chain omega-3 PUFA EPA and DHA, could reduce the tissue omega-6/omega-3 ratio to a level that probably existed during millions of years of human evolution [37]. This ratio dramatically increased in recent millennia due to deep changes in dietary habits following the transition from the hunter-gatherer lifestyle to agricultural societies. This change could therefore be one of the crucial factors leading to the rise

of the so-called diseases of civilization, further skewed towards omega-6 PUFA by the agricultural revolution in the 19th century and the massive use of corn (with its high omega-6 PUFA content) in western societies during the 20th century."…

-Division of Medicine, Department of Hepatology, Gastroenterology and Metabolism, Rudolf-Virchow-Hospital, Charité University Medicine, Germany

-Lipid Clinic, Experimental and Clinical Research Center (ECRC), Max-Delbrück-Center for Molecular Medicine and Charité University Medicine, Germany

-Institute of General Pathology, Catholic University School of Medicine, Rome, Italy

-The Synergistic Innovation Center for Food Safety and Nutrition, State Key Laboratory of Food Science and Technology, and School of Food Science and Technology, Jiangnan University, Wuxi, Jiangsu, China

-Department of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, NC, USA

-Department of Physiology, National Taiwan University College of Medicine, Taiwan

-Department of Biochemistry, School of Medicine, Cancer Research Institute, Infection Signaling Network Research Center, Chungnam National University, Republic of Korea

-Research Center for Biotechnology Applied to Cosmetology, Catholic University School of Medicine, 00168 Rome, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537707/

Importance of a balanced omega 6/omega 3 ratio for the maintenance of health: nutritional recommendations

"The modification of dietary patterns has led to a change in fatty acid consumption, with an increase in the consumption of ω-6 fatty acids and a marked reduction in the consumption of ω-3 fatty acids. This in turn has given rise to an imbalance in the ω-6/ω-3 ratio, which is now very different from the original 1:1 ratio of humans in the past. Given the involvement of ω-6 and ω-3 essential fatty acids in disease processes, the present article examines changes in dietary patterns that have led to the present reduction in the consumption of ω-3 essential fatty acids, and to study the importance of the ω-6/ω-3 balance in maintaining good health. In addition, an assessment is made of the established recommendations for preventing a poor intake of ω-3 essential fatty acids, and the possible options for compensating the lack of these fatty acids in the diet."

-Clinical Nutrition and Dietetics Unit, La Paz University Hospital, Madrid, Spain

https://pubmed.ncbi.nlm.nih.gov/21666970/

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…"There are a number of fatty acids which do not need to be obtained through diets because they are naturally synthesized by the human body itself and are termed as nonessential fatty acids [1]. On the other hand, omega-3 (ω-3) and omega-6 (ω-6) fatty acids (Figure 1) are known as

essential fatty acids because both of them cannot be synthesized by the body itself and need to be uptaken through diets. The omega-3 fatty acids can be obtained by consuming the plant and marine fish oil. Docosahexaenoic acid (C22:6 n-3) and eicosapentaenoic acid (C20:5 n-3) are primarily obtained through marine resources (mainly fishes and algae). More surprisingly, these compounds are not actually produced by the fishes themselves, yet fishes accumulate them by consuming microalgae or small fishes that have already accumulated them in their tissues [2, 3]. The important forms of omega-3 fatty acids are α-linolenic acid (ALA), eicosapentaenoic acid, and docosahexaenoic acid. Likewise, linoleic acid (LA; C18:2 n-6) and arachidonic acid (AA; C20:4 n-6) are the most useful form of omega-6 fatty acids, which can be synthesized by the human body through conversion from linoleic acid."…

"In the last decade, the polyunsaturated fatty acids (PUFAs) have shown convincing results in the area of biomedical research, especially for their role in prevention against diseases. Omega-3 PUFAs has proved to be critical for human biological systems and are essential for the development of the nervous system during late pregnancy period [4]. Similarly, in adults, its deficiency can lead to severe abnormal conditions like neural and visual disorders, learning disabilities, obesity, cardiovascular disease (CVD), inflammation, and cancer. Omega-3 can be a vital component of the human diet to avoid such abnormal conditions. A number of trial studies have been carried out to investigate the health benefits of the omega-3 PUFAs, including primary and secondary preventions. The aim of the previous studies was not only restricted to their beneficial effects against cardiovascular disease, but also to evaluate its beneficiary roles against inflammatory diseases, Alzheimer's, diabetes, and depression. In this review, the health benefit of omega-3 has been discussed with explanations regarding the alternate potential plant sources for the production of these compounds on the basis of recent studies."….

Imbalance of Omega-6/Omega-3 Fatty Acid Ratio in Modern Diets

"The diet habit of human is changed drastically during modern era, when compared with the ancient civilizations [5]. It is assumed that the early foods were rich in omega-3 fatty acids and a well-balanced ω-6/ω-3 ratio (e.g., 1=1), but the situation is totally changed. Modern diets have a high concentration of saturated fatty acids and also ω-6 fatty acids instead of ω-3. So, this diet shift has created a disturbance in ω-6/ω-3 ratio of 1:1 to a ratio of higher than 15:1 [6]. This conversion of diets has invited a greater risk of cardiovascular diseases and higher susceptibility to other diseases [5, 6]. According to nutrition experts, a diet composed of omega-6/omega-3 in a ratio of less than 5:1 is highly recommended [7]. But, in western countries, the diet mainly consumed is richer in omega-6 and estimated as 20 times higher than its omega-3 content [7, 8].

A dose of 0.3–0.5 grams of EPA and 0.8–1.1 grams of DHA is mainly recommended on a daily basis [9]. The European Food Safety Agency (EFSA) has made certain recommendations to intake

at least 250mg/day of combined dose of EPA and DHA for adults to protect them against cardiovascular diseases [10]. Only in a few countries, including Japan, Korea, Philippines, Finland, Norway, Sweden, and Iceland, the population's diet consists of at least 250mg of ω-3 on a daily basis [11]. The statistical data from previous researches show that the current dose in most parts of the world is still far below the required levels recommend by the world health organizations."…

Importance of Omega-3 PUFAs for Human Health

"Omega-3 PUFA has now considered being a vital component of human diet after their consistently proven health benefits. It is helpful in maintaining cell physiological processes and other important pathways in the body. It is essential for normal functioning of tissues and organs, and its deficiency can cause abnormalities. Till now, various studies have been conducted to investigate its effects in different health domains, such as cancer, cardiovascular disease, chronic inflammatory diseases, diabetes type 2, neurological disorders, growth and development, depression, and vision [12, 13].

Many studies have been conducted in recent years to investigate and eliminate the causes of modern diseases related to the dietary habits of the humans [14]. Omega-3 PUFAs have provided a breakthrough in medical research, after its presence was noticed in the diet of Greenland Eskimos that have low mortality rate due to coronary heart disease (CHD) [15]. It has become quite clear that if a healthy diet is followed, it can remarkably reduce the risk of CHD in population [16]. For such purpose, ALA, EPA, and DHA are comprehensively studied. Studies have shown the effectiveness of EPA and DHA in primary and secondary prevention of cardiovascular diseases (CVD) [17]. It has been observed through clinical research that the omega-3 PUFA intake lowers the triglycerides (TG) levels in Type-2 Diabetic (T2D) patients [18]. Research studies have proved the effectiveness of marine-based omega-3 PUFAs (EPA and DHA) against some most common types of cancer, including prostate [19], breast [20, 21], and colorectal cancer [22]. The omega-3 PUFAs are also helpful in the formation of protective lipid mediators against inflammatory diseases and disorders [23]. Inflammation may be involved in many chronic diseases such as diabetes, cancer, coronary heart disease, obesity, rheumatoid arthritis, and mental illness [24]. A research which has been made recently also suggested that a low serum DHA is a significant risk factor for the development of Alzheimer's disease [25]. Brain health and other growth and developmental processes that occur throughout the life cycle can be enhanced by taking control diets of balanced n-6/n-3 ratio [26, 27]. Therefore, appropriate amounts of dietary ω3 fatty acids are critical for healthy life."…

-State Key Laboratory of Crop Genetics and Germplasm Enhancement, College of Horticulture, Nanjing Agricultural University, Nanjing, Jiangsu 210095, China

-Laboratory of Biotechnology, Chinese Academy of Tropical Agricultural Sciences, Wenchang, Hainan 571339, China

-Department of Agriculture, Abdul Wali Khan University Mardan, Mardan, Pakistan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5339522

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…"Our results suggest that the potential cardiovascular benefit of ALA [an omega-3] is achieved only when dietary LA [an omega-6] is reduced concomitantly rather than fed with high LA diet. The increased nitrosative stress in the unstressed heart with high dietary LA suggests that biomarkers of nitrosative stress may offer a useful early marker of the effects of dietary fat on oxidative tissue stress."

-Nutrition Research Program, Child and Family Research Institute, Department of Pedicatrics, University of British Columbia, Vancouver, British Columbia, Canada.
https://www.ncbi.nlm.nih.gov/pubmed/17720770

Immune regulation and anti-cancer activity by lipid inflammatory mediators

"Rodent and clinical studies have documented that myeloid cell infiltration of tumors is associated with poor outcomes, neutrophilia and lymphocytopenia. This contrasts with increased lymphocyte infiltration of tumors, which is correlated with improved outcomes. Lifestyle parameters, such as obesity and diets with high levels of saturated fat and/or omega (ω)-6 polyunsaturated fatty acids (PUFAs), can influence these inflammatory parameters, including an increase in extramedullary myelopoiesis (EMM). While tumor secretion of growth factors (GFs) and chemokines regulate tumor-immune-cell crosstalk, lifestyle choices also contribute to inflammation, abnormal pathology and leukocyte infiltration of tumors. A relationship between obesity and high-fat diets (notably saturated fats in Western diets) and inflammation, tumor incidence, metastasis and poor outcomes is generally accepted. However, the mechanisms of dietary promotion of an inflammatory microenvironment and targeted drugs to inhibit the clinical sequelae are poorly understood. Thus, modifications of obesity and dietary fat may provide preventative or therapeutic approaches to control tumor-associated inflammation and disease progression. Currently, the majority of basic and clinical research does not differentiate between obesity and fatty acid consumption as mediators of inflammatory and neoplastic processes. In this review, we discuss the relationships between dietary PUFAs, inflammation and neoplasia and experimental strategies to improve our understanding of these relationships. We conclude that dietary composition, notably the ratio of ω-3 [omega-3] vs ω-6 PUFA regulates tumor growth and the frequency and sites of metastasis that together, impact overall survival (OS) in mice."

-University of Nebraska Medical Center, Nebraska Medical Center

https://pubmed.ncbi.nlm.nih.gov/30447537/

A high ratio of dietary n-3 [omega-3] / n-6 [omega-6] polyunsaturated fatty acids improves obesity-linked inflammation and insulin resistance through suppressing activation of TLR4 in SD rats

"Dietary ratios of n-3/n-6 [omega-3 / omega-6] polyunsaturated fatty acids (PUFAs) have been implicated in controlling markers of metabolic disorders, including obesity, insulin resistance (IR), inflammation, and lipid profiles, which are also presumed to be partly related to type 2 diabetes mellitus (T2DM). However, molecular mechanisms of the different PUFAs related to metabolic disorders have not been systematically addressed. The present study aimed to investigate the impact of dietary n-3/n-6 PUFA ratios on obesity and IR and, further, to determine the underlying mechanisms. For 16 weeks, 32 SD male rats, randomly divided into four groups (n = 8 per group), received one of the following diets: normal chow, high saturated fatty acid (SFA), high n-3/n-6 PUFA ratio (1 : 1, $PUFA^{1:1}$), or low n-3/n-6 PUFA ratio (1 : 4, $PUFA^{1:4}$). Following the experimental diet period, metabolic parameters related to obesity and IR were measured. Compared to SFA diet-fed rats, $PUFA^{1:1}$ diet-fed rats exhibited decreased body and visceral fat weight, lowered blood lipids, and improved glucose tolerance and insulin sensitivity. Interestingly, these changes were accompanied with decreased expression levels of circulating pro-inflammatory cytokines, including tumor necrosis factor α, interleukin-6, and C-reactive protein. Moreover, the TLR4 protein and mRNA levels were markedly down-regulated by $PUFA^{1:1}$ compared with SFA; however, $PUFA^{1:4}$ diet-fed rats failed to exhibit these changes. Cumulatively, our data highlight a role for a $PUFA^{1:1}$ diet in the prevention of obesity and related metabolic disorders by suppressing the activation of TLR4, a critical modulator of pro-inflammatory cytokines."

-Department of Nutrition and Food Hygiene and the Ministry of Education Key Lab of Hazard Assessment and Control in Special Operational Environment, School of Public Health, Fourth Military Medical University,
https://pubmed.ncbi.nlm.nih.gov/24074743

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…"The opposing effects of these families of PUFA relate to their competition for similar enzymes involved in their metabolism, including desaturases, elongases and enzymes involved in eicosanoid synthesis such as cyclo-oxygenases and lypoxygenases. The metabolism of n-6 [omega-6] PUFA produces proinflammatory eicosanoids such as prostaglandin E2, but the presence of n-3 [omega-3] PUFA inhibits their synthesis [29]. The ratio of n -6/n-3 PUFA is thus of considerable importance. There is some controversy as to whether or not this fatty acid ratio is

truly important [30], but historical trends suggest that a lower n-6/n-3 ratio is potentially associated with a decreased incidence of cancer [31,32].”…

-Department of Human Health and Nutritional Sciences, College of Biological Science, University of Guelph, , Ontario, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3096965/

Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century

“The apparent increased consumption of LA [omega-6], which was primarily from soybean oil, has likely decreased tissue concentrations of EPA [omega-3] and DHA [omega-3] during the 20th century.”…

”The estimated per capita consumption of soybean oil increased >1000-fold throughout the 20th century. As a consequence, the amount of LA increased >3-fold, and the amount of ALA doubled. Because the amount of ALA increased and amounts of n−3 [omega-3] EPA and DHA remained relatively stable, the total amount of n−3 fatty acids actually increased slightly. However, the net effect of increasing dietary LA, rather than these modest increases in dietary n−3 fatty acids, likely decreased the n−3 EPA and DHA status of human tissues over the 20th century.”

-From the Section on Nutritional Neuroscience, Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism (TLB, CER, SFM, and JRH) and the Laboratory of Clinical Translation Studies, National Institute on Alcohol Abuse and Alcoholism (RRR), National Institutes of Health, Bethesda, MD.

-Supported by a gift from John M Davis and the Intramural Research Program of the National Institute on Alcohol Abuse and Alcoholism.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3076650/

Polyunsaturated fatty acids, inflammation and immunity

“Consumption of n-6 polyunsaturated fatty acids greatly exceeds that of n-3 polyunsaturated fatty acids. The n-6 polyunsaturated fatty acid arachidonic gives rise to the eicosanoid family of inflammatory mediators (prostaglandins, leukotrienes and related metabolites) and through these regulates the activities of inflammatory cells, the production of cytokines and the various balances within the immune system. Fish oil and oily fish are good sources of long chain n-3 polyunsaturated fatty acids. Consumption of these fatty acids decreases the amount of arachidonic acid in cell membranes and so available for eicosanoid production. Thus, n-3 polyunsaturated fatty acids act as arachidonic acid antagonists. Components of both natural and acquired immunity, including the production of key inflammatory cytokines, can be affected by n-3 polyunsaturated fatty acids. Although some of the effects of n-3 fatty acids may be brought

about by modulation of the amount and types of eicosanoids made, it is possible that these fatty acids might elicit some of their effects by eicosanoid-independent mechanisms. Such n-3 fatty acid-induced effects may be of use as a therapy for acute and chronic inflammation, and for disorders which involve an inappropriately activated immune response."

-Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, UK.
https://pubmed.ncbi.nlm.nih.gov/12142955

Human requirement for N-3 polyunsaturated fatty acids

"The diet of our ancestors was less dense in calories, being higher in fiber, rich in fruits, vegetables, lean meat, and fish. As a result, the diet was lower in total fat and saturated fat, but contained equal amounts of n-6 and n-3 essential fatty acids. Linoleic acid (LA) is the major n-6 fatty acid, and alpha-linolenic acid (ALA) is the major n-3 fatty acid. In the body, LA is metabolized to arachidonic acid (AA), and ALA is metabolized to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The ratio of n-6 to n-3 essential fatty acids was 1 to 2:1 with higher levels of the longer-chain polyunsaturated fatty acids (PUFA), such as EPA, DHA, and AA, than today's diet. Today this ratio is about 10 to 1:20 to 25 to 1, indicating that Western diets are deficient in n-3 fatty acids compared with the diet on which humans evolved and their genetic patterns were established. The n-3 and n-6 EPA are not interconvertible in the human body and are important components of practically all cell membranes. The N-6 and n-3 fatty acids influence eicosanoid metabolism, gene expression, and intercellular cell-to-cell communication. The PUFA composition of cell membranes is, to a great extent, dependent on dietary intake. Therefore, appropriate amounts of dietary n-6 and n-3 fatty acids need to be considered in making dietary recommendations. These two classes of PUFA should be distinguished because they are metabolically and functionally distinct and have opposing physiological functions; their balance is important for homeostasis and normal development. Studies with nonhuman primates and human newborns indicate that DHA is essential for the normal functional development of the retina and brain, particularly in premature infants. A balanced n-6/n-3 ratio in the diet is essential for normal growth and development and should lead to decreases in cardiovascular disease and other chronic diseases and improve mental health. Although a recommended dietary allowance for essential fatty acids does not exist, an adequate intake (AI) has been estimated for n-6 and n-3 essential fatty acids by an international scientific working group. For Western societies, it will be necessary to decrease the intake of n-6 fatty acids and increase the intake of n-3 fatty acids. The food industry is already taking steps to return n-3 essential fatty acids to the food supply by enriching various foods with n-3 fatty acids. To obtain the recommended AI, it will be necessary to consider the issues involved in enriching the food

supply with n-3 PUFA in terms of dosage, safety, and sources of n-3 fatty acids."

-The Center for Genetics Nutrition and Health, Washington, DC, USA.
https://pubmed.ncbi.nlm.nih.gov/10901194/

The relation between the omega-3 index and arachidonic acid is bell shaped: synergistic at low EPA+DHA status and antagonistic at high EPA+DHA status

"Introduction: The relation between docosahexaenoic (DHA) and eicosapentaenoic (EPA) vs. arachidonic acid (AA) seems characterized by both synergism and antagonism."…

"Conclusion: Both synergism and antagonism might aim at a balance between ω6 and ω3 long-chain polyunsaturated fatty acid (LCP) to maintain homeostasis. Synergism might be a feature of low LCPω3 status. AA becomes suppressed by antagonism from an RBC-EPA+DHA >8g%."

-Laboratory Medicine, University Medical Center Groningen (UMCG), 9700 RB Groningen, The Netherlands.
https://pubmed.ncbi.nlm.nih.gov/21715149/

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"A diet including 2-3 portions of fatty fish per week, which corresponds to the intake of 1.25 g EPA (20:5n-3) + DHA (22:6n-3) per day, has been officially recommended on the basis of epidemiological findings showing a beneficial role of these n-3 long-chain PUFA in the prevention of cardiovascular and inflammatory diseases. The parent fatty acid ALA (18:3n-3), found in vegetable oils such as flaxseed or rapeseed oil, is used by the human organism partly as a source of energy, partly as a precursor of the metabolites, but the degree of conversion appears to be unreliable and restricted. More specifically, most studies in humans have shown that whereas a certain, though restricted, conversion of high doses of ALA to EPA occurs, conversion to DHA is severely restricted. The use of ALA labelled with radioisotopes suggested that with a background diet high in saturated fat conversion to long-chain metabolites is approximately 6% for EPA and 3.8% for DHA. With a diet rich in n-6 PUFA, conversion is reduced by 40 to 50%. It is thus reasonable to observe an n-6/n-3 PUFA ratio not exceeding 4-6. Restricted conversion to DHA may be critical since evidence has been increasing that this long-chain metabolite has an autonomous function, e.g. in the brain, retina and spermatozoa where it is the most prominent fatty acid. In neonates deficiency is associated with visual impairment, abnormalities in the electroretinogram and delayed cognitive development. In adults the potential role of DHA in neurological function still needs to be investigated in depth. Regarding cardiovascular risk factors DHA has been shown to reduce triglyceride concentrations. These findings indicate that future attention will have to focus on the adequate provision of DHA which can reliably be achieved

only with the supply of the preformed long-chain metabolite."

-Vitamin Research Department, F. Hoffman-Roche Ltd, Basel, Switzerland.
https://pubmed.ncbi.nlm.nih.gov/9637947

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…"Because most diets are already very rich in n-6 PUFAs, greater focus needs to be placed on incorporating n-3 PUFAs into the diet. Dietary sources of n-3 PUFAs are readily available but in limited quantities. Many foods contain ALA, including certain vegetable oils, dairy products, flaxseed, walnuts and vegetables [3]. Fatty fish, such as mackerel, herring and salmon, provide an excellent source of the long-chain derivatives of ALA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [2]."…

-National Centre for Agri-Food Research in Medicine and the Division of Stroke and Vascular Disease, St Boniface Hospital Research Centre
-Department of Physiology, Faculties of Medicine and Pharmacy, University of Manitoba, Winnipeg, Manitoba
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719153/

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"Previous information suggests that human beings once evolved on diets with a balanced 1:1 ratio of n-6 to n-3 FAs [12]. Unfortunately, in modern Westernized diets this once balanced ratio appears to have shifted up to 15/1-17/1 [12]. Modern diets now provide around 80 to 90% of polyunsaturated fatty acids as n-6 LA and are lacking in n-3 FAs—creating an unnatural balance of LA to α-linoleic acid, EPA and DHA [13]. Rising soybean oil intakes during the Twentieth century are thought to be one driver behind rising n-6 LA intakes and reduced EPA and DHA tissue concentrations [14].

Oily fish and their associated n-3 content have been linked to an array of health benefits. Increased n-3 FA intakes elevate EPA and DHA levels in blood lipids, modifying the structure of cell membranes and membrane proteins which have extended roles in cell signaling and gene expression [15]. DHA plays a key role in brain and eye development while EPA and DHA together alter cell and tissue receptiveness in a manner that provides optimal conditions for development, growth and the preservation of health [15]. Unfortunately n-3 status is generally poor—a large global survey of n-3 profiles showed that Europe has very low blood levels (<4%) of EPA+DHA in erythrocytes, increasing chronic disease risk [16]."

-Nutritional Insight Limited, London, United Kingdom
-Edited by: Alessio Molfino, Sapienza University of Rome, Italy
-Reviewed by: Annette Lucy West, University of Southampton, United Kingdom; Caroline Elizabeth Childs, University of Southampton, United Kingdom

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6861329

n-3 fatty acids and human health: defining strategies for public policy

"The last quarter of the 20th century was characterized by an increase in the consumer's interest in the nutritional aspects of health. As a result, governments began to develop dietary guidelines in addition to the traditional recommended dietary allowances, which have been superseded now by dietary reference intakes. In addition to governments, various scientific societies and nongovernmental organizations have issued their dietary advice to combat chronic diseases and obesity. Human beings evolved on a diet that was balanced in n-6 and n-3 essential fatty acid intake, whereas Western diets have a ratio of n-6/n-3 of 16.74. The scientific evidence is strong for decreasing the n-6 and increasing the n-3 intake to improve health throughout the life cycle. This paper discusses the reasons for this change and recommends the establishment of a Nutrition and Food Policy, instead of a Food and Nutrition Policy, because the latter subordinates the nutritional aspects to the food policy aspects. Nutrition and food planning comprise a tool of nutrition and food policy, whose objectives are the achievement of the adequate nutrition of the population as defined by nutritional science. The scientific basis for the development of a public policy to develop dietary recommendations for essential fatty acids, including a balanced n-6/n-3 ratio is robust. What is needed is a scientific consensus, education of professionals and the public, the establishment of an agency on nutrition and food policy at the national level, and willingness of governments to institute changes. Education of the public is essential to demand changes in the food supply."

-Dr. Artemis P. Simopoulos M.D
-The Center for Genetics, Nutrition and Health, Washington, USA.
https://pubmed.ncbi.nlm.nih.gov/11837998

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…"It is well known that the Western diet is relatively poor in n-3 PUFAs [omega-3] and rich in n-6 [omega-6] PUFAs [12]. Because arachidonic acid (ARA, C20:4n-6) is a precursor to proinflammatory mediators, the role of an increased dietary intake of ARA, or of its metabolic precursor (linoleic acid (LA), C18:2n-6), in elevating the inflammatory process is debated [1, 13]"…

"Furthermore, because n-6 and n-3 FAs compete for the same enzyme pathways, their metabolism is largely affected by the availability of the substrates and by the affinity of ALA and LA for the different enzymes. "…

…"These two classes of EFA metabolites are not interconvertible and are metabolically and

functionally distinct, where they have opposite physiological functions; n-6 FA derivatives have prothrombotic, proaggregatory, and proinflammatory properties while the n-3 metabolites have anti-inflammatory, antiproliferative, and antiatherosclerotic activity [12]. As a consequence, the balance of EFAs is important for good equilibrium and function of several tissues and biological machinery."…

-Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy
-Department of Agricultural, Food and Environmental Sciences, University of Perugia, Perugia, Italy
-School of Biological Sciences, The University of Hong Kong, Hong Kong
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7025069/

Omega-3 & Reproduction

Prolonging the female reproductive lifespan and improving egg quality with dietary omega-3 fatty acids

"Women approaching advanced maternal age have extremely poor outcomes with both natural and assisted fertility. Moreover, the incidence of chromosomal abnormalities and birth defects increases with age. As of yet, there is no effective and practical strategy for delaying ovarian aging or improving oocyte quality. We demonstrate that the lifelong consumption of a diet rich in omega-3 fatty acids prolongs murine reproductive function into advanced maternal age, while a diet rich in omega-6 fatty acids is associated with very poor reproductive success at advanced maternal age. Furthermore, even short-term dietary treatment with a diet rich in omega-3 fatty acids initiated at the time of the normal age-related rapid decline in murine reproductive function is associated with improved oocyte quality, while short-term dietary treatment with omega-6 fatty acids results in very poor oocyte quality. Thus, omega-3 fatty acids may provide an effective and practical avenue for delaying ovarian aging and improving oocyte quality at advanced maternal age."

…"Armed with the knowledge that the shift in human dietary habits over the last 100 years toward a very high omega-6 to omega-3 fatty acid ratio is accompanied by a concurrent downward trend in the fertility rates for women over the age of 35 in Western societies (Baird et al., 2005), we sought to determine the impact of a diet rich in omega-3 fatty acids on reproductive success at advanced maternal age. Based on the results of the current study, we now have evidence that mice on an omega-3 fatty acid-rich diet are able to successfully reproduce well beyond the normal expected reproductive lifespan for these animals. Although the average litter was slightly smaller (4.4 ± 1.9 offspring/litter) for dams at advanced maternal age (> 10 months) on the omega-3-rich diet compared to younger cohorts of animals (6.0 ± 2.7

offspring/litter) on the same diet, the survival of the offspring born to dams at advanced maternal age was remarkably high at 89%. In stark contrast, aged animals (> 10 months) maintained on a standard laboratory rodent chow or an omega-6 fatty acid-rich diet (designed to mimic the typical Western diet) had extremely poor reproductive success. These are striking findings and suggest that if this holds true in the human, the increase in dietary omega-6 fatty acids in the human diet over the last 100 years may actually be detrimental to the reproductive success of women of advanced maternal age."

-Department of Surgery and the Vascular Biology Program, Children's Hospital Boston, Boston, MA, 02115, USA
-Department of Surgery, Harvard Medical School, Boston, MA, 02115, USA
-Vincent Center for Reproductive Biology, Department of Obstetrics and Gynecology, Massachusetts General Hospital
-Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Boston, MA, 02115, USA
-Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5624332/

Relevance of Fatty Acids to Sperm Maturation and Quality

"Almost 50% of infertility cases are associated with human male infertility. The sperm membrane is a key structure influencing sperm morphology and function in normal and pathological conditions. The fatty acid profile determines the performance not only of sperm motility but also of acrosomal reaction and sperm-oocyte fusion. This review presents available knowledge on the role of fatty acid composition in human sperm and spermatogenesis and discusses the influence of dietary fatty acids on the sperm fatty acid profile. Recent studies in biological sciences and clinical researches in this field are also reported. The topic object of this review has potential application in medicine by identifying potential causes of infertility."…

"The testes and sperm have a characteristic lipid composition that is highly enriched in PUFAs, predominantly docosapentaenoic acid (DPA, 22:5n-6) in rodents and DHA in humans [25] and other mammals [26–28]. LA and ALA together with their metabolites, EPA and DHA, are deposited in reproductive tissues and potentially influence the reproductive function and fertility. As reported above, in the sperm plasma membrane, lipid composition and the degree of PUFA unsaturation are relevant to the membrane fluidity, flexibility, and receptor function. Such features are largely involved in the membrane fusion events occurring in fertilization. Really, it would be taken into consideration that the lipid component of the spermatozoon membrane, as a part of the membrane microdomains (plasma membrane microdomains are involved in sperm motility, ability to penetrate the zona pellucida, and other capacitation-dependent changes), influences the membrane characteristics that are required for reaching and fusing with the oocyte. Additionally, it has been shown that the n-3 and n-6 PUFAs are essential for the

reproductive activity, representing about 30% to 50% of the total FA amount in the membrane of mammal spermatozoa, and contribute to acrosome responsiveness [28].

In assessing the influence of PUFAs on male reproduction capability, the activity of metabolites generated from PUFAs (PUFA metabolism is reported above) should also be taken into consideration. On this point, prostaglandins and SPM are involved in the regulation of inflammation and infection, with these last ones being processes involved in affecting male fertility [25, 26]. Moreover, the skipped diene structure of the PUFA makes them susceptible to peroxidation and possibly alters the membrane characteristics. In this regard, reduction in human semen quality, as a consequence of smoking, infection, irradiation, varicocele, oligozoospermia, and drug exposure, has been linked to oxidative stress and lipoperoxidation [25].”…

“In recent studies, lack of dietary n-3 PUFAs affected the spermatids. FADS2-KO mice fed with a PUFA-deficient diet except LA and ALA failed to produce mature spermatids and as a result created a defect on the acrosome formation [38]. Iizuka-Hishikawa et al. [11] reported that the loss of lysophosphatidic acid acyltransferase 3 caused a drastic reduction of DHA-containing phospholipids in mouse spermatids and led to excess cytoplasm around its head, which is normally removed by surrounding Sertoli cells via endocytosis in the final stage of spermatogenesis.”…

“Reports suggest that the type of diet potentially contributes to male fertility. Among the nutrients, supplemented carbohydrates and proteins do not have a remarkable effect on male fertility [53]. On the other hand, human and animal studies demonstrated that high intake of unsaturated, saturated, and trans-FAs inversely affected semen quality [54, 55].”

“Dietary fats may influence testicular function. However, most of the published literature on this field used semen quality parameters as the only proxy for testicular function. Minguez-Alarcón et al. [103] reported in healthy young Spanish men that MUFA intake was inversely associated with serum blood levels of testosterone and inhibin B whereas a positive association was observed between the intake of n-6 PUFAs and LH concentrations. In addition, the intake of trans-FAs was associated with lower testosterone. The intake of n-3 PUFAs was positively related to testicular volume while the intake of n-6 PUFAs and trans-FAs was inversely related to testicular volume.

Rats fed with an EFA-deficient diet developed testicular atrophy, and inclusion of LA did not prevent this incident and in fact they became infertile [104]. Separation of Sertoli cells and germ cells from rats fed with a fat-free diet for 9–14 days showed a shift in the lipid profile of both cell types towards a typical EFA deficiency pattern [105].”

…”FAs, available for cellular function and membrane composition, can derive from exogenous

sources or de novo synthesis. In particular, dietary sources of ALA, DHA, and EPA are crucial to maintain an adequate supply in n-3 PUFA metabolism [114, 115].”…

“Spermatogenesis is a complex process that involves the development of spermatozoa in the seminal tubules. The differentiation of spermatogonia into spermatozoa requires the participation of several cell types and the correct FA profile that contributes to a normal spermatogenetic process [117]. The importance of lipid composition, especially phospholipids, in the plasma membrane and semen plasma for spermatozoon function has since long been recognized [72]. PUFA level influences sperm maturation, motility, and acrosome reaction [118], and men with different seminal characteristics due to reproductive pathologies such as varicocele, infections, or others had shown different FA profiles [59]. Particularly, PUFAs may modulate oxidative stress, ROS production, and the inflammatory processes in spermatogenesis.

Sperm FA profiles and the beneficial and detrimental effects of dietary fatty acids are the current focus of research in the field of nutrition and male reproduction. In humans, diet is difficult to standardize, and research is mainly focused on the effect of dietary changes on male reproduction traits using an in vitro approach that does not take into account the dietary effect on spermatogenesis or on animal models.”

-Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy
-Department of Agricultural, Food and Environmental Sciences, University of Perugia, Perugia, Italy
-School of Biological Sciences, The University of Hong Kong, Hong Kong
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7025069/

The effects of vitamin D and omega-3 fatty acids co-supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in patients with gestational diabetes.

“Overall, vitamin D and omega-3 fatty acids co-supplementation for 6 weeks among GDM women had beneficial effects on some biomarkers of inflammation, oxidative stress and pregnancy outcomes.”

-Department of Gynecology and Obstetrics, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.
-Endocrinology and Metabolism Research Center, Department of Gynecology and Obstetrics, School of Medicine, Arak University of Medical Sciences, Arak, Iran.
-Department of Gynecology and Obstetrics, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran.
-Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran.
-Barij Medicinal Plants Research Center, Kashan, Iran.

-Anatomical Sciences Research Center, Kashan University of Medical Sciences, Kashan, Iran.
-Department of Gynecology and Obstetrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
https://www.ncbi.nlm.nih.gov/pubmed/29299042

Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions

"The corollaries of the obesity epidemic that plagues developed societies are malnutrition and resulting biochemical imbalances. Low levels of essential n-3 polyunsaturated fatty acids (n-3 PUFAs) have been linked to neuropsychiatric diseases, but the underlying synaptic alterations are mostly unknown. We found that lifelong n-3 PUFAs dietary insufficiency specifically ablates long-term synaptic depression mediated by endocannabinoids in the prelimbic prefrontal cortex and accumbens. In n-3-deficient mice, presynaptic cannabinoid CB(1) receptors (CB(1)Rs) normally responding to endocannabinoids were uncoupled from their effector G(i/o) proteins. Finally, the dietary-induced reduction of CB(1)R functions in mood-controlling structures was associated with impaired emotional behavior. These findings identify a plausible synaptic substrate for the behavioral alterations caused by the n-3 PUFAs deficiency that is often observed in western diets."

-INSERM U862, Physiopathology of Synaptic Plasticity Group, Neurocentre Magendie, Bordeaux Cedex, France.
https://pubmed.ncbi.nlm.nih.gov/21278728/

Omega-3 Supplements

"Docosahexaenoic acid (DHA) [omega-3] is uniquely concentrated in the brain, and is essential for its function, but must be mostly acquired from diet. **Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol, whereas the transporter at blood brain barrier is specific for phospholipid form of DHA**. Here we show that oral administration of DHA to normal adult mice as lysophosphatidylcholine (LPC) (40mg DHA/kg) for 30 days increased DHA content of the brain by >2-fold. In contrast, the same amount of free DHA did not increase brain DHA, but increased the DHA in adipose tissue and heart. Moreover, LPC-DHA treatment markedly improved the spatial learning and memory, as measured by Morris water maze test, whereas free DHA had no effect. The brain derived neurotrophic factor increased in all brain regions with LPC-DHA, but not with free DHA. These studies show that dietary LPC-DHA efficiently increases brain DHA content and improves brain function in adult mammals, thus providing a novel nutraceutical approach for the prevention and treatment of neurological

diseases associated with DHA deficiency, such as Alzheimer's disease."

-Department of Medicine, University of Illinois at Chicago
-Department of Anatomy and Cell Biology, University of Illinois at Chicago
-Jesse Brown VA Medical Center
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5596017/

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"Unfortunately, not only medications but also dietary supplements or nutraceuticals could lead to adverse effects. Despite the benefits listed above, there are potential risks associated with excessive usage of n-3 PUFAs. Important potential adverse effects include altered platelet function. The presence of EPA and DHA leads to the production of thromboxane A3, which is a less potent platelet activator than thromboxane A2. Supplementation of EPA and DHA, therefore, may affect platelet activation because of the different eicosanoids produced, which leads to an antithrombotic effect that causes detrimental effects for wound healing [100]. The potential for adverse effects on wound healing may be at its greatest immediately after trauma or surgery. The effect on wound healing likely depends on the amount and the duration of supplementation, and the severity of the wound. Another side effect can be represented by lipid peroxidation. Lipid peroxidation is characterized by a free radical attack on an unsaturated fatty acid and can occur in the presence of oxygen. Long-chain, highly unsaturated fatty acids such as EPA and DHA, which accumulate in cell membranes, are at high risk of peroxidation. If antioxidants are not provided at adequate concentrations, membrane phospholipid fatty acids can be vulnerable to peroxidation and free radicals can form as a result. Lipid peroxidation can be detrimental because of effects on the stability of cell membranes and also as a result of free radical attacks on proteins and DNA [101]. The effects of lipid peroxidation can be avoided by supplementing diets enriched in n-3 PUFAs with antioxidants. Further problems may come from toxin exposure (given the potential presence not only of useful marine bioactives [102,103,104] but also of sea contaminants) and nutrient-drug interactions. In humans, the interaction with simvastatin was displayed and a decrease in its blood lipid concentrations was observed [105]. For other medication, nutrient-drug interactions may exacerbate adverse effects that can occur with n-3 PUFAs supplementation alone. N-3 PUFAs supplementation is contra-indicated during antiplatelet and anticoagulant treatment because of the synergistic effect on bleeding times when administered together [106].

Clinicians should understand the adverse effects that may occur with n-3 PUFAs supplementation, and that potential risks should be assessed in conjunction with the potential benefits. Adverse effects are likely to be dose-dependent. It is necessary to understand the necessary dosages and which dietary concentration to aim for, when recommending n-3 PUFAs

supplementation."

-Human and Clinical Nutrition Unit, Department of Medical, Oral and Biotechnological Sciences, University G. D'Annunzio, 66100 Chieti, Italy;

-Cardiology Unit, Cardiology Department, San Camillo De Lellis Hospital, Manfredonia, Foggia, Italy

-Department of Internal and Specialistic Medicine DIBIMIS, University of Palermo, Palermo, Italy;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6357022/

Omega-3s & Pregnancy

…"We now know that major changes have taken place in the food supply over the last 100 years, when food technology and modern agriculture led to enormous production of vegetable oils high in ω-6 fatty acids, and changed animal feeds from grass to grains, thus increasing the amount of ω-6 fatty acids at the level of LA (from oils) and arachidonic acid (AA) (from meat, eggs, dairy). This led to very high amounts of ω-6 fatty acids in the food supply for the first time in the history of human beings.[11–13] Traditionally, animals grazed. Grass contains ALA (ω-3), whereas grains, corn and soya (which are now fed to animals) are high in LA (ω-6). This imbalance in the amount of ω-6 and ω-3 fatty acids is a new phenomenon that was never a part of human evolution11 (figure 1, table 2). Human beings evolved on a diet that had equal amounts of ω-6 and ω-3 fatty acids. This balanced ratio of ω-6 to ω-3 is critical to human development during pregnancy and lactation, in the prevention of chronic diseases and in their management.9 14 15 The typical Western diet now provides an ω-6 to ω-3 ratio of around 16:1. High dietary intake of ω-6 fatty acids as occurs today leads to increases in white adipose tissue and chronic inflammation, which are the 'hallmarks of obesity'.[7 8] ω-6 and ω-3 fatty acids specifically metabolise to prostaglandins, thromboxane and leukotrienes. Prostaglandin E2 from AA leads to differentiation and proliferation of adipose tissue and prostaglandin F2α also from AA prevents the browning of white adipose tissue, which is the good fat tissue as it increases thermogenesis, burning fat through the release of heat.[7 8 16]"…

-The Center for Genetics, Nutrition and Health, Washington, DC, USA

-Saint Luke's Mid America Heart Institute, Kansas, Missouri, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5093368/

Maternal DHA equilibrium during pregnancy and lactation is reached at an erythrocyte DHA content of 8 g/100 g fatty acids

"Low long-chain PUFA (LC-PUFA, or LCP) consumption relates to suboptimal neurodevelopment,

coronary artery disease, and [postpartum (PP)] depression. Maternal-to-infant LCP transport during pregnancy and lactation is at the expense of maternal status, a process known as biomagnification. Despite biomagnification, maternal and infant LCP status generally declines during lactation.

To assess the

1) turning point of biomagnification [level from which maternal (m)LCP status exceeds infant (i)LCP status];

2) LCP equilibrium (steady-state-level from which mRBC-LCP stop declining during lactation);

3) corresponding iLCP-status; and

4) the relationship between RBC-DHA and RBC-arachidonic acid (AA), we measured RBC-fatty acids in 193 Tanzanian mother-infant pairs with no, intermediate (2-3 times/wk), and high (4-5 times/wk) freshwater fish consumption at delivery and after 3 mo of exclusive breast-feeding. At 3 mo, mRBC-DHA was lower than the corresponding iRBC-DHA up to a mRBC-DHA of 7.9 g%. mRBC-DHA equilibrium, with equivalent mRBC-DHA at both delivery and at 3 mo PP, occurred at 8.1 g%. This mRBC-DHA equilibrium of 8.1 g% corresponded with an iRBC-DHA of 7.1-7.2 g% at delivery that increased to 8.0 g% at 3 mo. We found between-group differences in mRBC-AA; however, no differences in iRBC-AA were observed at delivery or 3 mo. Relations between RBC-DHA and RBC-AA were bell-shaped.

We conclude that, at steady-state LCP intakes during lactation:

1) biomagnification occurs up to 8 g% mRBC-DHA;

2) mRBC-DHA equilibrium is reached at 8 g%;

3) mRBC-DHA equilibrium corresponds with an iRBC-DHA of 7 g% at delivery and 8 g% after 3 mo;
4) unlike RBC-DHA, mRBC-AA and iRBC-AA are independently regulated in these populations; and
5) bell-shaped RBC-DHA vs. RBC-AA-relations might support uniform iRBC-AA. A (maternal) RBC-DHA of 8 g% might be optimal for infant neurodevelopment and adult cardiovascular disease incidence."

-Laboratory Medicine, University Medical Center Groningen, 9700 RB, Groningen, The Netherlands.
https://pubmed.ncbi.nlm.nih.gov/21270355

Omega-6 & Reproduction

…"This study was the first to investigate the relationship between the intake of FAs and pregnancy outcome among pregnant women in Korea. Despite adequate levels of omega-3 FAs,

women who had high levels of omega-6 FAs tended to have lower birth weight infants. Therefore, reducing excessive omega-6 FAs intake of pregnant women in Korea will improve maternal nutritional status and also have more positive outcomes of pregnancy."

-Department of Nutritional Science and Food Management, Ewha Womans University, Seoul, South Korea

-Department of Nutrition Consultation, Seoul National University Hospital, Healthcare System Gangnam Center, Seoul, South Korea

-Department of Occupational and Environmental Medicine, Ewha Womans University, College of Medicine, Seoul, South Korea

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5911376

Oral Cancer

"Background and purpose: The primary cannabinoids, Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and Delta(8)-tetrahydrocannabinol (Delta(8)-THC) are known to disturb the mitochondrial function and possess antitumor activities. These observations prompted us to investigate their effects on the mitochondrial O(2) consumption in human oral cancer cells (Tu183). This epithelial cell line overexpresses bcl-2 and is highly resistant to anticancer drugs."…

Key results: A rapid decline in the rate of respiration was observed when Delta(9)-THC or Delta(8)-THC was added to the cells. The inhibition was concentration-dependent, and Delta(9)-THC was the more potent of the two compounds. Anandamide (an endocannabinoid) was ineffective; suggesting the effects of Delta(9)-THC and Delta(8)-THC were not mediated by the cannabinoidreceptors. Inhibition of O(2) consumption by cyanide confirmed the oxidations occurred in the mitochondrial respiratory chain. Delta(9)-THC inhibited the respiration of isolated mitochondria from beef heart.

Conclusions and implications: These results show the cannabinoids are potent inhibitors of Tu183 cellular respiration and are toxic to this highly malignant tumor."

-Department of Pediatricsy, State University of New York, Upstate Medical University, Syracuse, NY, USA.

https://pubmed.ncbi.nlm.nih.gov/20516734/

Organs

…"Endocannabinoids are important regulators of organ homeostasis."…

-Institutes of Physiology I and Molecular Psychiatry, Life and Brain Center, University of Bonn, Bonn, Germany

-Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz,

Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3831960

■■■

"Endocannabinoids and cannabinoid CB1 receptors are known to play a generalized role in energy homeostasis. However, clinical trials with the first generation of CB1 blockers, now discontinued due to psychiatric side effects, were originally designed to reduce food intake and body weight rather than the metabolic risk factors associated with obesity. In this review, we discuss how, in addition to promoting energy intake, endocannabinoids control lipid and glucose metabolism in several peripheral organs, particularly the liver and adipose tissue. Direct actions in skeletal muscle and pancreas are also emerging. This knowledge may help in the design of future therapies for the metabolic syndrome."

-Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Italy
https://pubmed.ncbi.nlm.nih.gov/23562074/

Osteoarthritis

"Osteoarthritis (OA) is associated with inflammation, chronic pain, functional limitations, and psychosocial distress. High Omega-3 (n-3) polyunsaturated fatty acids (PUFAs) are associated with lower levels of inflammatory mediators, anti-nociception, and adaptive cognitive/emotional functioning. High Omega-6 (n-6) PUFAs are associated with inflammation, nociception, and psychological distress. While findings related to n-3 supplementation in knee OA are mixed, consideration of the n-6:n-3 ratio and additional outcome measures may provide improved understanding of the potential relevance of these fatty acids in OA. Based on recommended and typical ranges of the n-6:n-3 ratio, we hypothesized that in adults with knee pain, those with a high n-6:n-3 ratio would have greater pain/functional limitations, experimental pain sensitivity, and psychosocial distress compared to those with a low n-6:n-3 ratio."

…"In adults with knee pain, a high n-6:n-3 ratio is associated with greater clinical pain/functional limitations, experimental pain sensitivity, and psychosocial distress compared to a low ratio group. Findings support consideration of the n-6:n-3 PUFA ratio and additional clinical endpoints in future research efforts."

-Department of Aging & Geriatric Research, University of Florida, Gainesville, FL, USA
-Pain Research & Intervention Center of Excellence, University of Florida
-Department of Anesthesia, Cincinnati Children's Hospital, Cincinnati, OH, USA
-Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL, USA

-Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, FL, USA
-Department of Biostatistics, University of Florida, Gainesville, Florida, USA
-Department of Psychology, University of Alabama at Birmingham, AL, USA
-Department of Medicine/ Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, AL, USA
-College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, USA
-Center of Excellence for Stress and Mental Health (CESAMH)
-VA San Diego Healthcare System
-University of California, San Diego, CA, USA
-Department of Medicine, University of Florida, Gainesville, FL, USA
-Biostatistics Department, School of Public Health University of Alabama at Birmingham, AL, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5701880/

Osteoporosis

Fatty acids and osteoarthritis: different types, different effects.

"While the association between obesity and osteoarthritis used to be solely regarded as a result of increased mechanical loading, systemic factors also likely play a role in the pathophysiology of osteoarthritis. Nutrient excess leading to obesity may result in lipotoxicity, which might be involved in the development of osteoarthritis. The different fatty acid types have distinct effects on inflammation. This review focusses on the currently available studies, summarizing the effects of the different fatty acid types on osteoarthritis and involved joint tissues. In animal studies omega-3 polyunsaturated fatty acids reduced the expression of inflammatory markers, cartilage degradation and oxidative stress in chondrocytes. In contrast, these markers were increased upon omega-6 polyunsaturated fatty acid and saturated fatty acid stimulation. Additionally, a decrease in pain and dysfunction was observed upon omega-3 supplementation in cats and dogs. In line, most human in vitro studies show pro-apoptotic and pro-inflammatory actions of saturated fatty acids. While all polyunsaturated fatty acids reduced markers of oxidative stress, omega-3 polyunsaturated fatty acids additionally decreased prostaglandin production. Human intervention studies with omega-3 polyunsaturated fatty acid supplementation may indicate a beneficial effect on pain and function and might be associated with less structural damage. In contrast, an adverse effect of saturated fatty acids on osteoarthritis has been observed. Monounsaturated fatty acids have been infrequently studied and findings are inconclusive. Existing studies indicate a promising effect of especially omega-3 polyunsaturated fatty acids on osteoarthritis signs and symptoms. However, more human intervention studies are warranted to draw robust conclusions."

- Department of clinical epidemiology, Leiden University Medical Center, RC Leiden, The Netherlands.
https://www.ncbi.nlm.nih.gov/pubmed/30081198

Osteoporosis and Fracture Risk

"Omega 3 and omega 6 polyunsaturated fatty acids (PUFAs) may modify bone status by several mechanisms, including opposing effects on inflammatory cytokines, modulation of prostaglandin E2 production, enhancement of calcium transport, and reducing urinary calcium excretion as reviewed by Farina et al. (2011). It is known that PUFAs and their derivatives can serve as ligands for PPAR α and γ, known to inhibit proinflammatory nuclear transcription factor κB (NFκB) and modulate differentiation of MSCs to adipocytes or osteoblasts

Long-chain PUFAs also serve as precursors in the production of proresolving lipid mediators, including lipoxins synthesized from arachidonic acid, and E-series and D-series resolvins synthesized from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), respectively. Lipoxins and resolvins appear to have a myriad of effects that promote the resolution of inflammation, and both classes of lipid mediators have been found to reduce bone loss induced by periodontitis in animal models. DHA was a more potent inhibitor of osteoclast differentiation in RAW 264.7 cells than EPA (Rahman et al., 2008). At this time, although EPA and DHA have potential to reduce age-associated bone loss, evidence from clinical studies is fragmentary and conflicting."

Susan Ettinger, in Nutritional Pathophysiology of Obesity and its Comorbidities, 2017
https://www.sciencedirect.com/topics/neuroscience/omega-6-fatty-acid

Regulation of osteoarthritis by omega-3 (n-3) polyunsaturated fatty acids in a naturally occurring model of disease

"To examine effects of high omega-3 (n-3) polyunsaturated fatty acid (PUFA) diets on development of osteoarthritis (OA) in a spontaneous guinea pig model, and to further characterise pathogenesis in this model. Modern diets low in n-3 PUFAs have been linked with increases in inflammatory disorders, possibly including OA. However, n-3 is also thought to increases bone density, which is a possible contributing factor in OA. Therefore we aim to determine the net influence of n-3 in disease development."

…"Dietary n-3 reduced disease in OA-prone animals. Most cartilage parameters were modified by n-3 diet towards those seen in the non-pathological BS2 strain – significantly active MMP-2, lysyl-pyridinoline and total collagen cross-links – the only exception being pro MMP-9 which was lower in the BS2, yet increased with n-3. GAG content was higher and denatured type II lower in the n-3 group. Subchondral bone parameters in the DH n-3 group also changed towards those

seen in the non-pathological strain, significantly calcium:phosphate ratios and epiphyseal bone density."

"Dietary n-3 PUFA reduced OA in the prone strain, and most disease markers were modified towards those of the non-OA strain, though not all significantly so. Omega-3 did not increase markers of pathology in either strain."

-Matrix Biology, Div. VPII, University of Bristol, Veterinary School, Langford, Bristol BS40 5DU, UK
-Stem Cell Biology, Cellular and Molecular Medicine, University of Bristol, Bristol BS8 1TD, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3176911/

Cannabinoids and the skeleton: from marijuana to reversal of bone loss

"The active component of marijuana, Delta(9)-tetrahydrocannabinol, activates the CB1 and CB2 cannabinoid receptors, thus mimicking the action of endogenous cannabinoids. CB1 is predominantly neuronal and mediates the cannabinoid psychotropic effects. CB2 is predominantly expressed in peripheral tissues, mainly in pathological conditions. So far the main endocannabinoids, anandamide and 2-arachidonoylglycerol, have been found in bone at 'brain' levels. The CB1 receptor is present mainly in skeletal sympathetic nerve terminals, thus regulating the adrenergic tonic restrain of bone formation. CB2 is expressed in osteoblasts and osteoclasts, stimulates bone formation, and inhibits bone resorption. Because low bone mass is the only spontaneous phenotype so far reported in CB2 mutant mice, it appears that the main physiologic involvement of CB2 is associated with maintaining bone remodeling at balance, thus protecting the skeleton against age-related bone loss. Indeed, in humans, polymorphisms in CNR2, the gene encoding CB2, are strongly associated with postmenopausal osteoporosis. Preclinical studies have shown that a synthetic CB2-specific agonist rescues ovariectomy-induced bone loss. Taken together, the reports on cannabinoid receptors in mice and humans pave the way for the development of 1) diagnostic measures to identify osteoporosis-susceptible polymorphisms in CNR2, and 2) cannabinoid drugs to combat osteoporosis."

-Bone Laboratory, the Hebrew University of Jerusalem, Jerusalem, Israel.
https://pubmed.ncbi.nlm.nih.gov/19634029

Cannabinoid receptors and the regulation of bone mass

"A functional endocannabinoid system is present in several mammalian organs and tissues. Recently, endocannabinoids and their receptors have been reported in the skeleton. Osteoblasts, the bone forming cells, and osteoclasts, the bone resorbing cells, produce the endocannabinoids anandamide and 2-arachidonoylglycerol and express CB2 cannabinoid receptors. Although CB2

has been implicated in pathological processes in the central nervous system and peripheral tissues, the skeleton appears as the main system physiologically regulated by CB2. CB2-deficient mice show a markedly accelerated age-related bone loss and the CNR2 gene (encoding CB2) in women is associated with low bone mineral density. The activation of CB2 attenuates ovariectomy-induced bone loss in mice by restraining bone resorption and enhancing bone formation. Hence synthetic CB2 ligands, which are stable and orally available, provide a basis for developing novel anti-osteoporotic therapies. Activation of CB1 in sympathetic nerve terminals in bone inhibits norepinephrine release, thus balancing the tonic sympathetic restrain of bone formation. Low levels of CB1 were also reported in osteoclasts. CB1-null mice display a skeletal phenotype that is dependent on the mouse strain, gender and specific mutation of the CB1 encoding gene, CNR1."

-Bone Laboratory, The Hebrew University of Jerusalem, Jerusalem, Israel.
-Institute of Molecular Psychiatry, University of Bonn, Bonn, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2219540/

Ovarian Cancer

"Ovarian cancer represents one of the leading cause of cancer-related deaths for women and is the most common gynecologic malignancy. In spite of relative low morbidity, ovarian cancer has a high fatality ratio, with overall 5-year survival of less than 30%. At present, there are inadequate treatment options for the management of advanced ovarian cancer, and therefore development of novel approaches for treatment of this disease are needed. Cannabinoids, the active components of Cannabis sativa linnaeous and their derivatives have received considerable attention in recent years due to their diverse pharmacological activities such as cell growth inhibition and tumor regression."…. "These results support a new therapeutic approach for the treatment of ovarian cancer. It is also conceivable that with available cannabinoids as lead compounds, non-habit forming agents that have higher biological effects could be developed."

- American Association for Cancer Research
http://cancerres.aacrjournals.org/content/66/8_Supplement/1084.1
bit.do/aacancer

Ovary

.."These data suggest that AEA [anandamide] is produced in the ovary, is under hormonal control

and plays a role in folliculogenesis, preovulatory follicle maturation, oocyte maturity and ovulation."...

- Endocannabinoid Research Group, Reproductive Sciences Section, Department of Cancer Studies & Molecular Medicine, University of Leicester, Leicester, United Kingdom,

- Assisted Conception Unit, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom,

- Department of Pathology, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2640464/

Overdose

Electrophysiologic properties of lidocaine, cocaine, and n-3 fatty-acids block of cardiac Na+ channels.

"Lidocaine and cocaine, two local anesthetics, and n-3 polyunsaturated fatty acids in fish oils, inhibit the voltage-gated Na(+) channels of cardiomyocytes. This inhibition by lidocaine and n-3 fish oil is associated with antiarrhythmic effects, whereas with cocaine lethal arrhythmias may occur. These electrophysiologic studies show that at the concentrations tested, the n-3 fish oil fatty acids and lidocaine share three actions on I(Na): a potent inhibition of I(Na); a strong voltage-dependence of this inhibition; and a large shift of the steady-state inactivation to hyperpolarized potentials. By contrast cocaine shares only the potent inhibition of I(Na). The voltage-dependence of the inhibition is much decreased with cocaine, which produces only a very small leftward shift of the voltage-dependence of inactivation. The large leftward shift of the steady-state inactivation seems very important in the prevention of fatal arrhythmias by the n-3 fatty acids. Thus, we suggest that it is lack of this effect by cocaine, which is one factor, that eliminates its ability to prevent fatal cardiac arrhythmias. Further we report that in cultured neonatal rat cardiomyocytes n-3 fish oil fatty acids terminate the tachycardia induced by the alpha(1) adrenergic agonist, phenylephrine, whereas cocaine accelerates the tachycardia and causes bouts of tachyarrhythmias."

-Department of Medicine, Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Harvard Medical School, Boston, MA 02215, USA.

https://www.ncbi.nlm.nih.gov/pubmed/14757121

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... "Sparse densities in lower brainstem areas controlling cardiovascular and respiratory functions may explain why high doses of delta 9-tetrahydrocannabinol [THC] are not lethal."

-National Institute of Mental Health, Bethesda, MD
https://pubmed.ncbi.nlm.nih.gov/2308954/

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…"Because cannabinoid receptors, unlike opioid receptors, are not located in the brainstem areas controlling respiration, lethal overdoses from Cannabis and cannabinoids do not occur." …

- National cancer institute
https://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq#section/_11

Oxidative Stress

Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress.

"Oxidative stress with reactive oxygen species generation is a key weapon in the arsenal of the immune system for fighting invading pathogens and initiating tissue repair. If excessive or unresolved, however, immune-related oxidative stress can initiate further increasing levels of oxidative stress that cause organ damage and dysfunction. Targeting oxidative stress in various diseases therapeutically has proven more problematic than first anticipated given the complexities and perversity of both the underlying disease and the immune response. However, growing evidence suggests that the endocannabinoid system, which includes the CB_1 and CB_2 G-protein-coupled receptors and their endogenous lipid ligands, may be an area that is ripe for therapeutic exploitation. In this context, the related nonpsychotropic cannabinoid cannabidiol, which may interact with the endocannabinoid system but has actions that are distinct, offers promise as a prototype for anti-inflammatory drug development. This review discusses recent studies suggesting that cannabidiol may have utility in treating a number of human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types 1 and 2 diabetes, atherosclerosis, Alzheimer disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain."

Department of Pharmacology and Toxicology, School of Medicine, and Center for Excellence in Cardiovascular-Renal Research, University of Mississippi Medical Center, Jackson, MS 39216, USA.
https://www.ncbi.nlm.nih.gov/pubmed/21238581

Fish oil omega-3 polyunsaturated fatty acids attenuate oxidative stress-induced DNA damage in vascular endothelial cells.

"Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), likely prevent cardiovascular disease, however their mechanisms remain unclear. Recently, the role of DNA damage in atherogenesis has been receiving considerable attention. Here, we investigated the effects of EPA and DHA on DNA damage in vascular endothelial cells to clarify their antiatherogenic mechanisms."

…"Our results suggested that EPA and DHA attenuate oxidative stress-induced DNA damage in vascular endothelial cells through upregulation of NRF2-mediated antioxidant response. Therefore omega-3 fatty acids likely help prevent cardiovascular disease, at least in part, by their genome protective properties."

-Department of Cardiovascular Physiology and Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan.

-Department of Cardiovascular Medicine, Fukushima Medical University, Fukushima, Japan.

https://www.ncbi.nlm.nih.gov/pubmed/29121093

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"Oxidative stress and inflammation are commonly present in many chronic diseases. These responses are closely related to pathophysiological processes. The inflammatory process can induce oxidative stress and vice versa through the activation of multiple pathways. Therefore, agents with antioxidant and/or anti-inflammatory activities are very useful in the treatment of many pathologies."…

-Research Unit in Environmental and Evolutionary Biology (URBE), Institute of Life, Earth and Environment (ILEE), University of Namur, Belgium.

-Pharmacology Department, Hanoi University of Pharmacy, Vietnam.

-VNU University of Science, Vietnam National University, Vietnam.

-Faculty of Fisheries, Vietnam National University of Agriculture, Vietnam.

https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32106612/

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…"Therefore, in contrast with previous reports in the literature, these results demonstrate that omega3 fatty acids reduce in vivo oxidant stress in humans."

-Department of Medicine and the West Australian Heart Research Institute, University of Western Australia, Perth, Australia

https://www.ncbi.nlm.nih.gov/pubmed/10905544

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…"There is accumulating evidence that supports a key role for the ECS in the modulation of ROS [Reactive Oxygen Species] production in different cell types. For example, extensive work carried out investigating the neuroprotective properties of cannabinoid ligands has revealed a crucial link between the ECS and redox homeostasis [57–60]. For example, anandamide has been reported to attenuate neurotoxicity in response to oxidative stress [58,61]. "…

-Division of Cell Signalling and Immunology, Sir James Black Centre, School of Life Sciences, University of Dundee, Dundee, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4852457

Baseline Oxidative Stress Is Associated with Memory Changes in Omega-3 Fatty Acid Treated Coronary Artery Disease Patients

"N-3 [omega-3] PUFA treatment may be more likely to improve immediate recall in patients with greater oxidative stress."

-MD Program, University of Toronto, Toronto, ON, Canada

-Hurvitz Brain Sciences Program, Sunnybrook Research Institute and Department of Psychiatry, University of Toronto, Toronto, ON, Canada

-Centre for Addiction and Mental Health and Departments of Psychiatry and Pharmacology/Toxicology, University of Toronto, Toronto, ON, Canada

-Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, ON, Canada

-Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, ON, Canada

-University Health Network at Toronto Rehabilitation Institute, Toronto, ON, Canada

-Hurvitz Brain Sciences Program, Sunnybrook Research Institute and Departments of Psychiatry and Pharmacology/Toxicology, University of Toronto, Toronto, ON, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5688343/

■■■

…"Antioxidant defense systems, including antioxidant enzymes, influence oxidative stress. Elevated oxidative stress can induce production of reactive oxygen species (ROS), malondialdehyde (MDA), 8-Hydroxy-2-deoxyguanosine (8-OHdG) and isoprostanes [64, 69], each of which can activate various transcription factors, including NF-κB, AP-1, p53, and STAT. Thus, this cascade can increase expression of genes encoding growth factors, inflammatory cytokines, and chemokines [70]. Oxidative stress is associated with the pathogenesis of multiple diseases, such as cardiovascular disease, cancer, diabetes, hypertension, aging, and atherosclerosis. Therefore, oxidative stress products can also be used as markers of the inflammatory response."…

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University,

Wenjiang, Chengdu, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

■■■

…"Oxidative stress induces nuclear factor (NF-κB), which is a transcription factor and causes inflammation."…

-Department of Cosmetic Raw Materials Chemistry, Medical University of Lodz, Lodz, Poland
-Department of Cosmetology and Aesthetic Dermatology, Medical University of Lodz, Lodz, Poland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4440198/

See also Omega-3 Supplements

Oxylipins

…"Oxylipins are fatty acids that have been converted into lipid signaling molecules by enzymes in the body. The omega-6 fatty acid arachidonic acid, and the omega-3 fatty acids EPA and DHA, are converted into a wide variety of oxylipins with diverse and important signaling pathways that mediate a number of biological functions (Funk 2001).

Most of the functions of oxylipins derived from arachidonic acid, also called eicosanoids, are well known and primarily associated with immuno-stimulatory events (which stimulate the immune system) and pro-coagulant actions (which promote blood coagulation). However, the actions of these oxylipins are typically oversimplified as "pro-inflammatory," when, in fact, over 90 bioactive omega-3 and omega-6 oxylipins with both pro- and anti-inflammatory effects are produced by enzymes — cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP).

Pro-inflammatory, pro-coagulant and immuno-stimulatory oxylipins are produced acutely in response to a diverse array of stimuli, such as injury to a blood vessel wall in order to initiate repair and immune cell recruitment, or to initiate blood clotting in response to injury to prevent hemorrhage (fig. 2). An injury to the vessel wall leads to an influx of calcium ions into the cell, which in turn stimulates the action of an intracellular enzyme that cleaves fatty acids from phospholipids (complex lipids that make up the cell membrane). This is followed by conversion of the released fatty acid into oxylipins, which initiate the recruitment of immune cells and stimulate signaling pathways to repair the injury via paracrine (signaling between neighboring cells) and autocrine (signaling within the same cell) pathways. Finally, after the injury has been repaired, the released fatty acids are converted into oxylipins that terminate the immuno-

stimulatory and repair mechanisms.

The interplay of the various oxylipins produces results in nuanced responses to specific events over the course of an injury such that the net physiological effect of the complex combination of oxylipins is key, rather than the absolute concentration of any one of the oxylipins alone (Serhan and Savill 2005). Because oxylipins initiate and terminate various immune responses in different body tissues, they are important players in diseases such as heart disease, chronic inflammation, autoimmune disorders and cancer."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

P

Pacemaker

"Low-voltage-activated or T-type Ca2+ channels (T-channels) are widely expressed, especially in the central nervous system where they contribute to **pacemaker** activities and are involved in the pathogenesis of epilepsy. Proper elucidation of their cellular functions has been hampered by the lack of selective pharmacology as well as the absence of generic endogenous regulations. We report here that both cloned (α1G, α1H and α1I subunits) and native T-channels are blocked by the endogenous cannabinoid, anandamide. **Anandamide, known to exert its physiological effects through cannabinoid receptors, inhibits T-currents independently from the activation of CB1/CB2 receptors, G-proteins, phospholipases and protein kinase pathways.** Anandamide appears to be the first endogenous ligand acting directly on T-channels at submicromolar concentrations. Block of anandamide membrane transport by AM404 prevents T-current inhibition, suggesting that anandamide acts intracellularly. Anandamide preferentially binds and stabilizes T-channels in the inactivated state and is responsible for a significant decrease of T-currents associated with neuronal firing activities. Our data demonstrate that anandamide inhibition of T-channels can regulate neuronal excitability and account for CB receptor-independent effects of this signaling molecule."

-IGH-CNRS UPR, 1142–141 rue de la Cardonille, F-34396 Montpellier cedex 05, France
-Department of Pharmacology, University of Virgina, 1300 Jefferson Park Avenue, Charlottesville, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC125779/

Paget's Disease

Also known as Osteitis Deformans

"Paget's disease of bone is a chronic bone disorder. Normally, there is a process in which your bones break down and then regrow. In Paget's disease, this process is abnormal. There is excessive breakdown and regrowth of bone. Because the bones regrow too quickly, they are bigger and softer than normal."

-MedlinePlus
-U.S. National Library of Medicine
https://medlineplus.gov/pagetsdiseaseofbone.html

■■■

"The possibility of an inflammatory cause of Paget disease is supported by evidence of clinical improvement after treatment with anti-inflammatory medications. Elevated *parathyroid hormone* in Paget disease also has been observed, but no firm evidence links the 2 disorders, and one case of Paget disease was diagnosed in a patient with idiopathic hypoparathyroidism. An osteogenic mechanism also has been proposed. Autoimmune, connective tissue, and vascular disorders are proposed as other possible etiologies."...

-Dr. Mujahed M Alikhan, MD;
-Chief Editor: Dr. Herbert S Diamond, MD
https://www.medscape.com/answers/334607-182919/what-is-the-role-of-inflammation-in-the-etiology-of-paget-disease

See also Osteoporosis

Pain

The Endocannabinoid System as a Potential Therapeutic Target for Pain Modulation

"The discovery of CB1 and CB2 receptors, their endogenous ligands (endocannabinoids), and the processes responsible for the biosynthesis, release, transport and metabolism of these compounds were a huge help in understanding the role of endocannabinoids in various physiological and pathological conditions, including pain modulation. Elevating endocannabinoid

levels locally by the inhibition of endocannabinoid degrading enzymes, FAAH and MAGL, using pharmacological agents, and thereby reducing the unwanted central effects of exogenous cannabinoids, also made an additional contribution to this knowledge."...

Dr. Ahmet Ulugöl - Department of Medical Pharmacology, Trakya University Faculty of Medicine, Edirne, Turkey
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4115931/

"The n-6 arachidonic acid (n-6 AA) derivatives 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamine (AEA) (Figure 1) have complex relationships with chronic pain and psychological distress. 2-AG and AEA act as endogenous ligands for cannabinoid receptors (i.e., endocannabinoids) to produce analgesic and anxiolytic effects [1, 8, 12, 33]."

-Section on Nutritional Neurosciences, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

-Department of Physical Medicine and Rehabilitation, Program on Integrative Medicine, University of North Carolina, Chapel Hill, NC,USA

-Center for Drug Discovery and Departments of Chemistry and Chemical Biology and Pharmaceutical Sciences, Northeastern University, Boston, MA, USA

-Department of Neurology, Program on Integrative Medicine, University of North Carolina, Chapel Hill, USA

-Nutrition Research and Metabolism Core, North Carolina Translational Clinical Sciences Institute, University of North Carolina, Chapel Hill, USA

-Anesthesia Section, Department of Perioperative Medicine, Clinical Center, National Institutes of Health, Bethesda, MD, USA

-Nutrition Department, Clinical Center, National Institutes of Health (NIH), Bethesda, MD 20892, USA

-Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4522350/

"Mammalian tissues contain at least two types of cannabinoid receptor, CB(1) and CB(2), both coupled to G proteins. CB(1) receptors are expressed mainly by neurones of the central and peripheral nervous system whereas CB(2) receptors occur centrally and peripherally in certain non-neuronal tissues, particularly in immune cells. The existence of endogenous ligands for cannabinoid receptors has also been demonstrated. The discovery of this 'endocannabinoid system' has prompted the development of a range of novel cannabinoid receptor agonists and antagonists, including several that show marked selectivity for CB(1) or CB(2) receptors. It has also been paralleled by a renewed interest in cannabinoid-induced antinociception. This review summarizes current knowledge about the ability of cannabinoids to produce antinociception in animal models of acute pain as well as about the ability of these drugs to suppress signs of tonic pain induced in animals by nerve damage or by the injection of an inflammatory agent. Particular attention is paid to the types of pain against which cannabinoids may be effective, the distribution pattern of cannabinoid receptors in central and peripheral pain pathways and the

part that these receptors play in cannabinoid-induced antinociception. The possibility that antinociception can be mediated by cannabinoid receptors other than CB(1) and CB(2) receptors, for example CB(2)-like receptors, is also discussed as is the evidence firstly that one endogenous cannabinoid, anandamide, produces antinociception through mechanisms that differ from those of other types of cannabinoid, for example by acting on vanilloid receptors, and secondly that the endocannabinoid system has physiological and/or pathophysiological roles in the modulation of pain."

-Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Scotland, Aberdeen, UK.
https://pubmed.ncbi.nlm.nih.gov/11164622/

Pain & Inflammation

The Endocannabinoid System, Cannabinoids, and Pain

"The endocannabinoid system is involved in a host of homeostatic and physiologic functions, including modulation of pain and inflammation. The specific roles of currently identified endocannabinoids that act as ligands at endogenous cannabinoid receptors within the central nervous system (primarily but not exclusively CB1 receptors) and in the periphery (primarily but not exclusively CB2 receptors) are only partially elucidated, but they do exert an influence on nociception. Exogenous plant-based cannabinoids (phytocannabinoids) and chemically related compounds, like the terpenes, commonly found in many foods, have been found to exert significant analgesic effects in various chronic pain conditions. Currently, the use of Δ9-tetrahydrocannabinol is limited by its psychoactive effects and predominant delivery route (smoking), as well as regulatory or legal constraints. However, other phytocannabinoids in combination, especially cannabidiol and β-caryophyllene, delivered by the oral route appear to be promising candidates for the treatment of chronic pain due to their high safety and low adverse effects profiles. This review will provide the reader with the foundational basic and clinical science linking the endocannabinoid system and the phytocannabinoids with their potentially therapeutic role in the management of chronic pain."

-Professor of Anesthesiology, Pain Research and Management Centers, Department of Anesthesiology, School of Medicine, University of Utah, Salt Lake City, Utah, USA
-Chief Executive Officer, ISA Scientific, Draper, Utah, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3820295/

"Arachidonic acid-derived prostaglandins not only contribute to the development of inflammation as intercellular pro-inflammatory mediators, but also promote the excitability of the peripheral somatosensory system, contributing to pain exacerbation. Peripheral tissues undergo many forms of diseases that are frequently accompanied by inflammation. The somatosensory nerves innervating the inflamed areas experience heightened excitability and generate and transmit pain signals. Extensive studies have been carried out to elucidate how prostaglandins play their roles for such signaling at the cellular and molecular levels. Here, we briefly summarize the roles of arachidonic acid-derived prostaglandins, focusing on four prostaglandins and one thromboxane, particularly in terms of their actions on afferent nociceptors. We discuss the biosynthesis of the prostaglandins, their specific action sites, the pathological alteration of the expression levels of related proteins, the neuronal outcomes of receptor stimulation, their correlation with behavioral nociception, and the pharmacological efficacy of their regulators. This overview will help to a better understanding of the pathological roles that prostaglandins play in the somatosensory system and to a finding of critical molecular contributors to normalizing pain."….

-Department of Psychiatry and Program in Neuroscience, McLean Hospital, Harvard Medical School, Belmont, MA USA

-Department of Biomedical Engineering, Hanyang University, Seoul,South Korea

-Department of Biomedical Sciences, Korea University, Seoul,South Korea

-Department of Physiology, College of Medicine, Korea University, Seoul, South Korea

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6975075/

Expression of the endocannabinoid system in fibroblasts and myofascial tissues

"The endocannabinoid (eCB) system, like the better-known endorphin system, consists of cell membrane receptors, endogenous ligands and ligand-metabolizing enzymes. Two cannabinoid receptors are known: CB(1) is principally located in the nervous system, whereas CB(2) is primarily associated with the immune system. Two eCB ligands, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are mimicked by cannabis plant compounds. The first purpose of this paper was to review the eCB system in detail, highlighting aspects of interest to bodyworkers, especially eCB modulation of pain and inflammation. Evidence suggests the eCB system may help resolve myofascial trigger points and relieve symptoms of fibromyalgia. However, expression of the eCB system in myofascial tissues has not been established. The second purpose of this paper was to investigate the eCB system in fibroblasts and other fascia-related cells. The investigation used a bioinformatics approach, obtaining microarray data via the GEO database

(www.ncbi.nlm.nih.gov/geo/). GEO data mining revealed that fibroblasts, myofibroblasts, chondrocytes and synoviocytes expressed CB(1), CB(2) and eCB ligand-metabolizing enzymes. Fibroblast CB(1) levels nearly equalled levels expressed by adipocytes. CB(1) levels upregulated after exposure to inflammatory cytokines and equiaxial stretching of fibroblasts. The eCB system affects fibroblast remodeling through lipid rafts associated with focal adhesions and dampens cartilage destruction by decreasing fibroblast-secreted metalloproteinase enzymes. In conclusion, the eCB system helps shape biodynamic embryological development, diminishes nociception and pain, reduces inflammation in myofascial tissues and plays a role in fascial reorganization. Practitioners wield several tools that upregulate eCB activity, including myofascial manipulation, diet and lifestyle modifications, and pharmaceutical approaches."

-Department of Osteopathic Manipulative Medicine, Michigan State University, East Lansing, MI, USA.
https://pubmed.ncbi.nlm.nih.gov/19083670

See also Beta-caryophyllene (β-caryophyllene)

Palmitylethanolamide (PEA)

Antinociceptive activity of the endogenous fatty acid amide, palmitylethanolamide.

"The endogenous fatty acid ethanolamide, palmitylethanolamide, alleviated, in a dose-dependent manner, pain behaviors elicited in mice by injections of formalin (5%, intraplantar), acetic acid (0.6%, 0.5 ml per animal, intraperitoneal, i.p.), kaolin (2.5 mg per animal, i.p.), and magnesium sulfate (120 mg per kg, i.p.). The antinociceptive effects of palmitylethanolamide were prevented by the cannabinoid CB2 receptor antagonist SR144528 [N-([1s]-endo-1.3.3-trimethylbicyclo[2.3.1]heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide], not by the cannabinoid CB1 receptor antagonist SR141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide x HCl]. By contrast, palmitylethanolamide had no effect on capsaicin-evoked pain behavior or thermal nociception. The endogenous cannabinoid, anandamide (arachidonylethanolamide), alleviated nociception in all tests (formalin, acetic acid, kaolin, magnesium sulfate, capsaicin and hot plate). These effects were prevented by the cannabinoid CB1 receptor antagonist SR141716A, not the cannabinoid CB2 receptor antagonist SR141716A. Additional fatty acid ethanolamides (oleylethanolamide, myristylethanolamide, palmitoleylethanolamide, palmitelaidylethanolamide) had little or no

effect on formalin-evoked pain behavior, and were not investigated in other pain models. These results support the hypothesis that endogenous palmitylethanolamide participates in the intrinsic control of pain initiation. They also suggest that the putative receptor site activated by palmitylethanolamide may provide a novel target for peripherally acting analgesic drugs."

Department of Experimental Pharmacology, University of Naples, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/11426841

Palmitic acid

Classified by U.S National Library of Medicine as an Irritant

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"Palmitic acid is found naturally in palm oil and palm kernel oil, as well as in butter, cheese, milk and meat."

-U.S National Library of Medicine
https://pubchem.ncbi.nlm.nih.gov/compound/Palmitic-acid

■■■

"Palmitic acid (PA), an abundant dietary saturated fatty acid, contributes to obesity and hypothalamic dysregulation in part through increase in oxidative stress, insulin resistance, and neuroinflammation. Increased production of reactive oxygen species (ROS) as a result of PA exposure contributes to the onset of neuronal apoptosis. "…

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5399885/

apoptosis - death of cells

Cannabinoid receptor 1 mediates palmitic acid-induced apoptosis via endoplasmic reticulum stress in human renal proximal tubular cells.

The endocannabinoid system (ECS) is activated at the onset of obesity and diverse metabolic diseases. Endocannabinoids mediate their physiological and behavioral effects by activating specific cannabinoid receptors, mainly cannabinoid receptor 1 (CB(1)R). Diabetic nephropathy (DN) is induced by apoptosis , and renal proximal tubule cells are an important site for the onset of DN. However, the pathophysiology of CB(1)R, especially in the hyperlipidemia of DN, has not been elucidated. Therefore, we examined the effect of **palmitic acid (PA)** on CB(1)R expression

and its related signal pathways in human renal proximal tubular cells (HK-2 cells). PA significantly increased CB(1)R mRNA and protein levels and induced CB(1)R internalization. PA-induced activation of CB(1)R is prevented by the treatment of AACOCF(3) (a cPLA(2) inhibitor), indomethacin and NS398 (a COX 2 inhibitors). Indeed, PA increased cPLA(2), and COX-2 but not COX-1. We also investigated whether the PA-induced activation of CB(1)R is linked to apoptosis. As a result, AM251 (a CB(1)R antagonist) [synthetic cannabinoid] attenuated PA-mediated apoptosis in a concentration-dependent manner. Furthermore, PA decreased GRP78 [glucose-regulated protein] expression and induced increases in the endoplasmic reticulum (ER) stress signaling pathways p-PERK, p-eIF2α, p-ATF4, and CHOP, which were blocked by AM251 treatment. Moreover, PA increased the Bax/Bcl-2 ratio, cleaved PARP, and caspase-3 levels. The PA-induced apoptotic effects were decreased with CB(1)R-specific antagonist (AM251) treatment and CB1 si-RNA transfection. In conclusion, PA induced apoptosis through ER stress via CB(1)R expression in human proximal tubule cells. Our results provide evidence that CB(1)R blockade may be a potential anti-diabetic therapy for the treatment of DN.

Bio-therapy Human Resources Center, Department of Veterinary Physiology, College of Veterinary Medicine, Chonnam National University, Gwangju, Korea.
https://www.ncbi.nlm.nih.gov/pubmed/20506110

apoptosis - cell death

hyperlipidemia - an abnormally high concentration of fats or lipids in the blood. (From Oxford / Google)

Palm Oil

Biological and Nutritional Properties of Palm Oil and Palmitic Acid: Effects on Health

“A growing body of evidence highlights the close association between nutrition and human health. Fat is an essential macronutrient, and vegetable oils, such as palm oil, are widely used in the food industry and highly represented in the human diet. Palmitic acid, a saturated fatty acid, is the principal constituent of refined palm oil. In the last few decades, controversial studies have reported potential unhealthy effects of palm oil due to the high palmitic acid content. In this review we provide a concise and comprehensive update on the functional role of palm oil and palmitic acid in the development of obesity, type 2 diabetes mellitus, cardiovascular diseases and cancer. The atherogenic potential of palmitic acid and its stereospecific position in triacylglycerols are also discussed.”

-Dipartimento di Scienze Motorie e del Benessere, Università di Napoli “Parthenope”, via Medina 40, Napoli, Italy

-CEINGE Biotecnologie Avanzate s.c.a r.l., via G. Salvatore 486, Napoli, Italy
-Dipartimento di Scienze e Tecnologie Ambientali Biologiche Farmaceutiche, Seconda Università degli Studi di Napoli, via G. Vivaldi 42, Caserta, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6331788/

Palmitoylethanolamide (PEA)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5429331/

Pancreatic Cancer

"Pancreatic cancer is cancer that forms in the cells of the pancreas. Pancreatic cancer begins in the tissues of your pancreas — an organ in your abdomen that lies behind the lower part of your stomach. Your pancreas releases enzymes that aid digestion and produces hormones that help manage your blood sugar."

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/pancreatic-cancer/symptoms-causes/syc-20355421

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"Effective strategies for preventing and treating cancer depend not only upon understanding genetic and exposure-induced factors, but also physiological factors that drive disease. DNA damage, caused by endogenous metabolites and exogenous agents, promotes mutations, a key driver of phenotypic changes that potentiate metastasis and enable recurrence after treatment [1]. While significant progress has been made in terms of understanding how genes and exposures modulate the risk of mutations, relatively little is known about the potential role of tissue physiology in modulating the risk of mutations in vivo. Of particular interest is the inflammatory state, a critical cancer risk factor that is associated with sweeping changes in tissue architecture due to immune cell infiltration and associated changes in the levels of cytokines and reactive oxygen and nitrogen species (RONS) [2–4]. Inflammation is a well-established tumor promoter that contributes to cancer growth, angiogenesis, and resistance to apoptosis [2,5]. In addition to the role of inflammation in cancer progression, it is increasingly recognized that inflammation-induced DNA damage may also drive mutations that contribute to both initiation and progression [3,6]. With recent advances that enable analysis of key factors that impact the risk

of mutation [7], here, we set out to determine how interactions between DNA damage and inflammation-induced physiological changes impact the risk of mutations in vivo."…

…"Pancreatic inflammation is a key risk factor for pancreatic cancer [11,16], one of the most deadly cancers; most patients who initially respond to radio-chemotherapy suffer relapse, such that only ~ 5% of patients survive more than 5 years after diagnosis [17]. Inflammation-induced DNA damage potentially plays an important role in driving mutations that enable pancreatic cancer initiation and recurrence. During inflammation there are high levels of RONS, which can induce cytotoxic and mutagenic DNA lesions, including abasic sites, oxidized bases (e.g., 8oxoG), deaminated bases (e.g., uracil and hypoxanthine) and ethenoadenine (eA) [18,19]. In addition to base damage, RONS also induce DNA double strand breaks (DSBs). DSBs are among the most toxic of DNA lesions and they can also be potently mutagenic due to the potential loss of vast stretches of chromosomes if not accurately repaired [1,20]."…

- Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

- Singapore–MIT Alliance for Research and Technology, Singapore,

-Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA- University of Washington, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4372043/

Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study

"Background: Meat intake has been associated with risk of exocrine pancreatic cancer, but previous findings have been inconsistent. This association has been attributed to both the fat and cholesterol content of meats and to food preparation methods. We analyzed data from the prospective Multiethnic Cohort Study to investigate associations between intake of meat, other animal products, fat, and cholesterol and pancreatic cancer risk."…

"Conclusion: Red and processed meat intakes were associated with an increased risk of pancreatic cancer. Fat and saturated fat are not likely to contribute to the underlying carcinogenic mechanism because the findings for fat from meat and dairy products differed. Carcinogenic substances related to meat preparation methods might be responsible for the positive association."

-Cancer Research Center of Hawaii, Honolulu, HI, USA.

https://pubmed.ncbi.nlm.nih.gov/16204695

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“Pancreatic cancer ranks as one of the most fatal forms of cancer, and therefore, new strategies aimed at improving the prognosis of this deadly disease are warranted. Recently, it was shown that cannabinoid administration leads to apoptosis of pancreatic tumor cells via CB2 receptor and ceramide-dependent up-regulation of p8 and ATF-4 and TRB3 stress–related genes (7). Another study showed that CB1 receptor antagonist AM251–induced cell death in pancreatic MIAPaCa-2 cells occurred via receptor-independent manner (19). Although the two studies describe contrasting mechanism of action of cannabinoids, both underline the importance of cannabinoids for the treatment of pancreatic cancer. In depth studies are therefore warranted to identify the mechanism of action of cell death induced by cannabinoids in pancreatic cancer.”

-Chemoprevention Program, Paul P. Carbone Comprehensive Cancer Center and Department of Dermatology, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin USA.

https://pubmed.ncbi.nlm.nih.gov/18199524/

Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes

“Pancreatic adenocarcinomas are among the most malignant forms of cancer and, therefore, it is of especial interest to set new strategies aimed at improving the prognostic of this deadly disease. The present study was undertaken to investigate the action of cannabinoids, a new family of potential antitumoral agents, in pancreatic cancer. We show that cannabinoid receptors are expressed in human pancreatic tumor cell lines and tumor biopsies at much higher levels than in normal pancreatic tissue. Studies conducted with MiaPaCa2 and Panc1 cell lines showed that cannabinoid administration (a) induced apoptosis, (b) increased ceramide levels, and (c) up-regulated mRNA levels of the stress protein p8. These effects were prevented by blockade of the CB(2) cannabinoid receptor or by pharmacologic inhibition of ceramide synthesis de novo. Knockdown experiments using selective small interfering RNAs showed the involvement of p8 via its downstream endoplasmic reticulum stress-related targets activating transcription factor 4 (ATF-4) and TRB3 in Delta(9)-tetrahydrocannabinol-induced apoptosis. Cannabinoids also reduced the growth of tumor cells in two animal models of pancreatic cancer. In addition, cannabinoid treatment inhibited the spreading of pancreatic tumor cells. Moreover, cannabinoid administration selectively increased apoptosis and TRB3 expression in pancreatic tumor cells but not in normal tissue. In conclusion, results presented here show that cannabinoids lead to apoptosis of pancreatic tumor cells via a CB(2) receptor and de novo synthesized ceramide-dependent up-regulation of p8 and the endoplasmic reticulum stress-related genes ATF-4 and TRB3. These findings may contribute to set the basis for a new therapeutic approach for the

treatment of pancreatic cancer."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, c/José Antonio Novais s/n, Madrid, Spain.

https://pubmed.ncbi.nlm.nih.gov/16818650/

Chronic stress accelerates pancreatic cancer growth and invasion: A critical role for beta-adrenergic signaling in the pancreatic microenvironment

"Pancreatic cancer cells intimately interact with a complex microenvironment that influences pancreatic cancer progression. The pancreas is innervated by fibers of the sympathetic nervous system (SNS) and pancreatic cancer cells have receptors for SNS neurotransmitters which suggests that pancreatic cancer may be sensitive to neural signaling. In vitro and non-orthotopic in vivo studies showed that neural signaling modulates tumour cell behavior. However the effect of SNS signaling on tumor progression within the pancreatic microenvironment has not previously been investigated. To address this, we used in vivo optical imaging to non-invasively track growth and dissemination of primary pancreatic cancer using an orthotopic mouse model that replicates the complex interaction between pancreatic tumor cells and their microenvironment. Stress-induced neural activation increased primary tumor growth and tumor cell dissemination to normal adjacent pancreas. These effects were associated with increased expression of invasion genes by tumor cells and pancreatic stromal cells. Pharmacological activation of β-adrenergic signaling induced similar effects to chronic stress, and pharmacological β-blockade reversed the effects of chronic stress on pancreatic cancer progression. These findings indicate that neural β-adrenergic signaling regulates pancreatic cancer progression and suggest β-blockade as a novel strategy to complement existing therapies for pancreatic cancer."…

-Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Australia

-Department of Visceral Surgery and Medicine, University Hospital Bern, Bern, Switzerland

-Centre for Drug Candidate Optimisation, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Australia

-Department of Mathematics and Statistics, The University of Melbourne, Parkville, Australia

-Clinic of Surgery, Cantonal Hospital, Schaffhausen, Switzerland

-Department of Pathology, The University of Melbourne, Parkville, Australia

-Department of Cancer Anaesthesia and Pain Medicine, Peter MacCallum Cancer Centre, East Melbourne, Australia

-Cousins Center for PNI, Semel Institute for Neuroscience and Human Behavior, UCLA AIDS Institute and Jonsson Comprehensive Cancer Center, University of California Los Angeles, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4102665

….“Pancreatic cancer (PC) remains one of the most lethal of malignancies and a major health burden [121], and is the fourth most common cause of death from cancer in the US [118]. There is a strong link between antecedent CP and PC [122]. CP leads to fibrosis, which is a common pathological feature and major risk factor for PC [123]. Pancreatic cancer results from dysregulation of oncogenes and tumor suppressor genes, as well as growth factors and their receptors, including epidermal growth factors, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and many cytokines, such as TGF-β, IL-1, IL-6, TNF-α, and IL-8, which modulate pathways involved in growth and differentiation [124, 125]. Shi, et al. has showed that VEGF is upregulated by low extracellular PH (acidosis), which occurs frequently around necrotic regions in tumors, and that acidosis activates IL-8 [126]. VEGF and IL-8 are important angiogenic factors in PC [126], and acidosis-promoted upregulation of these genes can be mediated through NF-κB and AP-1 transactivation and cooperation [127].”…

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, Chengdu, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

Pancreatitis

“The pancreas is a large gland behind the stomach and close to the first part of the small intestine. It secretes digestive juices into the small intestine through a tube called the pancreatic duct. The pancreas also releases the hormones insulin and glucagon into the bloodstream. Pancreatitis is inflammation of the pancreas. It happens when digestive enzymes start digesting the pancreas itself. Pancreatitis can be acute or chronic. Either form is serious and can lead to complications. Acute pancreatitis occurs suddenly and usually goes away in a few days with treatment.”…

- Medline Plus

- U.S National Library of Medicine

https://medlineplus.gov/pancreatitis.html

Inhibitory mechanism of omega-3 fatty acids in pancreatic inflammation and apoptosis

“Oxidative stress is regarded as a major pathogenic factor in acute pancreatitis. Inflammation

and apoptosis linked to oxidative stress has been implicated in cerulein-induced pancreatitis as an experimental model of acute pancreatitis. Recently, we found that reactive oxygen species mediate inflammatory cytokine expression and apoptosis of pancreatic acinar cells stimulated with cerulein. Omega-3 fatty acids show antioxidant action in various cells and tissues. In the present study, we investigated whether omega-3 fatty acids inhibit cytokine expression in cerulein-stimulated pancreatic acinar cells and whether omega-3 fatty acids suppress apoptotic cell death in pancreatic acinar cells exposed to hydrogen peroxide. We found that omega-3 fatty acids, such as docosahexaenoic acid (DHA) and alpha-linolenic acid (ALA), suppressed the expression of inflammatory cytokines (IL-1beta, IL-6) and inhibited the activation of transcription factor activator protein-1 in cerulein-stimulated pancreatic acinar cells. DHA and ALA inhibited DNA fragmentation, inhibited the decrease in cell viability, and inhibited the expression of apoptotic genes (p53, Bax, apoptosis-inducing factor) induced by hydrogen peroxide in pancreatic acinar cells. In conclusion, omega-3 fatty acids may be beneficial for preventing oxidative stress-induced pancreatic inflammation and apoptosis by inhibiting inflammatory cytokine and apoptotic gene expression of pancreatic acinar cells."

-Department of Food and Nutrition, Brain Korea 21 Project, College of Human Ecology, Yonsei University, Seoul, Korea.

https://pubmed.ncbi.nlm.nih.gov/19723085/

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…"Pancreatitis, caused by pancreatic duct obstruction, trypsinogen gene mutation, or alcoholism, is an inflammatory disease of the pancreas [117]. Acute pancreatitis (AP) incidence ranges from 4–45 per 100,000 patients per year and increases annually by approximately 1.3–4.0% in most developed countries. AP is one of the most common gastrointestinal causes for hospitalization in the US, and chronic pancreatitis (CP) is less common than AP. However, CP patients experience chronic abdominal pain and exocrine and/or endocrine insufficiency, leading to reduced quality of life [118]. Pancreatitis is characterized by acinar cell destruction and activation of inflammatory cells, including macrophages, neutrophils, and granulocytes, which secrete inflammatory cytokines [117, 119]. These cytokines further activate pancreatic stellate cells (PSCs) to promote CP [120]. Pancreatitis development requires various molecular pathways, such as NF-κB, MAPK, and JAK-STAT, which play critical roles in inflammatory cell activation during pancreatitis [117]."…

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu, China

- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, Chengdu, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548/

Acute pancreatitis promotes the generation of two different exosome populations

"Acute pancreatitis is a frequent illness, being the 3rd leading cause of hospitalization due to gastrointestinal disease[1]. It is an inflammatory process of the pancreas that, in the severe forms, is related to systemic inflammatory response and organ failure[2]. Currently there is no specific treatment available for pancreatitis beyond supportive care[3]. This fact points to an incomplete understanding of the pathological mechanisms involved in the disease. From the first description of acute pancreatitis in 1895, it has been evaluated a number of mediators potentially involved in the progression of the disease from the local pancreatic damage to systemic inflammation. Along these years, hydrolytic enzymes, hormones, oxygen free radicals, cytokines, bioactive lipids and virtually any known molecule that can be suspected to have a role in the process, have been analyzed[4,5,6,7]. Unfortunately, this knowledge has not turned into the development of useful pharmacological treatments for the management of the disease.

Some of the lost pieces of this puzzle involve those mediators that do not circulate in a soluble form but packaged in microvesicles, including extracellular vesicles and exosomes. Exosomes are small extracellular vesicles that range between 30–200nm in diameter that act as intercellular messengers by transferring signaling molecules, including proteins, small RNAs and lipids, to target cells. A number of studies have provided evidence of their implication in the pathogenesis of several diseases, being cancer and inflammation the fields in which exosome research has more expanded the last years[8]. In particular, the role of exosomes in the progression of acute pancreatitis from the local damage to the systemic inflammation has been described[9,10].

In previous studies, using an experimental model of taurocholate-induced acute pancreatitis in rats, we reported the generation and release to the bloodstream of a particular population of exosomes with the ability to reach and activate alveolar macrophages9. Interestingly, the proteomic analysis of exosomes purified from plasma of rats with acute pancreatitis did not showed the presence of pancreatic proteins. By contrast, it revealed a significant amount of proteins of supposedly hepatic origin, including apolipoproteins, mannose-binding protein or hemoglobin subunits. These observations suggest that, during acute pancreatitis, liver could be the source of exosomes that activate the inflammatory response in the lung. On the other hand, although we identified in the ascitic fluid the presence of exosomes allegedly released by the pancreas, it still remains to determine its composition and its potential role in the systemic effects of acute pancreatitis.

Here we characterized the two different populations of exosomes generated in an experimental model of acute pancreatitis in rats. The first one, purified from ascitic fluid, is generated by the pancreas while the second population of exosomes, collected from plasma, appeared to be

released by the liver. We observed that, in addition to remarkable differences in protein and micro-RNA (mi-R) content, these exosomes showed significant differences in body distribution as well as in their physiopathological roles."

-Department of Experimental Pathology, Institut d'Investigacions Biomèdiques de Barcelona, Consejo Superior de Investigaciones Científicas (IIBB-CSIC), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

-Gastrointestinal & Pancreatic Oncology Group, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd)-IDIBAPS-Hospital Clínic de Barcelona, Barcelona, Spain

-Proteomics Facility, Institut d'Investigacions Biomèdiques de Barcelona (IIBB), Consejo Superior de Investigaciones Científicas/Universitat Autònoma de Barcelona (CSIC/UAB), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

-Pancreatic Unit, Department of Gastroenterology, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL - Fundación FISABIO), Alicante, Spain

https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC6934470

Parkinson's Disease

Transgenic conversion of omega-6 into omega-3 fatty acids in a mouse model of Parkinson's disease.

"We have recently identified a neuroprotective role for omega-3 polyunsaturated fatty acids (n-3 PUFAs) in a toxin-induced mouse model of Parkinson's disease (PD). Combined with epidemiological data, these observations suggest that low n-3 PUFA intake is a modifiable environmental risk factor for PD. In order to strengthen these preclinical findings as prerequisite to clinical trials, we further investigated the neuroprotective role of n-3 PUFAs in Fat-1 mice, a transgenic model expressing an n-3 fatty acid desaturase converting n-6 PUFAs into n-3 PUFAs. Here, we report that the expression of the fat-1 transgene increased cortical n-3:n-6 PUFA ratio (+28%), but to a lesser extent than dietary supplementation (92%). Such a limited endogenous production of n-3 PUFAs in the Fat-1 mouse was insufficient to confer neuroprotection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity as assessed by dopamine levels, tyrosine hydroxylase (TH)-positive neurons and fibers, as well as nigral Nurr1 and dopamine transporter (DAT) mRNA expression. Nevertheless, higher cortical docosahexaenoic acid (DHA) concentrations were positively correlated with markers of nigral dopaminergic neurons such as the number of TH-positive cells, in addition to Nurr1 and DAT mRNA levels. These associations are consistent with the protective role of DHA in a mouse model of PD. Taken together, these data suggest that dietary intake of a preformed DHA supplement is more effective in reaching

the brain and achieving neuroprotection in an animal model of PD."

-Centre de Recherche du CHUL (CHUQ), Axe Neurosciences, Québec, QC, Canada.
https://www.ncbi.nlm.nih.gov/pubmed/21115966

Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties

"We have recently demonstrated that two plant-derived cannabinoids, Delta9-tetrahydrocannabinol and cannabidiol (CBD), are neuroprotective in an animal model of Parkinson's disease (PD), presumably because of their antioxidant properties. To further explore this issue, we examined the neuroprotective effects of a series of cannabinoid-based compounds, with more selectivity for different elements of the cannabinoid signalling system, in rats with unilateral lesions of nigrostriatal dopaminergic neurons caused by local application of 6-hydroxydopamine. We used the CB1 receptor agonist arachidonyl-2-chloroethylamide (ACEA), the CB2 receptor agonist HU-308, the non-selective agonist WIN55,212-2, and the inhibitors of the endocannabinoid inactivation AM404 and UCM707, all of them administered i.p. Daily administration of ACEA or WIN55,212-2 did not reverse 6-hydroxydopamine-induced dopamine (DA) depletion in the lesioned side, whereas HU-308 produced a small recovery that supports a possible involvement of CB2 but not CB1 receptors. AM404 produced a marked recovery of 6-hydroxydopamine-induced DA depletion and tyrosine hydroxylase deficit in the lesioned side. Possibly, this is caused by the antioxidant properties of AM404, which are derived from the presence of a phenolic group in its structure, rather than by the capability of AM404 to block the endocannabinoid transporter, because UCM707, another transporter inhibitor devoid of antioxidant properties, did not produce the same effect. None of these effects were observed in non-lesioned contralateral structures. We also examined the timing for the effect of CBD to provide neuroprotection in this rat model of PD. We found that CBD, as expected, was able to recover 6-hydroxydopamine-induced DA depletion when it was administered immediately after the lesion, but it failed to do that when the treatment started 1 week later. In addition, the effect of CBD implied an upregulation of mRNA levels for Cu,Zn-superoxide dismutase, a key enzyme in endogenous defenses against oxidative stress. In summary, our results indicate that those cannabinoids having antioxidant cannabinoid receptor-independent properties provide neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons occurring in PD. In addition, the activation of CB2 (but not CB1) receptors, or other additional mechanisms, might also contribute to some extent to the potential of cannabinoids in this disease."

-Department of Biochemistry and Molecular Biology III, Faculty of Medicine, Complutense University, 28040-Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/17196181/

Inhibition by Anandamide of 6-Hydroxydopamine-Induced Cell Death in PC12 Cells

"6-hydroxydopamine (6-OHDA) is a selective neurotoxin that is widely used to investigate cell death and protective strategies in models of Parkinson's disease. Here, we investigated the effects of the endogenous cannabinoid, anandamide, on 6-OHDA-induced toxicity in rat adrenal phaeochromocytoma PC12 cells. Morphological analysis and caspase-3 activity assay revealed that anandamide inhibited 6-OHDA-induced apoptosis. The protection was not affected by antagonists of either cannabinoid receptors (CB1 or CB2) or the vanilloid receptor TRPV1. Anandamide-dependent protection was reduced by pretreatment with LY294002 (inhibitor of phosphatidylinositol 3-kinase, PI3K) and unaffected by U0126 (inhibitor of extracellularly-regulated kinase). Interestingly, phosphorylation of c-Jun-NH2-terminal kinase (JNK) in cells exposed to 6-OHDA was strongly reduced by anandamide pre-treatment. Furthermore, 6-OHDA induced c-Jun activation and increased Bim expression, both of which were inhibited by anandamide. Together, these data demonstrate antiapoptotic effects of anandamide and also suggest a role for activation of PI3K and inhibition of JNK signalling in anandamide-mediated protection against 6-OHDA."

-School of Natural Sciences, National University of Ireland, Galway, Ireland
-School of Medicine, National University of Ireland, Galway, Ireland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2825649/

Periodontal Disease

See Gum Disease (Periodontal Disease)

Peroxisome proliferator-activated receptors (PPARs)

PPARs and lipid ligands in inflammation and metabolism

"Peroxisome proliferator-activated receptors (PPARs) belong to a family of ligand-activated nuclear receptors that includes the estrogen, thyroid hormone, and glucocorticoid receptors[1].

The PPAR family consists of three subtypes encoded by three separate genes: PPAR-α (NR1C1), PPAR-β/δ (NR1C2), and PPAR-γ (NR1C3). Distinct PPAR subtype tissue distributions[2,3] and unique ligand-binding pockets drive separate but often complementary patterns of gene expression in response to PPAR ligands[4]. PPAR activation occurs upon cognate synthetic or endogenous ligand binding to the ligand-binding domain (LBD). Activated PPARs heterodimerize with retinoid X receptors (RXRs), another class of nuclear receptor, which subsequently bind to the hexameric direct repeat peroxisome proliferator response elements (PPRE)[5,6] and recruit co-activator protein complexes to positively regulate expression of target genes (Figure 1A). PPARs also mediate ligand-dependent repression of inflammatory gene expression through the association with co-repressor protein complexes[7].”…

“The PPAR subtype structural similarities contribute to the partial overlapping function of PPARs across different tissues. In hepatocytes, PPAR-α positively regulates fatty acid β-oxidation, ketogenesis, and gluconeogenesis, while suppressing amino acid catabolism and inflammatory responses8. PPAR-α plays anti-inflammatory roles in smooth muscle cells and vascular endothelial cells[9,10]. PPAR-β/δ (PPAR-δ) plays roles in lipid metabolism[11], fatty acid oxidation and energy dissipation[12], anti-inflammation[13], and colon cancer[14]. PPAR-γ is an essential modulator of fat cell differentiation[15-17] and lipid storage and plays important anti-inflammatory roles in macrophages[18,19] and other tissues such as the colon[20]. PPAR-γ also contributes to insulin sensitivity[21], in part through the regulation of adiponectin, an adipo(cyto)kine that enhances insulin sensitivity[22].”

-Department of Medicine, Division of Digestive Diseases, University of California-Los Angeles, Los Angeles, California, USA

-Department of Cellular and Molecular Medicine, University of California-San Diego, La Jolla, California, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437919

An update on PPAR activation by cannabinoids

“Some cannabinoids activate the different isoforms of PPARs (α, β and γ), as shown through the use of reporter gene assays, binding studies, selective antagonists and knockout studies. Activation of all isoforms, but primarily PPARα and γ, mediates some (but not all) of the analgesic, neuroprotective, neuronal function modulation, anti-inflammatory, metabolic, anti-tumour, gastrointestinal and cardiovascular effects of some cannabinoids, often in conjunction with activation of the more traditional target sites of action such as the cannabinoid CB1 and CB2 receptors and the TRPV1 ion channel. PPARs also mediate some of the effects of inhibitors of endocannabinoid degradation or transport. Cannabinoids may be chaperoned to the PPARs by fatty acid binding proteins. The aims of this review are to update the evidence supporting PPAR

activation by cannabinoids and to review the physiological responses to cannabinoids that are mediated, and not mediated, by PPAR activation.”….

-School of Medicine, Royal Derby Hospital, University of Nottingham
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4882496/

Pesticides

…“Pesticides such as chlorpyrifos and diazinon alter normal eCB [endocannabinoid] system function [152], [153]. We hypothesize that eating organic foods lacking pesticide residues may promote eCB homeostasis. Piperonyl butoxide, which is a synergist added to insecticides such as pyrethrum, is an efficacious but low-potency antagonist of CB1 [154]. Phthalates are plasticizers added to water bottles, tin cans, food packaging, and even the enteric coating of pharmaceutical pills. Phthalates may act as endocrine disruptors and carcinogens. They also block CB1 as allosteric antagonists [155].”…

- GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom,
- Department of Family Medicine, University of Vermont, Burlington, Vermont, United States of America,
- Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei, Pozzuoli, Napoli, Italy,
-St. Joseph's Hospital and Medical Center, United States of America,
https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24622769

Plants

…“The discovery of cannabinoid receptors occurring naturally throughout the vertebrate body and the availability of highly selective and potent canabimimetics led to the identification of a naturally occurring lipid signaling system termed the endocannabinoid system. Interestingly, the endocannabinoid system dates back very long in the evolution because it exists as an ancient plant signaling system regulating the plant immunity-related genes in response to infection and stress [1].”…

-Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, United State
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044336

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“The activation of N-acylphosphatidylethanolamine (NAPE) metabolism in plants appears to be

associated mostly with cellular stresses. In response to pathogen elicitors, NAPE is hydrolzyed by phospholipase-D (PLD), and corresponding medium-chain, saturated N-acylethanolamines (NAEs) are released by plant cells where they act as lipid mediators to modulate ion flux and activate defense gene expression. In desiccated seeds of higher plants, long-chain, saturated and unsaturated NAEs are prevalent, but are rapidly metabolized during the first few hours of imbibition, a period of substantial osmotic stress. NAPE synthesis is increased in seeds during this same period of rapid rehydration. A membrane-bound enzyme designated NAPE synthase has been purified from imbibed cottonseeds and its unusual biochemical properties suggest that it may scavenge free fatty acids in vivo. This feature of NAPE metabolism may be unique to higher plants a may be a mechanism for the rapid recycling of fatty acids back into membrane-associated NAPE. **Altogether, increasing evidence indicates that NAPE metabolism in plants shares functional similarities with NAPE metabolism in animal systems, including signal transduction and cellular protection. In particular, the emerging role of released NAEs as lipid mediators in plant defense signaling represents an intriguing parallel to 'endocannabinoid signaling' in several mammalian cell types.**"

-Department of Biological Sciences, Division of Biochemistry and Molecular Biology, University of North Texas, Denton, TX, USA

https://pubmed.ncbi.nlm.nih.gov/11106793/

Beyond Cannabis: Plants and the Endocannabinoid System

"Plants have been the predominant source of medicines throughout the vast majority of human history, and remain so today outside of industrialized societies. One of the most versatile in terms of its phytochemistry is cannabis, whose investigation has led directly to the discovery of a unique and widespread homeostatic physiological regulator, the endocannabinoid system. While it had been the conventional wisdom until recently that only cannabis harbored active agents affecting the endocannabinoid system, in recent decades the search has widened and identified numerous additional plants whose components stimulate, antagonize, or modulate different aspects of this system. These include common foodstuffs, herbs, spices, and more exotic ingredients: kava, chocolate, black pepper, and many others that are examined in this review."

-PHYTECS, Los Angeles CA, USA.

https://pubmed.ncbi.nlm.nih.gov/27179600/

Plant Based Diet

Effectiveness of omega-3 polyunsaturated fatty acids against microbial pathogens

…"There is a plethora of data that elucidates the antimicrobial value of various phytochemicals and dietary compounds (Morais-Braga et al., 2012; Kalia et al., 2015). Phytochemical compounds are naturally occurring compounds produced by plants and their biological activity has an impact on human health (Babajide et al., 2013; Mukherjee et al., 2013; Moss and Ramji, 2016). Sources include vegetables, legumes, nuts, fruits, and seeds (Nascimento et al., 2000; Wall et al., 2010). Studies have shown that such dietary products can provide humans with nourishment, and are the reservoirs of several therapeutic compounds for various diseases such as cardiovascular diseases, diabetes, hypertension, and cancer (Burlingame et al., 2009; Lopez-Romero et al., 2015; Pagliaro et al., 2015; Mattos et al., 2016; Mileski et al., 2016; Moss and Ramji, 2016). The FAs, among several phytochemical compounds, are equally important for human development and growth. Several types of FAs including omega-3 polyunsaturated FAs (PUFAs) have been found to play significant roles in human eye-and brain-related conditions (Carballeira, 2008; Das, 2008; Richard et al., 2008; Desbois and Smith, 2010; Desbois and Lawlor, 2013)."…

-Department of Microbiology, College of Basic Medical Sciences, Dalian Medical University, Dalian, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5964344

Dietary Protein and Changes in Biomarkers of Inflammation and Oxidative Stress in the Framingham Heart Study Offspring Cohort

"Dietary protein, particularly from plant sources, may be associated with beneficial changes in the inflammatory burden in aging populations."…

"A considerable proportion of dietary protein, notably in most Western populations, comes from animal sources (i.e., dairy, poultry, meat), and some of this protein intake has been shown to be associated with proinflammatory and pro-oxidative states (22, 27–32)."…

-Nutritional Epidemiology, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University
-Tufts University Friedman School of Nutrition Science and Policy, Boston, MA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6483052/

See also Atherosclerosis

Plasticity

"The adaptability of an organism to changes in its environment or differences between its various habitats." - *Oxford Languages / Google*

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"Endogenous cannabinoids (endocannabinoids, eCBs) are ubiquitous regulators of synaptic transmission in the brain, mediating numerous forms of short- and long-term plasticity, and having strong influences on synapse formation and neurogenesis. Their roles as retrograde messengers that suppress both excitatory and inhibitory transmission are well-established. Yet, despite intensive investigation, many basic aspects of the eCB system are not understood. This brief review highlights recent advances, problems that remain unresolved, and avenues for future exploration. While 2-arachidonoylglycerol (2-AG) is probably the major eCB for intercellular CB1R-dependent signalling, anandamide (AEA) has come to the forefront in several novel contexts, both as a dual endovanilloid/endocannabinoid that regulates synaptic transmission acutely and as the source of a steady eCB tone in hippocampus. Complexities in the cellular processing of 2-AG are receiving renewed attention, as they are increasingly recognized as major determinants of how 2-AG affects cells. Long-standing fundamental issues such as the synthesis pathway for AEA and the molecular mechanism(s) underlying cellular uptake and release of eCBs remain problematical."…

-Bradley E Alger

-Departments of Physiology and Psychiatry, University of Maryland School of Medicine, Program in Neuroscience, Baltimore, MD 21201, USA

https://pubmed.ncbi.nlm.nih.gov/22289914

Polyunsaturated Fatty Acids (PUFAs)

Fatty acid; common name	Abbreviation	Short hand
Omega-3	n−3, ω−3	
α-Linolenic acid (alpha-Linolenic acid)	ALA	18:3n-3
Eicosapentaenoic acid	EPA	20:5n-3

Fatty acid; common name	Abbreviation	Short hand
Docosahexaenoic acid	DHA	22:6n-3
Omega-6	n−6, ω−6	
Linoleic acid	LA	18:2n-6
γ-Linolenic acid (gamma-Linolenic acid)	GLA	18:3n-6
Arachidonic acid	AA, ARA	20:4n-6

-Department of Nutritional Sciences, Faculty of Medicine (Bazinet), University of Toronto, Toronto, Ont.
-Division of Cardiac Surgery, Department of Surgery (Chu), Western University, London, Ont.
-Lawson Health Research Institute (Chu), London, Ont.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3971029/

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…"Fatty acids are the main components of lipids and play a key role as structural components of cellular membranes, affecting the physical state of the membranes, as storage lipids and as signaling molecules that impact the immune system in various ways [1]. Oxylipins is the collective term for oxygenated polyunsaturated fatty acids (PUFAs) and metabolites and includes the eicosanoids, which are an important group of oxygenated C20 PUFAs [2]. These compounds represent the prostaglandins, thromboxanes, prostacyclins, leukotrienes, lipoxins, hepoxilins, hydro(pero)xy fatty acids, hydroxylated fatty acids and epoxy derivatives [3,4]. In mammalian cells they are mainly synthesized from eicosatrienoic acid [20:3(n-6), dihomo-γ-linolenic acid (DGLA)], eicosatetraenoic acid [20:4(n-6), arachidonic acid (AA)] and eicosapentaenoic acid [20:5(n-3), EPA] [3] as well as from docosahexaenoic acid [22:6(n-3), DHA] [5]. They are synthesized through the actions of cyclooxygenases (COX) [6], lipoxygenases (LOX) [7], cytochrome P450s (CYP450s) [4,8,9], or non-enzymatic pathways [10]. "…

-Department of Microbial, biochemical and food Biotechnology, University of the Free State, Bloemfontein, South Africa
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3475069/

Effects of Omega-3 Fatty Acids on Immune Cells

"The immune system is a defense system that protects organisms from invading pathogens, such as viruses or bacteria. It comprises a heterogeneous group of cells, i.e., immune cells, as well as cell-independent mechanisms. Immune cells can be broadly divided into two main categories according to their properties and defense mechanisms: cells of the innate and cells of the

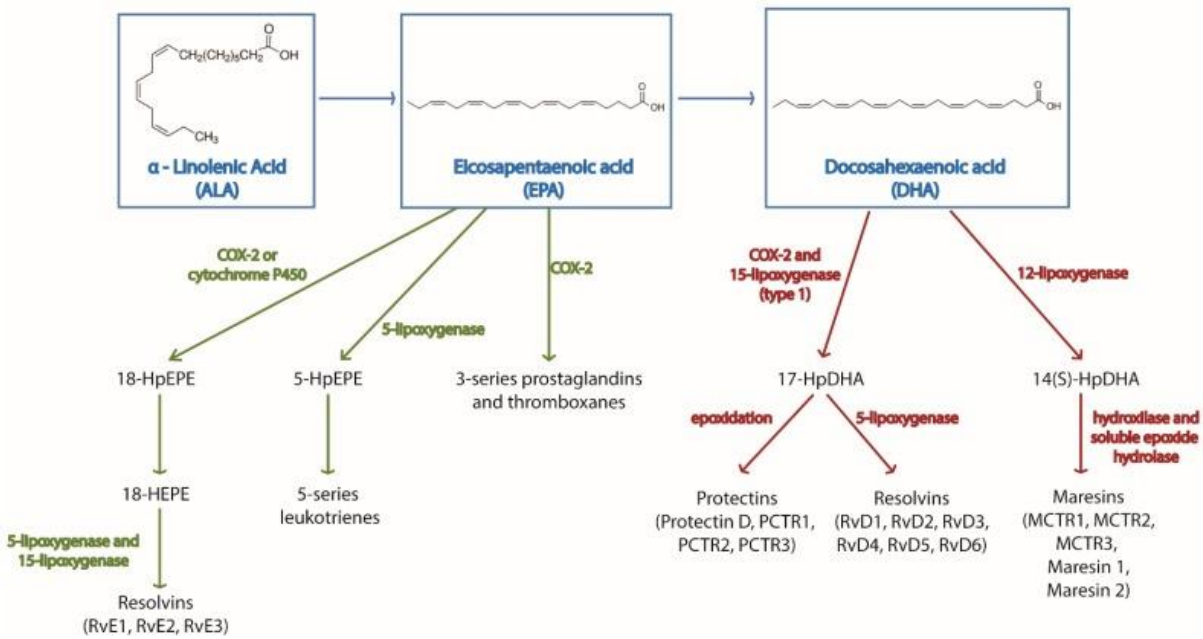
adaptive immune system. Cells from the innate immune system, namely macrophages, neutrophils, eosinophils, basophils, mast cells, natural killer cells, and dendritic cells, are the first cellular line of defense. Their mode of action is generally fast but with limited specificity. Cells from the adaptive immune system, namely B cells and T cells, have a higher level of specificity, but their activation is delayed. However, cells from the adaptive immune system develop memory against pathogens after a first confrontation, and their speed and efficiency against a previously faced pathogen is greatly enhanced during a second encounter.

Coordination of the different immune cells and regulation of their activity is of crucial importance for mounting an effective immune defense. This task is often accomplished by the secretion of cytokines and chemokines, i.e., molecules secreted by cells, including but not restricted to immune cells, that attract immune cells into the site of infection and regulate their activation or their suppression [1,2].

A healthy and balanced diet is essential for the correct function of every part of our organism, including the immune system. Additionally, some dietary factors have been found to have immune-regulatory properties, including micronutrients such as Vitamin D or macronutrients such as fatty acids [3]. The impact of dietary polyunsaturated fatty acids (PUFAs) on the immune system has been investigated for decades, with special focus on the omega-3 PUFAs α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is found in nuts and seeds whereas EPA and DHA are the main components of fish oil [4,5]. For a comprehensive review of the sources of omega-3 fatty acids, we recommend Cholewski et al. [6].

EPA and DHA can also be synthesized from ALA [7], a process that involves several steps orchestrated by multiple elongases, desaturases, and β-oxidases [8]. However, the synthesis of EPA from ALA occurs at a low rate in mammals [9]. Of note, the same enzymes are employed by omega-6 fatty acids for their metabolic pathways.

Both omega-3 and omega-6-derived metabolites have important immune-regulatory functions. These metabolites are generally known as pro-resolving mediators (SPMs) and can be classified



in different families—prostaglandins, leukotrienes, thromboxanes, maresins, protectins, and resolvins. Their synthesis is orchestrated by cyclooxygenase, lipoxygenase, or cytochrome P450 enzymes [10]. A summary of the metabolites produced from omega-3 fatty acids and the enzymes regulating their synthesis is found in Figure 1. Omega-3 and omega-6 substrates compete for these enzymes [11], as well as for the above mentioned elongases and elastases. Therefore, in the presence of omega-3 fatty acids, the competition for the enzymes reduces the synthesis of omega-6-derived metabolites, which also have effects on immune cells. This competition constitutes an additional level of immune-regulation by omega-3 fatty acids."

-Department of Physiology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Sweden

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6834330/

Arachidonic acid and other unsaturated fatty acids and some of their metabolites function as endogenous antimicrobial molecules: A review

…"Our body is endowed with several endogenous anti-microbial compounds such as interferon, cytokines, free radicals, etc. However, little attention has been paid to the possibility that lipids could function as antimicrobial compounds. In this short review, the antimicrobial actions of various polyunsaturated fatty acids (PUFAs, mainly free acids) and their putative mechanisms of

action are described. In general, PUFAs kill microbes by their direct action on microbial cell membranes, enhancing generation of free radicals, augmenting the formation of lipid peroxides that are cytotoxic, and by increasing the formation of their bioactive metabolites, such as prostaglandins, lipoxins, resolvins, protectins and maresins that enhance the phagocytic action of leukocytes and macrophages. Higher intakes of α-linolenic and cis-linoleic acids (ALA and LA respectively) and fish (a rich source of eicosapentaenoic acid and docosahexaenoic acid) might reduce the risk pneumonia. Previously, it was suggested that polyunsaturated fatty acids (PUFAs): linoleic, α-linolenic, γ-linolenic (GLA), dihomo-GLA (DGLA), arachidonic (AA), eicosapentaenoic (EPA), and docosahexaenoic acids (DHA) function as endogenous anti-bacterial, anti-fungal, anti-viral, anti-parasitic, and immunomodulating agents. A variety of bacteria are sensitive to the growth inhibitory actions of LA and ALA in vitro. Hydrolyzed linseed oil can kill methicillin-resistant Staphylococcus aureus. Both LA and AA have the ability to inactivate herpes, influenza, Sendai, and Sindbis virus within minutes of contact. AA, EPA, and DHA induce death of Plasmodium falciparum both in vitro and in vivo. Prostaglandin E1 (PGE1) and prostaglandin A (PGA), derived from DGLA, AA, and EPA inhibit viral replication and show anti-viral activity. Oral mucosa, epidermal cells, lymphocytes and macrophages contain and release significant amounts of PUFAs on stimulation. PUFAs stimulate NADPH-dependent superoxide production by macrophages, neutrophils and lymphocytes to kill the invading microorganisms. Cytokines induce the release of PUFAs from cell membrane lipid pool, a potential mechanism for their antimicrobial action. AA, EPA, and DHA give rise to lipoxins (LXs), resolvins, protectins, and maresins that limit and resolve inflammation and have antimicrobial actions. Thus, PUFAs and their metabolites have broad antimicrobial actions. "…

-Undurti N. Das
-UND Life Sciences, USA
-BioScience Research Centre, GVP College of Engineering Campus, India
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6052656/

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…"Omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFA) are essential fatty acids (EFA) and play a vital role in cellular and physiological functions [1, 2]. They serve key functions in various organ systems and contribute to growth and development, cardiovascular health, immune responses, psychological health as well as the prevention for many diseases [3]. The precursors, both linoleic acid and α-linolenic acid, cannot be synthesized de novo in animals, but must be supplied from the diet. Their longer chain and more unsaturated metabolites are then synthesized from their respective precursors though the synthesis rates are quite low [4, 5].

Despite decades of interest in essential fatty acids, little is known about the complete profiles of

PUFA distribution within viscera and tissues throughout the whole body. It has long been appreciated that particular PUFAs are selectively concentrated in particular organs and tissues, some examples being linoleic acid enrichment in liver [6, 7], α-linolenic acid enrichment in skin and fur [8], docosahaexenoic acid (DHA) in brain [9], and n-6 docosapentaenoic acid (DPAn-6) in testes [10]. Many studies have described PUFA profiles in major organs in young rats [11] such as, rat blood, muscle and some viscera [12], as well as autopsy studies in human subjects [13].”….
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4555191/

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…“The omega-3 fatty acids are a group of polyunsaturated fatty acids defined by a double bond at the third carbon from the methyl end of the carbon chain. Humans do not possess the necessary omega-3 desaturase to add a double bond at the 15th carbon of a long chain fatty acid and are, therefore, unable to endogenously synthesize alpha-linoleic acid (ALA 18:3n-3) and linoleic acid (LA 18:2n-6) making them essential fatty acids. Omega-6 PUFAs are also essential fatty acids and generally have metabolically distinct effects to omega-3 PUFAs. While the human body cannot synthesize omega-3 and omega-6 PUFAs, it does have the capacity to further metabolize these fatty acids through stages of elongation and desaturation. ALA can be metabolized to eicosapentaenoic acid (EPA 20:5n-3) and docosahexaenoic acid (DHA 22:6n-3) by Δ6 desaturase and Δ5 desaturase respectively, while LA is converted to arachidonic acid (AA 22:4n-6). However, the conversion of ALA to DHA is very inefficient with <10% conversion in females and <3% in males [31,32]. While ALA is the preferred substrate for Δ6 desaturase, an abundance of dietary linoleic acid has been shown to suppress conversion of ALA to DHA [33], which may be a confounding factor in these studies. There is recent evidence to suggest that supplementing with stearidonic acid (18:3n-3) may improve the efficiency of conversion to DHA, indicating Δ6 desaturase as a rate limiting step [34]. There is also a degree of individual variation in the lipidome following omega-3 supplementation in humans which may be a factor in the equivocal metabolic changes measured in many human supplementation trials [35].

It is thought that hominids’ diets during the Paleolithic era were high in seafood and low in seeds and vegetable oils, which led to an omega-3/omega-6 ratio of approximately 1:1 [36]. Given the likelihood that early human ancestors’ diets were already high in omega-3 intake it may not have conferred any evolutionary benefit to develop the ability to synthesize omega-3 PUFAs. During the agricultural revolution, with changes to food production in the Neolithic era this n-3/n-6 ratio began to diverge and now in the typical western diet is thought to be as much as 20:1, with omega-3 PUFA intake predominantly from ALA [37]. Although unlikely to be a primary driver, the

divergence in the n-3/n-6 ratio has happened concurrently with the rise in CVD and states of chronic inflammation. Briefly, omega-6 PUFAs are associated with the production of pro-inflammatory mediators while omega-3 PUFAs produce less potent inflammatory mediators and inflammatory resolving proteins and so manipulating this ratio may bring about positive health outcomes.

The potential therapeutic benefit of a diet with high omega-3 content was first observed due to the lower incidence of CVD in Greenland Inuit populations [17]. Subsequent studies observed that a period of omega-3 supplementation reduced risk factors associated with CVD, such as the lowering of plasma triacylglycerides (TAGs) and an increase in high density lipoproteins at the expense of low density lipoproteins, as well as decreasing in platelet aggregation [35,38,39]. Yet, when end point measures such as cardiovascular disease are taken together in a meta-analysis the results of omega-3 supplementation are equivocal [40,41,42,43]. We hypothesize that while a given period of omega-3 supplementation leads to a significant increase in omega-3 content of various tissues it may not be sufficient to dramatically reduce the n-6/n-3 ratio.

The results of studies in animals in which the n-6/n-3 ratio is substantially reduced have been largely positive regarding insulin sensitivity and resolving inflammation."…

-Health and Exercise Sciences Research Group, School of Sport, University of Stirling, Scotland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4663562/

Postpartum Depression

Imbalance between Omega-6 and Omega-3 Polyunsaturated Fatty Acids in Early Pregnancy Is Predictive of Postpartum Depression in a Belgian Cohort

"While studies revealed that the omega-3 polyunsaturated fatty acids (n-3 PUFA) and their mediators would be able to regulate several biological processes involved into the development of postpartum depression (PPD), evidence from observational studies remains mixed. The aim of the present study was to investigate the association between maternal erythrocyte n-3 PUFA, measured in early pregnancy, and the risk of PPD. A Belgian cohort of 72 healthy women was screened. Erythrocyte fatty acids were analysed using gas chromatography. PPD was assessed using the Bromley Postnatal Depression Scale by phone interview one year after delivery. We observed a significant negative association between docosahexaenoic acid (DHA) levels and the risk of postpartum depression in the adjusted model ($p = 0.034$). Higher n-6/n-3 and arachidonic acid (AA)/eicosapentaenoic acid (EPA) ratios were significantly associated with an increased odds

of PPD (p = 0.013 and p = 0.043, respectively). Women with an omega-3 index <5% had a 5-fold increased risk of depressive episode than did those with an omega-3 index ≥5% (OR 5.22 (95% CI 1.24–21.88)). A low n-3 PUFA status, alone and combined with high n-6 PUFA status, in early pregnancy was associated with a greater risk of PPD. Management of maternal n-3 PUFA deficiency can be a simple, safe and cost-effective strategy for the prevention of this major public health issue."

-Department of Public Health, University of Liège, Belgium;
-Department of Obstetrics and Gynecology, CHR Citadelle Hospital, University of Liège
-Metastasis Research Laboratory, GIGA-CANCER, University of Liège
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6521039

■■■

…"The deficits in omega-3 PUFA levels have been reported in other populations with mood disorders, including lower DHA [Docosahexaenoic acid] and total n-3 PUFAs in postpartum depression 31) and lower DHA and EPA in social anxiety disorder.32) "….

-Department of Psychiatry and Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan
-Graduate Institute of Neural and Cognitive Sciences, China Medical University, Taichung, Taiwan
-Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry, Tokyo, Japan
-Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, Korea
-Address for correspondence: Kuan-Pin Su, MD, PhD, Department of Psychiatry, China Medical University Hospital
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4540034

■■■

…"DHA is rapidly accumulated in the brain during gestation and early infancy, and the availability of DHA via transfer from maternal stores impacts the degree of DHA incorporation into neural tissues." …

-DSM Nutritional Products, R&D Human Nutrition and Health, Boulder, CO, USA
-DSM Nutritional Products, R&D Human Nutrition and Health, Basel, Switzerland;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772061/

Since pregnant mothers provide DHA (Docosahexaenoic acid / omega-3s) to the child this could potentially lead to DHA deficiencies in the mother, which would in turn potentially cause more inflammation and depression.

Post-traumatic Stress Disorder (PTSD)

"Posttraumatic stress disorder (PTSD) is now well known to be a function-impairing anxiety syndrome that develops in a subpopulation of individuals who are exposed to a severe emotional trauma or traumas. PTSD is associated with abnormalities in physiological substrates that regulate stress, fear and anxiety."…

-Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA
-Department of Veterans Affairs Medical Center, Cincinnati, OH, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749915/

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…"Overall, there is strong evidence that PTSD is associated with a pro-inflammatory state that may account for the high comorbid disease burden associated with this disorder. There is some evidence that inflammatory proteins may be causal agents for producing some symptoms of PTSD. This has been studied more extensively in depression where there is compelling evidence that elevated cytokine levels are associated with sickness behavior, fatigue, anhedonia, and impaired concentration. The PTSD field is at the beginning stages of understanding how immune factors can contribute to trauma-related symptoms. The evidence to date suggests that immune factors can influence threat reactivity and hyperarousal in addition to sickness behavior. Future studies will need to test this with controlled experimental manipulations to better understand what specific symptoms are provoked by cytokines and what circuits in the brain are affected by trafficking of peripheral cytokines across the blood brain barrier. "…

-National Center for PTSD, VA Medical Center, USA
https://www.ptsd.va.gov/publications/rq_docs/V29N4.pdf

Translational evidence for a role of endocannabinoids in the etiology and treatment of posttraumatic stress disorder.

"Recently, an accumulating body of evidence has implicated the endocannabinoid system in the etiology of PTSD, and targets within this system are believed to be suitable for treatment development."…"There is convincing evidence from multiple studies for reduced endocannabinoid availability in PTSD."… "Of particular relevance is evidence showing reduced levels of the endocannabinoid anandamide"...

- Department of Psychiatry, New York University School of Medicine

- United States Department of Veterans Affairs National Center for Post-traumatic Stress Disorder
http://www.ncbi.nlm.nih.gov/pubmed/25456347

Does cannabis use modify the effect of post-traumatic stress disorder on severe depression and suicidal ideation? Evidence from a population-based cross-sectional study of Canadians

"This study provides preliminary epidemiological evidence that cannabis use may contribute to reducing the association between post-traumatic stress disorder and severe depressive and suicidal states. There is an emerging need for high-quality experimental investigation of the efficacy of cannabis/cannabinoids for the treatment of post-traumatic stress disorder."

-British Columbia Centre on Substance Use, Vancouver, BC, Canada
-School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
-Department of Medicine, University of British Columbia, St. Paul's Hospital, Vancouver, BC, Canada
-British Columbia Centre for Disease Control, Vancouver, BC, Canada
-Department of Psychology, University of British Columbia, Kelowna, BC, Canada
-Department of Epidemiology, Brown University School of Public Health, Providence, RI, USA
https://journals.sagepub.com/doi/10.1177/0269881119882806

The Endocannabinoid System Modulating Levels of Consciousness, Emotions and Likely Dream Contents.

…"In this regard, an accumulative body of evidence in human and animal models has been reported regarding the role of the endocannabinoid system in the control of emotional states and dreams. Moreover, preliminary studies in humans have indicated that treatment with cannabinoids may decrease post-traumatic stress disorder symptoms, including nightmares.

CONCLUSION:

Thus, based on a review of the literature available in PubMed, this article hypothesizes a conceptual framework within which the endocannabinoid system might influence the generation of dream experiences."

-Laboratory of Molecular and Integrative Neurosciences, School of Medicine, Health Sciences Division,Anáhuac Mayab University, Mérida-Progreso Highway
-Aging Research Group, Health Sciences Division, Anahuac Mayab University
-Intercontinental Neuroscience Research Group, Mérida, Yucatán, Mexico.
https://www.ncbi.nlm.nih.gov/pubmed/28240187

Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study.

"These results suggest that abnormal CB1 receptor mediated anandamide signaling is implicated in the etiology of PTSD, and provide a promising neurobiological model to develop novel, evidence-based pharmacotherapies for this disorder…."

"Moreover, there is an emerging body of evidence demonstrating an important role for [cannabinoid 1] CB1 receptor-mediated endocannabinoid signaling in the extinction of aversive memories. Augmenting levels of anandamide in the amygdala modulates short-term fear extinction, thereby resulting in long-term reduction in fear and highlighting the endocannabinoid system as a candidate system for developing novel pharmacotherapies for PTSD. CB1 receptors are the most abundant G-protein-coupled receptors in the central nervous system and are found in high concentrations within an amygdala-hippocampal-cortico-striatal circuit responsible for processing and storing fear-related memories and coordinating fear-related behaviors. Animal studies have shown that chronic stress is associated with decreased brain levels of the endocannabinoid anandamide and CB1 receptor adaptations which in turn give rise to an anxious/depressive phenotype."....

-Molecular Imaging Program, Department of Psychiatry and Radiology, New York University School of Medicine
-Steven and Alexandra Cohen Veterans Center for the Study of Posttraumatic Stress
Traumatic Brain Injury, Department of Psychiatry, New York University Langone Medical Center
-Positron Emission Tomography Center, Department of Diagnostic Radiology, Yale University School of Medicine
-Center for Advanced Medical Imaging Sciences, Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School
-Department of Veterans Affairs National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division
-Department of Psychiatry, Yale University School of Medicine
-Department of Anatomy and Biology, and Biological Chemistry, University of California
-Department of Neurobiology and Child Study Center, Yale University School of Medicine,
-John Hopkins School of Medicine
https://www.ncbi.nlm.nih.gov/pubmed/23670490
bit.do/ptsdstress

When time stands still: an integrative review on the role of chronodisruption in posttraumatic stress disorder.

..."Furthermore, direct and indirect human and animal PTSD research suggests circadian system linked neuroendocrine, immune, metabolic and autonomic dysregulation with blunted diurnal rhythms, specific sleep pattern pathologies and cognitive deficits, as well as **endocannabinoid and neuropeptide Y system alterations** and altered circadian gene expression, linking circadian

misalignment to PTSD pathophysiology."

-Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
-Veterans Affairs Center of Excellence for Stress and Mental Health
-Department of Psychiatry, University of California
-VA San Diego Healthcare System, San Diego, California, USA
-Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin, Berlin, Germany.
http://www.ncbi.nlm.nih.gov/pubmed/25023884

Reductions in Circulating Endocannabinoid Levels in Individuals with Post-Traumatic Stress Disorder Following Exposure to the World Trade Center Attacks

"Endocannabinoid (eCB) signaling has been identified as a modulator of adaptation to stress, and is integral to basal and stress-induced glucocorticoid regulation. Furthermore, interactions between eCBs and glucocorticoids have been shown to be necessary for the regulation of emotional memories, suggesting that eCB function may relate to the development of post-traumatic stress disorder (PTSD)."….

"In conclusion, the finding of reduced concentrations of circulating 2-AG in PTSD is consistent with current biological formulations of PTSD. For example, in addition to the relationship between eCBs (AEA and 2-AG), cortisol and the stress response (Hill and Tasker, 2012), there are substantial interactions between eCBs and other systems found to be dysfunctional in PTSD. CB1 receptors on sympathetic terminals, for instance, regulate noradrenaline release (Ishac et al., 1996), and decrements in eCB signaling at noradrenergic terminals have been shown to result in elevated sympathetic outflow (Srivastava and Lutz, 2012), as is seen in PTSD (Pervanidou and Chrousos, 2010). Furthermore, eCBs (as well as PEA and OEA) possess anti-inflammatory actions (Hansen, 2010), such that reduced eCB signaling could contribute to a basal pro-inflammatory state (Beyer et al., 2010), as has also been documented for PTSD (Spivak et al., 1997; Baker et al., 2001; Plantinga et al., 2013). Finally, eCB signaling promotes the release of NPY (Gamber et al., 2005), which has been demonstrated in association with stress resiliency (Morgan et al., 2000; Yehuda et al., 2006; Sajdyk et al., 2008; Cohen et al., 2012). Reductions in NPY have been found in PTSD (Rasmusson et al., 2000; Sah et al., 2009), which have increased in association with PTSD recovery (Yehuda et al., 2006). Thus, diminished eCB function may additionally result in a deficit in the recruitment of NPY. These biological findings, in the context of known involvement of the eCB system in emotional memory extinction and recall, stress buffering and adaptation, as well as HPA function, suggest the possibility of a pivotal role for the eCB system in PTSD. A deficit in eCB function is consistent with all of the major symptom dimensions of PTSD, and represents a novel candidate system for

further investigation in the pathophysiology and treatment of the disorder. Trials examining the effect of agents that potentiate eCB signaling in PTSD, either alone or in conjunction with treatments that modulate glucocorticoid signaling, will provide proof of principal for the contribution of eCB signaling to PTSD, and will help to elucidate more precisely the respective functional roles of 2-AG and AEA in PTSD development and expression."

-The Hotchkiss Brain Institute and Departments of Cell Biology & Anatomy and Psychiatry, University of Calgary, Calgary AB, Canada-Laboratory of Neuroendocrinology, The Rockefeller University, New York NY USA

-Traumatic Stress Studies Division, Mount Sinai School of Medicine and James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA-Department of Epidemiology, Columbia Mailman School of Public Health, New York, NY, USA

-Neuroscience Research Center and Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee WI, USA

-Direct correspondence to: Matthew N. Hill, Ph.D., Hotchkiss Brain Institute, University of Calgary

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3870889/

Omega-3 Fatty Acids Prevent Post-Traumatic Stress Disorder-Induced Memory Impairment

"Post-traumatic stress disorder (PTSD) is a psychiatric disorder that can happen after exposure to a traumatic event. Post-traumatic stress disorder is common among mental health disorders that include mood and anxiety disorders. Omega-3 fatty acids (OMGs) are essential for the maintenance of brain function and prevention of cognition dysfunctions. However, the possible effect of OMG on memory impairment induced by PTSD has not been studied. In here, such an effect was explored using a rat model of PTSD. The PTSD-like behavior was induced in animals using a single-prolonged stress (SPS) rat model of PTSD (2 h restraint, 20 min forced swimming, 15 min rest, 1–2 min diethyl ether exposure). The OMG was administered orally at a dose of 100 mg omega-3 polyunsaturated fatty acid (PUFA)/100 g body weight/day. Spatial learning and memory were assessed using the radial arm water maze (RAWM) method. Changes in oxidative stress biomarkers, thiobarbituric acid reactive substances (TBARS), and brain derived neuroptrophic factor (BDNF) in the hippocampus following treatments were measured. The results revealed that SPS impaired both short- and long-term memory ($p < 0.05$). Use of OMG prevented memory impairment induced by SPS. Furthermore, OMG normalized SPS induced changes in the hippocampus that reduced glutathione (GSH), oxidized glutathione (GSSG), GSH/GSSG ratios, the activity of catalase, glutathione peroxidase (GPx), and TBARSs levels. In conclusion, the SPS model of PTSD-like behavior generated memory impairment, whereas OMG prevented this impairment, possibly through normalizing antioxidant mechanisms in the hippocampus."...

-Department of Biological Sciences, School of Science, University of Jordan, Amman, Jordan;

-Department of Biology, Yarmouk University, Irbid, Jordan
-Department of Clinical Pharmacy, Jordan University of Science and Technology, Irbid , Jordan;
-Department of Medical Science, Irbid Faculty, Al-Balqa Applied University, Irbid, Jordan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6468674/

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"Several laboratories, including ours, have demonstrated that one very important function of the endocannabinoids is to regulate the response of the brain to stress. Animals and humans need to cope with physical and psychological stresses in order to survive, but stress responses have a cost. For example, we know that long term stress exposure results in depression and post traumatic stress disorder in humans. The endogenous cannabinoid system is a stress buffer, it turns down the hormonal and behavioral responses to stress. In addition, the endocannabinoid system is itself turned on or, in some cases, turned off by stress."

- Dr. Cecilia J. Hillard, PhD, Associate Dean for Research; Professor; Director, Neuroscience Research Center, Medical College of Wisconsin
https://www.mcw.edu/departments/pharmacology-and-toxicology/faculty/cecilia-hillard-phd
bit.do/hillard-phd

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".....NYU School of Medicine, and colleagues are the first to demonstrate through brain imaging that people with PTSD have markedly lower concentrations of at least one of these neurotransmitters -- an endocannabinoid known as anandamide -- than people without PTSD. Their study, which was supported by three grants from the National Institutes of Health, illuminates an important biological fingerprint of PTSD that could help improve the accuracy of PTSD diagnoses, and points the way to medications designed specifically to treat trauma."
-NYU Langone Medical Center
https://www.sciencedaily.com/releases/2013/05/130514085016.htm

PTSD and the Attenuating Effects of Fish Oils: Results of Supplementation After the 2011 Great East Japan Earthquake

"In fact, in an open label trial in patients with physically injury, we previously found that PTSD symptoms were significantly alleviated by taking DHA-rich fish oil [30]."

By Daisuke Nishi, Yuichi Koido, Naoki Nakaya, Toshimasa Sone, Hiroko Noguchi, Kei Hamazaki, Tomohito Hamazaki and Yutaka Matsuoka
https://www.intechopen.com/books/new-insights-into-anxiety-disorders/ptsd-and-the-attenuating-effects-of-fish-oils-results-of-supplementation-after-the-2011-great-east-j

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…"In conclusion, our findings point to FAAH as a contributor to PTSD after PTBI, possibly through the modulation of aversive memories by extinction processes. These data suggest a role for endocannabinoid signaling in the development and maintenance of PTSD and hint at the therapeutic potential of endocannabinoid systems-modulating drugs for PTSD patients.[5]"

-Cognitive Neuroscience Section, National Institute of Neurological Disorders and Stroke–National Institutes of Health, Bethesda, MD, USA

-Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa, Italy

-Magnetic Resonance Research Centre on Nervous System Diseases, University of Genoa, Genoa, Italy

-Department of Molecular Neuroscience, George Mason University, Fairfax, VA, USA

-Department of Psychology, George Mason University, Fairfax, VA, USA

-Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, USA

-Department of Radiology, Johns Hopkins University, Baltimore, MD, USA

-Department of Medicine, Imperial College London, London, UK

-Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

-Traumatic Brain Injury Research Laboratory, Kessler Foundation Research Center, West Orange, NJ, USA

The work was supported by the US National Institute of Neurological Disorders and Stroke intramural research program and a project grant from the US Army Medical Research and Material Command administrated by the Henry M Jackson Foundation (Vietnam Head Injury Study Phase III: a 30-year post-injury follow-up study).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3309545/

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"Posttraumatic stress disorder, an area of large unmet medical needs, is characterized by persistence of fear memories and maladaptive stress responses. In rodents, elevation of the endocannabinoid anandamide due to inhibition of fatty acid amide hydrolase (FAAH) facilitates fear extinction and protects against the anxiogenic effects of stress. "…

…"Our data provide preliminary human evidence that FAAH inhibition can improve the recall of fear extinction memories and attenuate the anxiogenic effects of stress, in a direct translation of rodent findings. The beneficial effects of FAAH inhibition on fear extinction, as well as stress- and affect-related behaviors, provide a strong rationale for developing this drug class as a treatment for posttraumatic stress disorder."….

"Accumulating evidence suggests that the endocannabinoid (eCB) system plays a critical role in the pathophysiology of PTSD. Elevation of the endogenous cannabinoid (eCB) anandamide (AEA)

via inhibition of its main degradative enzyme, fatty acid amid hydrolase (FAAH), promotes the consolidation of fear extinction memories and protects against anxiogenic effects of stress in preclinical models [7, 8, 9, 10, 11, 12, 13]. "

-Center for Social and Affective Neuroscience, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

-Hotchkiss Brain Institute and Mathison Centre for Mental Health Research and Education, Cummings Scool of Medicine, University of Calgary, Calgary, Alberta, Canada

-Department of Cell Biology and Anatomy, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

-Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

https://www.sciencedirect.com/science/article/pii/S0006322319315896

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…"There is also preliminary data indicating that cannabis and related compounds can manage PTSD symptoms related to hyperarousal, anxiety responses to exteroceptive triggers and situational trauma-reminders [(Bremner et al., 1996; Jetly et al., 2015)]. While these clinical observations need to be substantiated in larger, replicate populations, they do hint at stress and anxiety-alleviating effects of cannabis. In fact, cannabis has long been anecdotally noted for its ability to reduce anxiety and elevate mood in non-clinical populations and, in part because of this, eCBs have attracted considerable interest in recent years as a target for a new class of drugs to treat anxiety and stress-related conditions [(Figure 1)]."…

-Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, USA

-Vanderbilt Brain Institute, Vanderbilt University, Nashville, USA

-Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, USA

-Vanderbilt Kennedy Center for Human Development, Vanderbilt University Medical Center, Nashville, USA.

-Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada

-Mathison Centre for Mental Health Research and Education, University of Calgary, Calgary, AB, Canada

-Departments of Cell Biology and Anatomy and Psychiatry, University of Calgary, Calgary, AB, Canada.

-Department of Anatomy and Neurobiology and Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA.

-Max Planck Institute of Psychiatry, Department of Stress Neurobiology & Neurogenetics, Munich, Germany.

-Laboratory of Behavioral and Genomic Neuroscience, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA.

https://www.ncbi.nlm.nih.gov/pubmed/28434588/

Change in blood levels of eicosapentaenoic acid and posttraumatic stress symptom: A secondary analysis of data from a placebo-controlled trial of omega3 supplements

"**Background**: Eicosapentaenoic acid (EPA) is suggested to be protective against posttraumatic stress disorder (PTSD) from two observational studies. We previously conducted a randomized controlled trial and found no effect of docosahexaenoic acid (DHA) for prevention of PTSD. This secondary analysis aimed to determine whether change in blood levels of EPA is associated with PTSD symptoms.

Results: In the omega3 supplements arm, changes in EPA+DHA (p=.023) and EPA (p=.001) as well as the EPA:AA ratio (p=.000) and EPA: DHA ratio (p=.013) were inversely correlated with PTSD severity. **Change in AA** [arachidonic acid / omega-6] **was positively correlated with PTSD severity** (p=.001).

Limitation: This trial was conducted at a single-center in Japan and PTSD symptoms in most participants were not serious.

Conclusions: Increased erythrocyte level of EPA during the trial was associated with low severity of PTSD symptoms in patients receiving omega3 supplements."

- Division of Health Care Research, Center for Public Health Sciences, National Cancer Center Japan, Japan

- Department of Psychiatry, National Disaster Medical Center, Japan.

- Department of Public Health, Faculty of Medicine, University of Toyama, Japan.

- Department of Mental Health Policy and Evaluation, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Japan.

- Department of Medicine, Toyama Jonan Onsen Daini Hospital, Japan.

https://pubmed.ncbi.nlm.nih.gov/27552592

See also Oxidative Stress , Reactive Oxygen Species (ROS) , Stress

Post-Traumatic Stress Disorder (PTSD) & Oxidative Stress

…"Post-traumatic stress disorder (PTSD) is a psychiatric disorder that occurs after exposure to a traumatic event. It involves both mood and anxiety disorders [1,2]. Approximately 20% of individuals exposed to a significant traumatic event will develop PTSD, and children may be at an

even higher risk [3]. Post-traumatic stress disorder prevalence rates are largely similar across countries, with the highest rates being found in post-conflict settings [4].

Oxidative stress has been implicated in the response to stress and in the pathogenesis of neurologic and psychiatric diseases [5]. Post-traumatic stress disorder constitutes a form of persistent life stress and is associated with increased oxidative stress and accelerated cellular aging. Clinical and structural neuroimaging studies have repeatedly found associations between PTSD and loss of neural integrity in the hippocampus, amygdala, medial prefrontal, and anterior cingulate cortices [6,7]. While several drugs and psychotherapies are used to treat PTSD, yet there is not enough reliable evidence to draw conclusions about the effectiveness of most treatments [8,9].

The value of nutritional supplements for the treatment of mental disorders stems from studying the association of some food deficiencies with mental disorders. The omega polyunsaturated fatty acids are categorized into n-3 (or omega-3) and n-6 (or omega-6) groups. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main bioactive constituents of omega-3, are not efficiently produced in humans and should consequently be taken directly from the diet, mainly by consuming fish [10]. The omega-3 fatty acids are important because they are essential for the maintenance and function of the brain in addition to cognition. Brain phospholipids are important for intact memory and cognitive functions [11]. In addition, neurodegenerative disease features a cognitive decrease paralleled by an insufficiency in blood and brain levels of DHA [12]. Dietary omega-3 fatty acid supplements enhance cognitive function, promote neuroplasticity, and improve neurological lesion.

Animal model for PTSD, namely the single-prolonged stress (SPS) model in rats, are very well established and widely used to study PTSD-like behaviors [13,14,15,16,17,18,19,20]. Moreover, omega-3 is well-absorbed in the rat gastrointestinal (GI) tract, where it is distributed to brain via the blood brain barrier [21,22,23,24]. In this study, we investigated the possible protective effect of omega-3 fatty acid on learning ability and memory functions in a rat model of PTSD-like behavior. In addition, the effect of omega-3 on oxidative stress biomarkers was investigated."…

-Department of Biological Sciences, School of Science, University of Jordan, Amman, Jordan;
-Department of Biology, Yarmouk University, Irbid, Jordan
-Department of Clinical Pharmacy, Jordan University of Science and Technology, Irbid , Jordan;
-Department of Medical Science, Irbid Faculty, Al-Balqa Applied University, Irbid, Jordan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6468674/

See also Oxidative Stress , Reactive Oxygen Species (ROS) , Stress

Postural Orthostatic Tachycardia Syndrome (POTS)

"a condition that affects blood flow. POTS causes the development of symptoms -- usually lightheadedness, fainting and an uncomfortable, rapid increase in heartbeat -- that come on when standing up from a reclining position and relieved by sitting or lying back down."

- Cleveland Clinic

https://my.clevelandclinic.org/health/diseases/16560-postural-orthostatic-tachycardia-syndrome-pots

Prefrontal Cortex

"Dysfunction of the prefrontal cortex (PFC) is a central feature of many psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), schizophrenia and bipolar disorder."…

-Department of Neurobiology, Yale University School of Medicine
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109197/

Molecular components and functions of the endocannabinoid system in mouse prefrontal cortex

…"Our data show that the endocannabinoid -retrograde signaling plays a prominent role in long-term synaptic plasticity at the excitatory synapses of the PFC. Alterations of endocannabinoid -mediated synaptic plasticity may participate to the etiology of PFC-related pathologies."

-INSERM U862, Equipe Physiopathologie de la plasticité synaptique, Bordeaux, France.
https://pubmed.ncbi.nlm.nih.gov/17684555/

Pregnancy

…"Disruptions in the balance of AEA [anandamide] levels and FAAH [Fatty acid amide hydrolase] activity have been implicated in poor implantation in the mouse (15). Low FAAH activity and high levels of AEA are apparent in the blood of women who suffer from spontaneous miscarriages (14). Furthermore, increased circulating AEA levels lead to poor implantation in patients undergoing in vitro fertilization as well as embryonic transfer procedures (13)."…

-Liggins Institute, University of Auckland, Auckland, New Zealand

https://journals.physiology.org/doi/full/10.1152/ajpendo.00495.2007

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…"Differences in n-3 LCPUFA intake exist among subgroups of the US population. For example, our recent analysis of NHANES (National Health and Nutrition Examination Survey) 2003–2014 data revealed differences in n-3 LCPUFA intake based on age, gender, and pregnancy status [25]. Overall, n-3 LCPUFA intake was significantly lower in women compared to men, younger participants (regardless of gender), and pregnant women (compared to their non-pregnant counterparts) [25]. Other analyses of NHANES data from 2003 to 2014 have further demonstrated lower n-3 LCPUFA intakes in pregnant women or women of child-bearing age and younger participants (compared to their male and older counterparts) [26,27]. These recent findings strongly suggest that n-3 LCPUFA intake is influenced by factors such as gender and pregnancy status."…

-Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE 68198, USA; (M.T.)
-College of Public Health, University of Nebraska Medical Center, Omaha, NE 68198, USA;
-Department of Nutritional Sciences, University of Arizona, Tucson, AZ 85721, USA;
-Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA 16802, USA;
-Division of Biomedical Sciences, School of Medicine, University of California Riverside, Riverside, CA 92521, USA
-College of Allied Health Professions, University of Nebraska Medical Center, Omaha, NE 68198, USA;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7400855/

The ins and outs of maternal-fetal fatty acid metabolism

"Fatty acids (FAs) are one the most essential substances in intrauterine human growth. They are involved in a number of energetic and metabolic processes, including the growth of cell membranes, the retina and the nervous system. Fatty acid deficiency and disruptions in the maternal-placental fetal metabolism of FAs lead to malnutrition of the fetus, hypotrophy and preterm birth. What is more, metabolic diseases and cardiovascular conditions may appear later in life. Meeting a fetus' need for FAs is dependent on maternal diet and on the efficiency of the placenta in transporting FAs to fetal circulation. "Essential fatty acids" are among the most important FAs during the intrauterine growth period. These are α-linolenic acid, which is a precursor of the n-3 series, linoleic acid, which is a precursor of the n-6 series and their derivatives, represented by docosahexaenoic acid and arachidonic acid. The latest studies have shown that medium-chain fatty acids also play a significant role in maternal-fetal metabolism. These FAs have significant effect on the transformation of the precursors into DHA, which may contribute to a relatively stable supply of DHA - even in pregnant women whose diet is low in FAs. The review discusses the problem of fatty acid metabolism at the intersection between a

pregnant woman and her child with reference to physiological pregnancy, giving birth to a healthy child, intrauterine growth restriction, preterm birth and giving birth to a small for gestational age child."

-University of Bielsko-Biała, Faculty of Health Sciences, Bielsko-Biała, Poland.
https://pubmed.ncbi.nlm.nih.gov/26345097/

Plasma phospholipids indicate impaired fatty acid homeostasis in preterm infants

Background: During fetal development, docosahexaenoic (DHA) [omega-3] and arachidonic acid (ARA) [omega-6] are particularly enriched in brain phospholipids. After preterm delivery, fetal enrichment of DHA and ARA via placental transfer is replaced by enteral and parenteral nutrition, which is rich in linoleic acid (LA) instead. Specific DHA and ARA enrichment of lipoproteins is reflected by plasma phosphatidylcholine (PC) species, whereas plasma phosphatidylethanolamine (PE) composition reflects hepatic stores."…

"**Results**: Phospholipid concentrations were higher in preterm infant than in cord plasma after correction for PMA. This was mainly due to postnatal increases in LA-containing PC and PE, resulting in decreased fractions of their DHA- and ARA-containing counterparts. These changes in preterm infant plasma phospholipids occurred during the time of transition to full enteral feeds (day 0-10 after delivery). Thereafter, the fraction of ARA-containing phospholipids further decreased, whereas that of DHA slowly reincreased but remained at a level 50% of that of PMA-matched cord blood.

Conclusions: The postnatal increase in LA-PC in preterm infant plasma results in decreased fractions of DHA-PC and ARA-PC. These changes are also reflected by PE molecular composition as an indicator of altered hepatic fatty acid homeostasis. They are presumably caused by inadequately high LA, and low ARA and DHA supply, at a stage of development when ARA-PC and DHA-PC should be high, probably reducing the availability of DHA and ARA to the developing brain and contributing to impaired neurodevelopment of preterm infants."

-Department of Neonatology, Faculty of Medicine, Eberhard-Karls-University, Calwer Straße 7, 72076, Tübingen, Germany
https://pubmed.ncbi.nlm.nih.gov/24464176/

Bioengineered Plants Can Be a Useful Source of Omega-3 Fatty Acids

"Omega-3 fatty acids have proven to be very essential for human health due to their multiple

health benefits. These essential fatty acids (EFAs) need to be uptaken through diet because they are unable to be produced by the human body. These are important for skin and hair growth as well as for proper visual, neural, and reproductive functions of the body. These fatty acids are proven to be extremely vital for normal tissue development during pregnancy and infancy. Omega-3 fatty acids can be obtained mainly from two dietary sources: marine and plant oils. Eicosapentaenoic acid (EPA; C20:5 n-3) and docosahexaenoic acid (DHA; C22:6 n-3) are the primary marine-derived omega-3 fatty acids. Marine fishes are high in omega-3 fatty acids, yet high consumption of those fishes will cause a shortage of fish stocks existing naturally in the oceans. An alternative source to achieve the recommended daily intake of EFAs is the demand of today. In this review article, an attempt has, therefore, been made to discuss the importance of omega-3 fatty acids and the recent developments in order to produce these fatty acids by the genetic modifications of the plants."…

-State Key Laboratory of Crop Genetics and Germplasm Enhancement, College of Horticulture, Nanjing Agricultural University, Nanjing, Jiangsu 210095, China

-Laboratory of Biotechnology, Chinese Academy of Tropical Agricultural Sciences, Wenchang, Hainan 571339, China

-Department of Agriculture, Abdul Wali Khan University Mardan, Mardan, Pakistan

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5339522

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…"Younger generations, women of childbearing age and pregnant mothers appear to be at particular risk of oily fish and omega-3 shortfalls. Declining EPA and DHA profiles of farmed fish and plant-based food movements are only likely to exacerbate already inadequate intakes. Urgent public health campaigns are needed to improve UK intakes, which should include a combined approach of dietary and supplemental sources."..

-Nutritional Insight Limited, London, United Kingdom

-Edited by: Alessio Molfino, Sapienza University of Rome, Italy

-Reviewed by: Annette Lucy West, University of Southampton, United Kingdom; Caroline Elizabeth Childs, University of Southampton, United Kingdom

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6861329

Maternal dietary imbalance between omega-6 and omega-3 fatty acids triggers the offspring's overeating in mice

"The increasing prevalence of obesity and its effects on our society warrant intensifying basic animal research for understanding why habitual intake of highly palatable foods has increased

due to recent global environmental changes. Here, we report that pregnant mice that consume a diet high in omega-6 (n-6) polyunsaturated fatty acids (PUFAs) and low in omega-3 (n-3) PUFAs (an n-6high/n-3low diet), whose n-6/n-3 ratio is approximately 120, induces hedonic consumption in the offspring by upregulating the midbrain dopaminergic system. We found that exposure to the n-6high/n-3low diet specifically increases the consumption of palatable foods via increased mesolimbic dopamine release. In addition, neurodevelopmental analyses revealed that this induced hedonic consumption is programmed during embryogenesis, as dopaminergic neurogenesis is increased during in utero access to the n-6high/n-3low diet. Our findings reveal that maternal consumption of PUFAs can have long-lasting effects on the offspring's pattern for consuming highly palatable foods."…

-Department of Molecular Genetics, Institute of Biomedical Sciences, Fukushima Medical University, Fukushima

-Laboratory of Nutritional Physiology, Department of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Josai University, Sakado, Saitama, Japan

-New Industry Creation Hatchery Center, Tohoku University, Sendai, Miyagi, Japan

Biodynamic Plant Institute Co., Ltd., Sapporo, Hokkaido, 001-0021, Japan

-Department of Behavioral Physiology, Graduate School of Innovative Life Science, University of Toyama, Sugitani, Toyama, Japan

-Department of Molecular Genetics, Institute of Biomedical Sciences, Fukushima Medical University, Fukushima, Japan

-Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences, Yokohama, Kanagawa, Japan

https://www.nature.com/articles/s42003-020-01209-4

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"To maintain a healthy pregnancy, it is important to meet increased nutritional needs. Fetal development requires an adequate maternal supply of nutrients that influence both fetal growth and organ development throughout gestation [1]. In particular, the fetus depends largely on the maternal supply of polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and arachidonic acid (AA) via the placenta [2]. The fetal availability of PUFAs depends on both placental transport and metabolism [3]. Factors influencing the ability of the placenta to mediate the transfer of nutrients from the mother to the fetus include quality of placentation, area available for exchange, placental metabolism and placental blood flow [4]. Impaired placental function is involved in obstetrical complications, such as preeclampsia, intrauterine growth restriction and gestational diabetes mellitus (GDM) [5]. Although the pathogeneses differ, they are associated with compromised PUFA transport [6], placental inflammation and oxidative stress [7]. Furthermore, the complication itself may also result in impaired maternal synthesis and metabolism of PUFA [8]. Hence, suboptimal PUFA availability and dysregulated metabolism might both contribute to, and be a result of, pregnancy complications. "…

-Department of Chemistry, Umeå University, Sweden;
-Department of Nursing, Umeå University, Sweden;
-Department of Clinical Sciences, Obstetrics and Gynecology, Umeå University, Sweden;
-Department of Clinical Sciences, Neurosciences, Umeå University, Sweden;
-Division of Obstetrics and Gynecology, Örnsköldsvik Hospital, Sweden
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7694173/

See also Breastfeeding , Nitric Oxide

Prenatal Ultrasound

The safety of prenatal ultrasound exposure in human studies

"Diagnostic ultrasound use in obstetrics has been growing rapidly to become an integral part of prenatal care today. The high proportion of exposure to prenatal ultrasound highlights the public health significance of routine ultrasound use. A majority of epidemiologic studies tends to support the safety of diagnostic ultrasound use during pregnancy. **However, there have been some reports that there may be a relation between prenatal ultrasound exposure and adverse outcome. Some of the reported effects include growth restriction, delayed speech, dyslexia, and non-right-handedness associated with ultrasound exposure.** Continued research is needed to evaluate the potential adverse effects of ultrasound exposure during pregnancy. These studies should measure the acoustic output, exposure time, number of exposures per subject, and the timing during the pregnancy when exposure(s) occurred, while controlling for potential confounding variables such as sociodemographic, medical, and obstetric risk factors. We recommend that a new consensus development conference be held to gather the needed data and provide guidelines for the future research needs, as well as respond to the rapid advances in this technology."

- Center for Devices and Radiological Health, Food and Drug Administration, Rockville, MD 20850, USA.
https://pubmed.ncbi.nlm.nih.gov/12071478/

Fetal Doppler: how to keep it safe?

"Ultrasound's record of safety seems to be perfect, with no undisputed reports of adverse effects in humans. However, all epidemiologic studies published so far are based on information obtained with pre-1992 machines, when allowed maximal in-situ intensity for fetal use was increased. Many fetuses are examined very early in pregnancy, a time of greater vulnerability.

Doppler can generate much higher level of acoustic energy than B-mode. The thermal index and the mechanical index are indicators of the 2 main potential effects of ultrasound including Doppler. To keep the fetus safe, knowledge of these potential bioeffects is mandatory as is understanding of how instrument controls alter the output. The 2 most important rules are: keep thermal index below 1 and use the lowest possible output for the shortest possible time compatible with obtaining diagnostic information."

-Department of Obstetrics and Gynecology and Rush Fetal and Neonatal Medicine Center, Rush University, Chicago, Illinois, USA

https://pubmed.ncbi.nlm.nih.gov/21048451/

Obstetric ultrasonography: a biophysical consideration of patient safety--the "rules" have changed

"We address the issue of health and safety in relation to exposure to diagnostic ultrasound, with particular emphasis given to obstetrics. In terms of fetal and maternal outcomes, the epidemiologic record of diagnostic ultrasound is exemplary but is primarily made on the basis of data derived from clinical devices whose outputs were relatively low compared with what is now allowable and available. The power outputs of clinical devices have been increasing over the past decade such that the potential for thermal and nonthermal insults is increased. For obstetric devices that use these higher outputs, the Food and Drug Administration now requires the presentation of 2 on-screen indexes, the thermal index and the mechanical index, in recognition of the 2 major mechanisms by which ultrasonography is known to affect cells and tissues. Greater responsibility for patient safety is now placed on the diagnostician; for the new indexes to be meaningful the diagnostician must be cognizant of the health and safety implications. The purpose of this article is to provide some guidance to the obstetrician in interpreting the indexes and to review the current status of ultrasonography biophysics in relation to the use of diagnostic ultrasound in obstetrics."

-Department of Obstetrics and Gynecology, School of Medicine and Dentistry, University of Rochester, New York, USA.

https://pubmed.ncbi.nlm.nih.gov/9704794/

"Is it safe for my baby?" acoustic exposure of diagnostic ultrasound

"As a form of energy, diagnostic ultrasound (DUS) has the potential to have effects on Living tissues, e.g. bioeffects. The two most likely mechanisms for bioeffects are heating and cavitation. Hyperthermia is considered teratogenic in human fetuses during the first trimester Actual temperature changes cannot be studied in the human fetus. The thermal index [TI) expresses the

potential for rise in temperature at the ultrasound's focal point. The mechanical index (MI) indicates the potential for the ultrasound to induce inertial cavitation in tissues. Nevertheless, cavitation has not been documented in mammalian fetuses, since there is not an air-water interface, which is needed for the cavitation mechanism. Since an output of TI over 1.5 is a known hazard, the question is: What are the settings in which such hazardous exposure occurs? Our conclusions regarding safety of DUS, based on the data that has been available till now, are the following: (1) Ultrasound end-users are poorly informed regarding safety issues during pregnancy. Further efforts in the realm of education and training are needed in order to improve knowledge of end-users about the acoustic output of the machines and safety issues. (2) First trimester ultrasound is associated with negligible rise in the thermal index. (3) Increased acoustic output Levels, as expressed by TI levels, are reached while performing obstetrical Doppler studies. In particular, TI Levels may reach 1.5 and above. Doppler procedures should be performed with caution and should be as brief as possible during obstetrical ultrasound. (4) Acoustic exposure levels during 3D/4D ultrasound examination, as expressed by TI are comparable to the two-dimensional B-mode ultrasound."

-Department of Obstetric and Genecology, Faculty of Health Sciences, Soroka University Medical Center, Ben-Gurion University of the Negev.

https://pubmed.ncbi.nlm.nih.gov/21874769/

A symposium on obstetrical ultrasound: is all this safe for the fetus?

"Diagnostic ultrasound is a form of energy that has the potential for effects in tissues (bioeffects). The 2 most likely mechanisms are heating and cavitation. The thermal index (TI) expresses the potential for rise in temperature. The MI indicates the potential for the ultrasound to induce inertial cavitation. Scarce data exist regarding instrument's acoustic output for routine ultrasound examinations. Data collected during routine ultrasound examinations (first trimester for viability, nuchal translucency, anatomy surveys including 3-dimensional/4-dimensional studies and growth studies) show that "gray-scale" B-mode ultrasound is associated with a negligible rise in TI. However, Doppler studies show significantly higher levels of TI, which can reach 1.5 and above."

-Department of Obstetrics and Gynecology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

https://pubmed.ncbi.nlm.nih.gov/22343238/

Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus

"Objective: To identify the temporal sequence of abnormal Doppler changes in the fetal circulation in a subset of early and severely growth-restricted fetuses.

Methods: This was a prospective observational study in a tertiary care/teaching hospital. Twenty-six women who were diagnosed with growth-restricted fetuses by local standards before 32 weeks' gestation and who had abnormal uterine and umbilical artery Doppler velocimetry were enrolled onto the study. To compare Doppler changes as a function of time, pulsed-wave Doppler ultrasound was performed on five vessels in the fetal peripheral and central circulations. Doppler examinations were performed twice-weekly and on the day of delivery if the fetal heart rate tracing became abnormal. Doppler indices were scored as abnormal when their values were outside the local reference limits on two or more consecutive measurements. Biometry for assessment of fetal growth was performed every 2 weeks. Computerized fetal heart rates were obtained daily. Delivery was based on a non-reactive fetal heart rate tracing and not on Doppler information. Patients with a severely growth-restricted fetus who were delivered for maternal indications such as pre-eclampsia were excluded. Perinatal outcome endpoints included: intrauterine death, gestational age at delivery, newborn weight, central nervous system damage of grade 2 or greater, intraventricular hemorrhage and neonatal mortality.

Results: Mean gestational age and newborn weight at delivery were 29 (standard deviation (SD), 2) weeks and 818 (SD, 150) g, respectively. The sequence of Doppler velocimetric changes was described by onset time cumulative curves that showed two time-related events. First, for each vessel there was a progressive increase in the percent of fetuses developing a Doppler abnormality. Second, severely growth-restricted fetuses followed a progressive sequence of acquiring Doppler abnormalities which were categorized into 'early' and 'late' Doppler changes. Early changes occurred in peripheral vessels (umbilical and middle cerebral arteries; 50% of patients affected 15-16 days prior to delivery). Late changes included umbilical artery reverse flow, and abnormal changes in the ductus venosus, aortic and pulmonary outflow tracts (50% of patients affected 4-5 days prior to delivery). The time interval between the occurrence of early and late changes was significantly different ($P < 0.0001$) and late changes were significantly associated with perinatal death ($P < 0.01$).

Conclusions: Doppler velocimetry abnormalities develop in different vessels of the severely growth-restricted fetus in a sequential fashion. Late changes in vascular adaptation by the severely growth-restricted fetus are the best predictor of perinatal death."

-Luigi Sacco Institute of Biological Sciences and Obstetrics and Gynecological Clinic, University of Milan, Milan, Italy.

https://pubmed.ncbi.nlm.nih.gov/11876805/

Neonatal Cranial Ultrasound: Are Current Safety Guidelines Appropriate?

"Ultrasound can lead to thermal and mechanical effects in interrogated tissues. We reviewed the literature to explore the evidence on ultrasound heating on fetal and neonatal neural tissue. The results of animal studies have suggested that ultrasound exposure of the fetal or neonatal brain may lead to a significant temperature elevation at the bone-brain interface above current recommended safety thresholds. Temperature increases between 4.3 and 5.6°C have been recorded. Such temperature elevations can potentially affect neuronal structure and function and may also affect behavioral and cognitive function, such as memory and learning. However, the majority of these studies were carried out more than 25 y ago using non-diagnostic equipment with power outputs much lower than those of modern machines. New studies to address the safety issues of cranial ultrasound are imperative to provide current clinical guidelines and safety recommendations."

-Department of Medical Imaging and Radiation Sciences, Monash University, Malvern, Victoria, Australia; Department of Medical Imaging, St. Francis Xavier Cabrini Hospital, Malvern, Victoria, Australia; Department of Medical Imaging, Mercy Hospital for Women, Heidelberg, Victoria, Australia.

-Monash Newborn, Monash Medical Centre, Clayton, Victoria, Australia; The Ritchie Centre, MIMR-PHI Institute of Medical Research, Melbourne, Victoria, Australia; Department of Pediatrics, Monash University, Clayton, Victoria, Australia.

https://pubmed.ncbi.nlm.nih.gov/27979665

Prion Disease

"Prion diseases comprise several conditions. A prion is a type of protein that can trigger normal proteins in the brain to fold abnormally."

-John Hopkins Medicine

https://www.hopkinsmedicine.org/health/conditions-and-diseases/prion-diseases

Nonpsychoactive cannabidiol prevents prion accumulation and protects neurons against prion toxicity.

"Prion diseases are transmissible neurodegenerative disorders characterized by the accumulation in the CNS of the protease-resistant prion protein (PrPres), a structurally misfolded isoform of its physiological counterpart PrPsen. Both neuropathogenesis and prion infectivity are

related to PrPres formation. Here, we report that the nonpsychoactive cannabis constituent cannabidiol (CBD) inhibited PrPres accumulation in both mouse and sheep scrapie-infected cells, whereas other structurally related cannabinoid analogs were either weak inhibitors or noninhibitory. Moreover, after intraperitoneal infection with murine scrapie, peripheral injection of CBD limited cerebral accumulation of PrPres and significantly increased the survival time of infected mice. Mechanistically, CBD did not appear to inhibit PrPres accumulation via direct interactions with PrP, destabilization of PrPres aggregates, or alteration of the expression level or subcellular localization of PrPsen. However, CBD did inhibit the neurotoxic effects of PrPres and affected PrPres-induced microglial cell migration in a concentration-dependent manner. Our results suggest that CBD may protect neurons against the multiple molecular and cellular factors involved in the different steps of the neurodegenerative process, which takes place during prion infection. When combined with its ability to target the brain and its lack of toxic side effects, CBD may represent a promising new anti-prion drug."

- Institute of Molecular at Cellular Pharmacology
(Institut de Pharmacologie Moléculaire et Cellulaire)
-Scientific Research National Center
(Centre National de la Recherche Scientifique, France.)
https://www.ncbi.nlm.nih.gov/pubmed/17804615

Probiotics

Probiotics are "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host".

-Food & Drug Administration (FDA) - Referenced
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5682732/

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"Synbiotics are composed of probiotics and prebiotics (the non-digestible food products beneficial for growth of helpful bacteria in large intestine and provides health promoting effects) [137]. Several reports have confirmed the reduction of oxidative stress in human body by consumption of synbiotics [138–141]."

…."Bifidobacterium and Lactobacillus are the key strains widely used as probiotics in commercial, pharmaceutical, and nutraceutical products [143, 144]. Many reports have frequently stated that the population of gut microbes gets altered in a person affected with RA [56, 145–147], and several animal studies have already proved that any alteration in gut microbiota corresponds to initiation of RA

(148).

In several animal and human studies, the health promoting benefits of probiotics has been extensively assessed. When RA-induced animal models were fed Lactobacillus casei, it led to improvised health conditions by reduction in levels of pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-12, and IL-17, IFN-γ, and TNF-α, while upregulating the secretion of regulatory cytokines like IL-10 and TGF-β [149–152].”

-Disease Biology Laboratory, School of Biotechnology, KIIT University, Bhubaneswar, Odisha, India Edited by: Marilia Seelaender, University of São Paulo, Brazil

Reviewed by: Dario Coletti, Sapienza Università di Roma, Italy; Emanuele Rinninella, Agostino Gemelli University Polyclinic, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5682732/

Probiotics: considerations for human health.

“Evidence for the role of probiotics in maintenance of health or prevention of disease is mounting and is supported in some cases by blinded, placebo-controlled human trials. Today, in an era of antibiotic-resistant pathogens and other looming microbial threats, the value of prevention of infection is recognized. Probiotics may play an important role in helping the body protect itself from infection, especially along the colonized mucosal surfaces of the gastrointestinal tract. Probiotic products are available in many different forms worldwide, including pills, powders, foods, and infant formula. In some cases, general health claims are made that cannot be substantiated for the specific strains and levels being used and consumers must therefore beware.”

-Dairy and Food Culture Technologies, 7119 S. Glencoe Ct., Centennial, CO 80122-2526, USA.

https://www.ncbi.nlm.nih.gov/pubmed/12723641/

Pro-Inflammation

Proinflammation: a common denominator or initiator of different pathophysiological disease processes.

“Proinflammation is a widespread phenomenon. It has an association with the stress (patho)physiology and is connected with various diseases. Recently, it has been discussed if proinflammation may represent a common (pre)condition in different disease states. Evidence for a common proinflammatory pattern in a variety of diseases is analyzed. Proinflammatory (pre)conditions and immune response patterns serve as a common modality in a number of

clinically separate diseases. Here, nitric oxide pathways often play a significant role as well. On molecular basis, proinflammation potentially illustrates a common denominator and/or an initiator. Like stress, proinflammation seems to be a crucial autoregulatory concept. It normally serves a positive biological goal: Proinflammatory activities, e.g., are initiated to overcome infection or invasion of potentially deleterious biological agents (bacteria, viruses, parasites etc.). While fighting invasion, proinflammation usually shortens biological 'battles' and therefore ameliorates disease-related detrimental or subjectively unpleasing phenomena. However, proinflammation has beneficial and deteriorating capacities and may yet exert detrimental effects. This is especially true, when the fine balance between the different immune response pathways, between anti- and proinflammatory mechanisms, can not be kept. This may occur when a challenge becomes overwhelming or when patterns of a chronic (patho)physiological activity are presented. Thus, proinflammation may represent a relatively unspecific, overlapping/ analogous state, underlying various clinical disease manifestations."

-The Mind/ Body Medical Institute, CareGroup
-Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.
https://www.ncbi.nlm.nih.gov/pubmed/12011758/

Prostaglandins and Inflammation

"Prostaglandins are lipid autacoids derived from arachidonic acid [omega-6]. They both sustain homeostatic functions and mediate pathogenic mechanisms, including the inflammatory response. They are generated from arachidonate by the action of cyclooxygenase (COX) isoenzymes and their biosynthesis is blocked by nonsteroidal anti-inflammatory drugs (NSAIDs), including those selective for inhibition of COX-2. Despite the clinical efficacy of NSAIDs, prostaglandins may function in both the promotion and resolution of inflammation.

This review summarizes insights into the mechanisms of prostaglandin generation and the roles of individual mediators and their receptors in modulating the inflammatory response. Prostaglandin biology has potential clinical relevance for atherosclerosis, the response to vascular injury and aortic aneurysm.

Inflammation is the immune system's response to infection and injury and has been implicated in the pathogeneses of arthritis, cancer and stroke, as well as in neurodegenerative and cardiovascular disease. Inflammation is an intrinsically beneficial event that leads to removal of offending factors and restoration of tissue structure and physiological function. The acute phase of inflammation is characterized by the rapid influx of blood granulocytes, typically neutrophils, followed swiftly by monocytes that mature into inflammatory macrophages that subsequently

proliferate and thereby affect the functions of resident tissue macrophages. This process causes the cardinal signs of acute inflammation: rubor (redness), calor (heat), tumor (swelling) and dolor (pain). Once the initiating noxious stimulus is removed via phagocytosis, the inflammatory reaction can decrease and resolve. During the resolution of inflammation, granulocytes are eliminated and macrophages and lymphocytes return to normal pre-inflammatory numbers and phenotypes. The usual outcome of the acute inflammatory program is successful resolution and repair of tissue damage, rather than persistence and dysfunction of the inflammatory response, which can lead to scarring and loss of organ function. It may be anticipated, therefore, that failure of acute inflammation to resolve may predispose to auto-immunity, chronic dysplastic inflammation and excessive tissue damage [(1)].

Prostaglandins play a key role in the generation of the inflammatory response. Their biosynthesis is significantly increased in inflamed tissue and they contribute to the development of the cardinal signs of acute inflammation. While the pro-inflammatory properties of individual prostaglandins during the acute inflammatory response are well established, their role in the resolution of inflammation is more controversial."

-Emanuela Ricciotti, PhD
-Garret A. FitzGerald, MD
-Institute for Translational Medicine and Therapeutics, University of Pennsylvania, Philadelphia, Pa
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3081099/

Prostaglandins

"Prostaglandins (PGs) are physiologically and pharmacologically active, lipid compounds resembling hormones which act through G-protein-linked receptors. PGs are found in almost all nucleated cells of the body but the name prostaglandin was coined due to their discovery in the prostate gland."

-Asha Kumari, in Sweet Biochemistry, 2018
-Department of Biochemistry, Pandit Bhagwat Dayal Sharma PGIMS, Rohtak, Haryana, India
https://www.sciencedirect.com/science/article/pii/B9780128144534000169

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"Arachidonic acid [omega-6] is one of the pivotal signaling molecules associated with inflammation, pain and homeostatic function. Drugs specifically targeting these signaling pathways represent more than 25% of annual pharmaceutical sales worldwide. However, chronic administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and rofecoxib (Vioxx), a potent

cyclooxygenase-2 inhibitor, have been associated with adverse cardiovascular events. Understanding the possible mechanisms underlying these adverse events is critical for evaluating the risks and benefits of this group of drugs and for development of safer drugs. Using a powerful metabolomics approach, 20-hydroxyeicosatetraenoic acid (20-HETE) was identified among many of arachidonic acid metabolic products as a likely culprit for adverse cardiovascular side effect associated with rofecoxib and NSAIDs."...

-Department of Internal Medicine, Division of Cardiovascular Medicine, University of California, Davis, CA
-Department of Veterans Affairs, Northern California Health Care System Mather, CA
-Department of Entomology and UC Davis Cancer Center, University of California, Davis, CA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3583533/

Prostaglandins in liver failure and transplantation: regeneration, immunomodulation, and cytoprotection. Prostaglandins in Liver Transplantation Research Group

"Prostaglandins (PG) are involved in the regulation of many physiological processes in the liver and play a major role in the pathophysiology and treatment of liver diseases. In addition to their effects of cell growth and immune function, PGs have shown cytoprotective effects on hepatocytes in various toxic, ischemic, and infectious models of liver injury. Although the mechanisms for these beneficial effects have not been precisely delineated, synthetic PG analogues have increasingly been used in patients with acute liver failure and chronic liver disease. There is also increasing evidence suggesting that PGs may reduce the early morbidity and mortality associated with liver transplantation, particularly in the context of primary graft nonfunction and renal dysfunction associated with cyclosporine and tacrolimus therapy. PG analogues have also been used for the treatment and control of recurrent hepatitis B virus infection in liver allograft recipients. The purpose of this review is to evaluate the role of PGs in hepatic physiology and disease and to review the use of synthetic PG analogues in the clinical settings of liver failure and transplantation."

-Toronto Hospital, Ontario, Canada.
https://www.ncbi.nlm.nih.gov/pubmed/9346646

Auto-immunity and prostaglandins

"Several auto-immune diseases have been described in human beings. Though the exact aetiological agent(s) is not known, clinical or subclinical viral infections and certain drugs are known to induce them. Hyperactivity of B-cells, possibly due to the loss of normal regulatory

control by T-cells may account for the increased synthesis of auto-antibodies in these diseases. Prostaglandins (PGs) are known to regulate immune response and fibrous tissue formation. Deficiency of PGE1 and/or thromboxane A2 (TxA2) and excess PGE2 seem to activate B-cells and suppress T-Cell function and enhance fibrosis. Viruses are known to block the enzyme delta-6-desaturase necessary for PGE1 synthesis and thus depress cell-mediated immune response. Drugs known to cause autoimmune disorders also seem to block PGE1 and/or TxA2 synthesis and enhance PGE2 formation which may lead to excess auto-antibody formation. Drugs like colchicine known to enhance TxA2 formation and the biological actions of PGE1 were found to be of benefit in Behcet's syndrome, vasculitis, amyloidosis, scleroderma and in controlling the auto-immune disease in adjuvant arthritis in rats, the renal disease in NZB/W mice and passively transferred vasculitis. Thus altered PG function may play a major role in auto-immunity."

-Dr Undurti N. Das, MD, DSc, FAMS, FRSC

https://www.ncbi.nlm.nih.gov/pubmed/7035343

Prostaglandin-cytokine crosstalk in chronic inflammation

"Chronic inflammation underlies various debilitating disorders including autoimmune, neurodegenerative, vascular and metabolic diseases as well as cancer, where aberrant activation of the innate and acquired immune systems is frequently seen. Since non-steroidal anti-inflammatory drugs exert their effects by inhibiting COX and suppressing PG biosynthesis, PGs have been traditionally thought to function mostly as mediators of acute inflammation. However, an inducible COX isoform, COX-2, is often highly expressed in tissues of the chronic disorders, suggesting an as yet unidentified role of PGs in chronic inflammation. Recent studies have shown that in addition to their short-lived actions in acute inflammation, PGs crosstalk with cytokines and amplify the cytokine actions on various types of inflammatory cells and drive pathogenic conversion of these cells by critically regulating their gene expression. One mode of such PG-mediated amplification is to induce the expression of relevant cytokine receptors, which is typically observed in Th1 cell differentiation and Th17 cell expansion, events leading to chronic immune inflammation. Another mode of amplification is cooperation of PGs with cytokines at the transcription level. Typically, PGs and cytokines synergistically activate NF-κB to induce the expression of inflammation-related genes, one being COX-2 itself, which makes PG-mediated positive feedback loops. This signalling consequently enhances the expression of various NF-κB-induced genes including chemokines to macrophages and neutrophils, which enables sustained infiltration of these cells and further amplifies chronic inflammation. In addition, PGs are also involved in tissue remodelling such as fibrosis and angiogenesis. In this article, we review

these findings and discuss their relevance to human diseases."

-Centre for Inflammation Research, Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, UK,
-Alliance Laboratory for Advanced Medical Research and Department of Drug Discovery Medicine, Medical Innovation Center, Kyoto University Graduate School of Medicine, Kyoto, Japan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6329627/

Prostaglandin deficiency

"Healthy cells from virtually all tissues synthesize a variety of prostaglandins, autacoids which can significantly alter cellular functions. An absolute or relative deficiency of prostaglandins has now been demonstrated in many diseases or clinical conditions. These include 'natural' disorders such as peptic ulcer disease and diabetes mellitus. These also include 'acquired' or iatrogenic conditions such as cyclosporine nephrotoxicity and the gastropathy induced by nonsteroidal anti-inflammatory drugs. We believe that the diversity of the disorders associated with prostaglandin deficiency may be wider and of greater pathogenetic importance than is currently recognized. We propose:

1) that prostaglandin deficiency will be demonstrated in many abnormalities which are now described as of uncertain etiology; and

2) that adverse effects from many commonly prescribed drugs may also be related to an unrecognized and unfavorable alteration in prostaglandin synthesis, disposal, or activity."

Clinical Research, G. D. Searle & Co., Skokie, IL. (***wholly owned trademark of Pfizer***)
https://www.ncbi.nlm.nih.gov/pubmed/2187202

Paracetamol effectively reduces prostaglandin E2 synthesis in brain macrophages by inhibiting enzymatic activity of cyclooxygenase but not phospholipase and prostaglandin E synthase.

"Epidemiological studies indicate that nonsteroidal anti-inflammatory drugs (NSAIDs) are neuroprotective, although the mechanisms underlying their beneficial effect remain largely unknown. Given their well-known adverse effects, which of the NSAIDs is the best for neurodegenerative disease management remains a matter of debate. Paracetamol is a widely used analgesic/antipyretic drug with low peripheral adverse effects, possibly related to its weak activity as inhibitor of peripheral cyclooxygenase (COX), the main target of NSAIDs."

…"paracetamol completely inhibited the synthesis of prostaglandin E(2) (PGE(2)) in lipopolysaccharide-stimulated microglia, when used at concentrations comparable to therapeutic doses. "

Laboratory of Pathophysiology, Istituto Superiore di Sanità, Rome, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/12605411

AM404, paracetamol metabolite, prevents prostaglandin synthesis in activated microglia by inhibiting COX activity

Results

"Our results show that AM404 inhibited LPS-mediated prostaglandin E2 (PGE2) production in OHSC, and LPS-stimulated PGE2 release was totally abolished in OHSC if microglial cells were removed. In primary microglia cultures, AM404 led to a significant dose-dependent decrease in the release of PGE2, independent of TRPV1 or CB1 receptors. Moreover, AM404 also inhibited the production of PGD2 and the formation of reactive oxygen species (8-iso-PGF2 alpha) with a reversible reduction of COX-1- and COX-2 activity. Also, it slightly decreased the levels of LPS-induced COX-2 protein, although no effect was observed on LPS-induced mPGES-1 protein synthesis."

Conclusions

"This study provides new significant insights about the potential anti-inflammatory role of AM404 and new mechanisms of action of paracetamol on the modulation of prostaglandin production by activated microglia."

-Department of Psychiatry and Psychotherapy, Laboratory of Translational Psychiatry, Faculty of Medicine, Medical Center – University of Freiburg, Hauptstr. 5, 79104 Freiburg, Germany

-Faculty of Biology, University of Freiburg, Freiburg, Germany

-Laboratory of Hepatic Encephalopathy and Portal Hypertension, Center of Applied and Experimental Pathology, University of Buenos Aires, Buenos Aires, Argentina

-Departamento de Biología Celular, Instituto Maimónides de Investigación Biomédica de Córdoba, Hospital Universitario Reina Sofía, Fisiología e Inmunología, Universidad de Córdoba, Córdoba, Spain

-Department of Pharmacology, Universidade Federal de Minas Gerais, Belo Horizonte, MG Brazil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5729401/

Arachidonic Acid Metabolites in Cardiovascular and Metabolic Diseases

"Lipid and immune pathways are crucial in the pathophysiology of metabolic and cardiovascular disease. Arachidonic acid (AA) and its derivatives link nutrient metabolism to immunity and inflammation, thus holding a key role in the emergence and progression of frequent diseases such as obesity, diabetes, non-alcoholic fatty liver disease, and cardiovascular disease. We herein present a synopsis of AA metabolism in human health, tissue homeostasis, and immunity, and explore the role of the AA metabolome in diverse pathophysiological conditions and diseases."…

“In addition, nutrient excess is associated with chronic inflammation, and obese and diabetic patients are prone to infections [127]. This observation was mechanistically linked to an impairment of leukocyte function, as lipid exposure hampers macrophage phagocytosis and efferocytosis [128,129,130,131]. Interestingly, autocrine actions of COX2-derived prostaglandins, such as PGE2 and PGD2, are implicated in this process, linking AA metabolism to macrophage function and immune surveillance in obese and diabetic patients [125,132]. As previously noticed, AA and its metabolites affect cell membrane fluidity, which is also important for phagocytosis and containment of microbes and may thus represent another link between AA metabolism and macrophage function.

Prostaglandins are among the most potent pro-inflammatory mediators, as reflected by their contribution to the development of toxic shock syndrome [133,134]. “…

-Department of Internal Medicine II, Medical University Innsbruck, Austria;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6274989

The role of nonsteroidal anti-inflammatory drugs in pediatric patients.

“Like in the adult population, nonsteroidal anti-inflammatory drugs (NSAIDS) are commonly used agents for their anti-inflammatory, anti-pyretic and analgesic effects in pediatrics. They are also used for some distinct indications in pediatrics such as Kawasaki disease, patent ductus arteriosus (PDA) closure, and Juvenile Idiopathic Arthritis (JIA). **The primary mechanism thought to cause their therapeutic effects is the inhibition of prostaglandin synthesis. NSAIDs inhibit cyclooxygenase (COX) which is an enzyme that is necessary for the formation of prostaglandins. Unfortunately, this same mechanism, the inhibition of prostaglandins, is thought to be the most likely cause of gastrointestinal (GI) mucosal damage, because prostaglandins through multiple mechanisms assist in the preparation and maintenance of the protective barrier of the mucosal lining of the stomach. Similarly, prostaglandins in the kidney promote intrarenal plasma flow and electrolyte balance. The efficacy and safety of NSAIDs must be considered in prescribing these agents.** The real conundrum of these therapies is determining the role of newer agents such as intravenous ibuprofen compared to existing alternatives. Available data for intravenous ibuprofen in adults is promising, but further studies are needed in pediatric patients to determine efficacy, place in therapy, and safety.”

-Department of Pharmacy, Wake Forest Baptist Medical Center, Medical Center Blvd., Winston Salem, NC 27157, United States.
https://www.ncbi.nlm.nih.gov/pubmed/21924358

Characterization of an AM404 Analogue, N-(3-Hydroxyphenyl)arachidonoylamide, as a Substrate and Inactivator of Prostaglandin Endoperoxide Synthase

…."The para isomer (AM404) acts as an inhibitor of PGHS [prostaglandin endoperoxide synthase](18), whereas we report here that the meta isomer serves as a substrate for PGHS."

-A. B. Hancock, Jr., Memorial Laboratory for Cancer Research, Departments of Biochemistry, Chemistry,
-Pharmacology, Vanderbilt Institute of Chemical Biology, Center in Molecular Toxicology
-Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2797370/

Ciprofloxacin reduces the stimulation of prostaglandin E(2) output by interleukin-1beta in human tendon-derived cells.

…"Ciprofloxacin reduces IL-1beta-induced PGE2 output in tendon-derived cells. The reduction in PGE2 output could modulate various cellular activities of IL-1beta, and may be implicated in fluoroquinolone-induced tendinopathy."

-Addenbrooke's Hospital, Cambridge, UK.
https://www.ncbi.nlm.nih.gov/pubmed/12810931

Low dose methotrexate decreases intraarticular prostaglandin and interleukin 1 levels in antigen induced arthritis in rabbits.

…"Our results show that MTX [Methotrexate], like dexamethasone, **reduces the intensity of** leukocyte afflux, protein leakage, synovial membrane PMN cell infiltrate, as well as the **intraarticular production of PGE2** [prostaglandin E2], TXB2, and IL-1 beta in the early phase of antigen induced arthritis in rabbits."

Rheumatology Division, School of Medicine, University of São Paulo, Brazil.
https://www.ncbi.nlm.nih.gov/pubmed/8970046

Inhibition of platelet prostaglandin synthetase by oral aspirin.

"Aspirin inhibits platelet function by permanently acetylating the cyclooxygenase that forms prostaglandins. "….

-The Journal of Clinical Investigations (1978 Feb) (Burch JW, Stanford N, Majerus PW.)
https://www.ncbi.nlm.nih.gov/pubmed/413839

Cannabinoids stimulate prostaglandin production by human gestational tissues through a tissue- and CB1-receptor-specific mechanism.

“Endocannabinoids have been implicated in the mechanisms of implantation, maintenance of pregnancy, and parturition in women. Intrauterine prostaglandin production and actions are also critical in each of these mechanisms. Hence, we have evaluated the effects of cannabinoids on prostaglandin biosynthesis by human gestational membranes.”….

”This study demonstrates a potential role for endocannabinoids in the modulation of prostaglandin production in late human pregnancy, with potentially important implications for the timing and progression of term and preterm labor and membrane rupture.”

-Liggins Institute, University of Auckland, Auckland, New Zealand.

https://www.ncbi.nlm.nih.gov/pubmed/18042663

See also: Inflammation , Pro-Inflammation

Metabolic Syndrome Exacerbates Inflammation and Bone Loss in Periodontitis

…”To further understand the potential mechanisms involved in MetS-boosted tissue inflammation, our in vitro studies showed that palmitic acid—the most abundant saturated fatty acid (SFA) and the major SFA in the HFD used in our animal study—potently enhanced LPS-induced proinflammatory gene expression in macrophages. In sum, this study demonstrated that MetS was associated with increased periodontal inflammation and alveolar bone loss in an LPS-induced periodontitis animal model. This study also suggests that SFA palmitic acid may play an important role in MetS-associated periodontitis by enhancing LPS-induced expression of inflammatory cytokines in macrophages.”

-Division of Endocrinology, Diabetes and Medical Genetics, Department of Medicine, College of Medicine, Medical University of South Carolina, Charleston, SC, USA

-Department of Oral Health Sciences, College of Dental Medicine, Medical University of South Carolina, Charleston, SC, USA

-Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4300302/

Increased saturated fatty acids in obesity alter resolution of inflammation in part by stimulating prostaglandin production

“Extensive evidence indicates that nutrient excess associated with obesity and type 2 diabetes activates innate immune responses that lead to chronic, sterile low-grade inflammation, and

obese and diabetic humans also have deficits in wound healing and increased susceptibility to infections. Nevertheless, the mechanisms that sustain unresolved inflammation during obesity remain unclear. In this study, we report that saturated free fatty acids that are elevated in obesity alter resolution of acute sterile inflammation by promoting neutrophil survival and decreasing macrophage phagocytosis. Using a targeted mass spectrometry-based lipidomics approach, we found that in db/db mice, PGE2/D2 levels were elevated in inflammatory exudates during the development of acute peritonitis. Moreover, in isolated macrophages, palmitic acid stimulated cyclooxygenase-2 induction and prostanoid production. Defects in macrophage phagocytosis induced by palmitic acid were mimicked by PGE2 and PGD2 and were reversed by cyclooxygenase inhibition or prostanoid receptor antagonism. Macrophages isolated from obese-diabetic mice expressed prostanoid receptors, EP2 and DP1, and contained significantly higher levels of downstream effector, cAMP, compared with wild-type mice. Therapeutic administration of EP2/DP1 dual receptor antagonist, AH6809, decreased neutrophil accumulation in the peritoneum of db/db mice, as well as the accumulation of apoptotic cells in the thymus. Taken together, these studies provide new insights into the mechanisms underlying altered innate immune responses in obesity and suggest that targeting specific prostanoid receptors may represent a novel strategy for resolving inflammation and restoring phagocyte defects in obese and diabetic individuals."

-Diabetes and Obesity Center, University of Louisville School of Medicine, Louisville, KY 40202, USA.
https://www.ncbi.nlm.nih.gov/pubmed/23785121

Natural anti-inflammatory agents for pain relief

…"NSAIDs' ability to interfere with the production of prostaglandin during the inflammatory cascade is the major mechanism cited for the anti-inflammatory success of these medications. [Figure 1].[112]"

…"Prostaglandins act as short-lived localized hormones that can be released by any cell of the body during tissue, chemical, or traumatic injury, and can induce fever, inflammation, and pain, once they are present in the intercellular space. Thromboxanes, which are also hormone activators, can regulate blood vessel tone, platelet aggregation, and clot formation to increase the inflammatory response.[92,82] The inflammatory pathway is a complex biochemical pathway which, once stimulated by injury, leads to the production of these and other inflammatory mediators whose initial effect is pain and tissue destruction, followed by healing and recovery.[34,51] A major component of the inflammatory pathway is called the arachidonic acid pathway because arachidonic acid is immediately released from traumatized cellular membranes. Membrane-based arachidonic acid is transformed into prostaglandins and thromboxanes partly

through the enzymatic action of cyclooxygenase (COX)[34,57]. There are two types of COX enzymes, COX-1 and COX-2. Both the enzymes act similarly, but selective inhibition (as accomplished by selective COX-2 inhibiting NSAIDs) can make a difference in terms of side effects.

Acetylsalicylic acid works by irreversibly disabling the COX enzymes to block the cascade [Figure 1]. NSAIDs have evolved from blocking both COX-1 and COX-2 to selectively only blocking COX-2 in order to inhibit the inflammatory response and reduce the production of inflammatory prostaglandins and thromboxanes. The major push to develop the selective COX-2 inhibitors has been the recognition of significant complications associated with the nonselective COX-1 and COX-2 NSAIDs. Nonselective NSAIDs' major side effects include significant gastrointestinal upset, gastritis, ulceration, hemorrhage, and even death. By locking COX-1, which also normally acts to protect the gastrointestinal mucosa, nonselective NSAIDs and aspirin can cause significant gastric tissue damage.[34,51,78,91,3,101,115]

Various studies have also shown that NSAIDs can delay muscle regeneration and may reduce ligament, tendon, and cartilage healing.[4,13,77] Specifically, NSAIDs are believed to wipe out the entire inflammatory mediated proliferative phase of healing associated with WBC actions (days 0–4). A study of the effects of NSAIDs on acute hamstring injuries was done in humans by Reynolds et al.,[93] and these investigators concluded that patients who used NSAIDs did not experience a greater reduction of pain and soft-tissue swelling when compared with the placebo group. Interestingly enough, the authors noted that the NSAIDs' group had worse pain associated with severe injuries compared with the placebo group.

The NSAIDs are also known to have adverse effects on kidney function.[31] Dehydration or preexisting chronic renal failure or disease, resulting in stimulation of the renin–angiotensin system, may predispose certain populations to acute renal failure through inhibition of prostaglandin synthesis, which can occur when taking NSAIDs.[31] The National Kidney Foundation asserts that approximately 10% of kidney failures per year are directly correlated to substantial overuse of NSAIDs."

-Department of Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
-Vanderbilt University, Nashville, TN, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3011108/

Effects of alcohol on gastric prostaglandin production and glutathione status

"Ethanol damages the gastric mucosa, an effect that can be protected against by cytoprotective prostaglandins (PGs) and exacerbated by inhibition of PGs"...

-Biochemical Society Transactions (1994)
-NEVILLE A. PUNCHARD ; DUNCAN J. WATSON ; JULIAN P. TEARE ; ELENA FITA-ROBINSON ; RICHARD PH. THOMPSON

https://portlandpress.com/biochemsoctrans/article-abstract/22/2/196S/88691/Effects-of-alcohol-on-gastric-prostaglandin?redirectedFrom=PDF

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"Prostaglandins (PG) are pleiotropic bioactive lipids involved in the control of many physiological processes, including key roles in regulating inflammation. This links PG to the modulation of the quality and magnitude of immune responses. T cells, as a core part of the immune system, respond readily to inflammatory cues from their environment, and express a diverse array of PG receptors that contribute to their function and phenotype. Here we put in context our knowledge about how PG affect T cell biology, and review advances that bring light into how specific T cell functions that have been newly discovered are modulated through PG. We will also comment on drugs that target PG metabolism and sensing, their effect on T cell function during disease, and we will finally discuss how we can design new approaches that modulate PG in order to maximize desired therapeutic T cell effects."...

-Department of Microbiology, University of Pennsylvania School of Medicine,Smillow Center for Translational Research, Philadelphia, PA, USA

-Department of Systems Pharmacology and Translational Therapeutics, Institute for Translational Medicine and Therapeutics, University of Pennsylvania, Philadelphia, PA, USA

-Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

https://www.sciencedirect.com/science/article/abs/pii/S1043661819310345

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"Although there is evidence to suggest that n−3 [omega-3] PUFAs have antiinflammatory properties [4], in the Western diet, n−6 PUFAs [omega-6] , particularly linoleic acid (18:2n−6), account for ~ 89% of the total PUFA energy intake [5]. Dietary linoleic acid can be metabolized through a series of desaturation and elongation reactions into arachidonic acid (20:4n−6) [6].

Arachidonic acid [omega-6] is the parent compound for multiple inflammatory eicosanoids [7]. In the cyclooxygenase pathway, arachidonic acid is converted into various bioactive lipid molecules including prostaglandin E2 [8]. Animal models of CRC have shown the connection between tumor formation and arachidonic acid with a positive correlation between increasing tissue concentrations of arachidonic acid, increased prostaglandin E2 production, and increased intestinal tumor number and size [9–12]. In addition, upregulation of cyclooxygenase-2 occurs in 50% of colon adenomas and 85% of colon cancers and is considered a key and early oncogenic event in colorectal carcinogenesis [13]. n−3 PUFAs are converted to eicosanoids through the same enzymatic pathways as arachidonic acid but produce series 3 eicosanoids that have less inflammatory actions compared with those of arachidonic acid–derived series 2 eicosanoids [7, 14,

15)."

-From the Divisions of General Internal Medicine (HJM), Public Health and Epidemiology, Vanderbilt Epidemiology Center (MJS, QC, QD, and WZ), Gastroenterology (WES and RMN), and Clinical Pharmacology (GLM), and the Department of Preventive Medicine (WES), Vanderbilt University School of Medicine, Nashville, TN; the Geriatric Research Education and Clinical Care, Department of Veterans Affairs, Tennessee Valley Healthcare System, Nashville, TN (HJM, MJS, QD, and WZ); and the Vanderbilt Ingram Cancer Center, Nashville, TN (HJM, MJS, QC, WES, QD, RMN, and WZ).

-The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the NIH.

-Supported by the National Cancer Institute (grants P50CA 95103, R01CA97386, R01CA143288, and K07CA114029). Surveys and sample collection and processing for this study were conducted by the Survey and Biospecimen Shared Resource, which is supported in part by grant P30CA68485.

-Address correspondence to HJ Murff, Vanderbilt Epidemiology Center, Institute of Medicine and Public Health, Sixth Floor, Suite 600, 2525 West End Avenue, Nashville, TN 37203-1738.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278245/

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…"Both arachidonic acid (AA) [omega-6] and EPA [omega-3] are metabolized in vivo by the cyclooxygenase, lipoxygenase, and epoxygenase pathways to prostaglandins [PGE2], hydroxy fatty acids as well as leukotrienes, and epoxy fatty acids, respectively. To assess the PUFA metabolic changes in the animals treated with EPA, we analyzed the plasma eicosanomic profiles of both treated and untreated animals by LC-MS. The method included all possible metabolites of AA and EPA from all three enzymatic pathways. Table 1 shows the detected metabolites of both fatty acids in plasma. The results show a lower concentration of AA metabolites in EPA+FuOx treated animals compared to control FuOx treated mice and a significantly lower concentration of inflammatory mediators, LTB4 (and its metabolite 12-Oxo LTB4) and PGE2 (as well as its metabolites, 13,14-dihydro-15-keto PGE2 and bicyclo PGE2) in EPA+FuOx treated animals. "….

-Veterans Affairs Medical Center, Wayne State University, Detroit, Michigan
-Karmanos Cancer Institute, Wayne State University, Detroit, Michigan
-Department of Internal Medicine, Wayne State University, Detroit, Michigan
-Department of Pathology, Wayne State University, Detroit, Michigan
-Lipidomics Core Facility, Wayne State University, Detroit, Michigan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4221533/

Omega-3 fatty acid is a potential preventive agent for recurrent colon cancer

…"Both AA [omega-6 / ω-6] and EPA [omega-3 / ω-3] are metabolized by the same enzymes to highly physiologically active lipid mediators such as prostaglandins, leukotrienes, hydroxy and epoxy fatty acids. However, metabolites of AA (an ω-6 PUFA) are pro-inflammatory, whereas

those derived from EPA (an ω-3 PUFA) are anti-inflammatory and participate in active resolution of inflammation [51–53]. “

-Veterans Affairs Medical Center, Wayne State University, Detroit, Michigan
-Karmanos Cancer Institute, Wayne State University, Detroit, Michigan
-Department of Internal Medicine, Wayne State University, Detroit, Michigan
-Department of Pathology, Wayne State University, Detroit, Michigan
-Lipidomics Core Facility, Wayne State University, Detroit, Michigan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4221533/

Eicosanoid Storm in Infection and Inflammation

“The overall impacts of the eicosanoid and cytokine storms on host survival are likely context dependent and will require greater focus on age, diet, and genetic variation in addition to the specific pathogenic assault and severity of trauma. Refined application of lipidomics methodologies and similar approaches will be critical to advance the understanding of eicosanoids in health and disease. With the ability that lipidomics brings to now assess changes in the majority of eicosanoid species simultaneously, determining both the pro-inflammatory and anti-inflammatory contributions of eicosanoids in specific diseases will likely accelerate.

The expanded view of eicosanoid signaling since the introduction of lipidomics is remarkably more complex, but the potential for improving therapeutic design is promising. Advancing treatment beyond NSAIDs may need to be more focused on isolating and correcting deficiencies in bioactive eicosanoids, rather than blunting entire pathways. The ability to now analyze hundreds of eicosanoids and related lipid species, alongside the handful of well-characterized prostaglandins and leukotrienes, provides a wealth of possibilities to understand and develop novel treatments for inflammatory and metabolic conditions. A better understanding of the cytokine storm and its integration with the eicosanoid storm that accompanies classic inflammation and its resolution should provide new insights leading to novel strategies for the understanding and treatment of infection and inflammation.”

-Department of Chemistry and Biochemistry and Department of Pharmacology, School of Medicine, University of California at San Diego, La Jolla, California, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4606863/

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…“Prostaglandin synthesis begins with the release of arachidonic acid from membrane phospholipids by phospholipase activity. Subsequently, arachidonic acid is converted into

prostaglandin H2 (PGH2) by cyclo-oxygenase via two independent catalytic steps.[10] Synthase enzymes then convert PGH2 into the specific prostaglandins produced by that cell such as PGD2, PGE2, PGF2α, prostacyclin, and thromboxane. Thus, cyclo-oxygenase activity is essential for normal prostaglandin production and cyclo-oxygenase is believed to be the rate-limiting enzyme in the prostaglandin synthetic pathway."…

-Department of Orthopaedics, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, USA.

https://pubmed.ncbi.nlm.nih.gov/12054171/

Prostaglandins, arachidonic acid, and inflammation

"The enzymatic oxidation of arachidonic acid has been shown to yield potent pathological agents by two major pathways. Those of the prostaglandin (PG) pathway, particularly PGE2, have been implicated as inflammatory mediators for many years. The discovery and biological activities of thromboxane A2 and prostacyclin as well as a destructive oxygen-centered radical as additional products of this biosynthetic pathway now require these to be considered as potential inflammatory mediators. Like PGE2, their biosynthesis is prevented by nonsteroidal anti-inflammatory agents. More recently, the alternative metabolic route, the lipoxygenase pathway, has been shown to yield a new class of arachidonic acid oxygenation products, called the leukotrienes, which also appear to be important inflammatory mediators. Unlike the prostaglandins, some of which play important roles as biological regulators, the actions of the lipoxygenase products appear to be exclusively of a pathological nature."

-F A Kuehl Jr, R W Egan

https://pubmed.ncbi.nlm.nih.gov/6254151/

See also Cyclooxygenase (COX)

Prostaglandins & Bruising

A role for prostacyclin in bruising symptomatology.

…"It is suggested that prostacyclin formed at the injured vessel surface collects within the first few seconds after injury inside the tissue space at the site of the bruise and, by influencing the formation of the platelet/fibrin plug and/or the leakage of blood from the vessels, plays a

significant role in modifying the development of bruising."

-Department of Pediatrics, University of Manitoba, Winnipeg, Canada.
https://www.ncbi.nlm.nih.gov/pubmed/1614775

Prostacyclin - is a prostaglandin member of the eicosanoid family of lipid molecules.

Prostaglandins & Sexual Dysfunction

Female Sexual Dysfunction: Therapeutic Options and Experimental Challenges

…"Prostaglandins (PG) are found in virtually all tissues and organs. They are autocrine and paracrine lipid molecules, which are quickly metabolized, and participate in a variety of physiological events, including blood flow regulation. Specifically, the PG isoform PGE1 (signaling through its EP2 receptor) causes smooth muscle relaxation in the vaginal, uterine, as well as penile smooth muscle [39]. PGE1/EP2 activation leads to increases in cAMP resulting in activation of protein kinase A, which causes smooth muscle relaxation. Prostaglandins have been used in male sexual dysfunction, especially erectile dysfunction (administered through penile injection), for some time and have displayed positive outcomes for certain women with genital sexual arousal disorder, most likely through increasing vaginal secretion and arterial smooth muscle relaxation [40]…

- Department of Physiology, Medical College of Georgia, Augusta, Georgia, USA
- Department of Pharmacology, University of Sao Paulo, Sao Paulo, SP, Brazil
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3008577/

Prostate Cancer

"Eicosanoids, the metabolites of arachidonic acid [omega-6], have diverse functions in the regulation of cancer including prostate cancer. This review will provide an overview of the roles of eicosanoids and endocannabinoids and their potential as therapeutic targets for prostate cancer treatment.

Prostate cancer is among the most diagnosed malignancies and contributes to cancer-related mortality rate in men. The vast majority of morbidity and mortality results from spread of the tumor beyond the prostate gland and/or tumor becoming hormone refractory. The process of

metastasis is a complex multistage process consisting of a series of sequential, interrelated steps that include growth, vascularization, adhesion, extravasation, and invasion. The discovery of new molecular targets to inhibit cell proliferation, growth, and invasion/migration is among the most important endeavors in prostate cancer therapy.

High fat diets, particularly ω-6 [omega-6] polyunsaturated fatty acids, are associated with prostate cancer development and progression [1, 2] and prostate cancer cell growth [3, 4]. On the other hand, diets rich in ω-3 fatty acids are associated with the lower incidents of the disease in some studies [1, 5], whereas other reports indicated no evidence of a significant reduced risk of prostate cancer [6] or even increased risk [7]. These opposing roles of fatty acids are consistent with the fact that diet is an important factor in the coincidence of prostate cancer. The high ratio of ω-3/ω-6 fatty acids in the diet has been suggested to prevent prostate cancer [8]. Although in one study showed that plant-based foods and fish diets do not reduce the prostate specific antigen (PSA) levels in prostate cancer patients, they significantly increase the PSA doubling times [9]."…

…"In BPH [benign prostatic hyperplasia] and prostate cancer tissues, PGE2 is the only major PG that is produced in significant amounts by the prostate and its levels are higher in prostate cancer tissues [51]. PGE2 stimulates growth of prostate cancer cells including PC-3 and LNCaP cells [52, 53]."…

"The ω-6 polyunsaturated fatty acid, AA, plays various important roles in prostate cancer. AA can be metabolized to numerous metabolites and act as endogenous lipid signaling molecules that may have diverse effects on prostate cancer cells. The balance and/or specific pathways of synthesis, degradation, and signal transduction activation will dictate prostate cancer cell fate and cancer development and progression."

-Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928987/

Expression of cyclooxygenase-2 in prostate carcinoma

"**Background:** Nonsteroidal antiinflammatory drugs inhibiting cyclooxygenase (COX) enzyme activity in both its constitutive (COX-1) and inducible (COX-2) isoforms were shown also to inhibit the development of colon carcinoma in animal models. COX-2 is an inducer of angiogenesis of new blood vessels. The expression of COX-1 and COX-2 in prostate tissues from patients with prostate carcinoma was investigated using reverse transcriptase-polymerase chain reaction (RT-PCR) and immunohistochemistry."…

"**Conclusions:** The results of the current study demonstrated that human prostate carcinoma

cells generated COX-2, and that COX-2 might play an important role in the proliferation of prostate carcinoma cells. These findings suggest that inhibition of COX-2 development may lead not only to inhibition of the proliferation and metastasis of prostate carcinoma but also to the inhibition of prostate carcinogenesis."

-Department of Urology, Osaka City University Medical School, Osaka, Japan.
https://pubmed.ncbi.nlm.nih.gov/10931458

A low dietary ratio of omega-6 to omega-3 Fatty acids may delay progression of prostate cancer.

"Prostate cancer (PCa) is the second leading cause of cancer-related deaths in men. Studies show that consumption of polyunsaturated fatty acids (PUFA) modulates the development and progression of prostate cancer. High amounts of omega-6 fatty acids have been linked with increased prostate cancer risk, whereas omega-3 fatty acids have been shown to inhibit PCa growth. However, because omega-3 and omega-6 are both essential fatty acids and part of a complete diet, it is more relevant to determine the ideal ratio of the two that would allow patients to benefit from the therapeutic properties of omega-3 fatty acids. LNCaP prostate cancer cells were treated with dietary-based ratios of omega-6 to omega-3 fatty acids under hormone-deprivation conditions, and effects on various cellular processes were determined. A low omega-6 to omega-3 PUFA ratio can delay the progression of cells toward castration-resistance by suppressing pathways involved in prostate cancer progression, such as the Akt/mTOR/NFκB axis. It also suppresses the expression of cyclin D1, and activation of caspase-3 and annexin V staining shows induction of proapoptotic events. Taken together, our data demonstrates that maintaining a low omega-6 to omega-3 fatty acids ratio can enhance efficacy of hormone ablation therapy."

-Dell Pediatric Research Institute, Department of Nutritional Sciences, The University of Texas at Austin, Austin, Texas, USA.
https://www.ncbi.nlm.nih.gov/pubmed/23659447

"**Endocannabinoids regulate growth and migration of a variety of cancer cells and have therapeutic potential in cancer treatment** [160, 164–177]. In prostate cancer, AEA, acting through the CB1 receptor, inhibits the EGF-induced proliferation of prostate carcinoma cells [178] by decreasing EGFR expression and increasing ceramide production. "…

"Inhibition of eCB hydrolysis by either pharmacological inhibitors or siRNA knockdown of the FAAH inhibits invasion of these cells [179, 183]. The combination of eCB hydrolysis inhibition and treatment with exogenous eCBs further inhibit cell invasion [179].

Furthermore, 2-AG can increase cell invasion due to its hydrolysis to AA and subsequent metabolism to 12-HETE [112], but it will inhibit invasion in the presence of the hydrolysis inhibitors [179].

These studies demonstrated that eCBs regulate prostate cancer proliferation and invasion, and their hydrolysis can dictate the differential effects of eCBs and responses."

Endocannabinoids

- Endocannabinoids, acting through CB1 receptor inhibit proliferation and invasion of prostate cancer cells.
- Hydrolysis of endocannabinoids affects the activity of endocannabinoids in the regulation of prostate cancer cells because it reduces the ligand concentrations and liberates the free AA.
- Endocannabinoids may regulate prostate cancer cells by non-receptor-mediated mechanisms.

-Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928987/

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"The bioactivity of omega-3 eCBs have also been demonstrated in cancer models. In this study, DHA-EA significantly induced the cell death of prostate cancer cells sensitive to androgen (LNCaP) and insensitive to androgen (PC3). Moreover, expression of CB1 and CB2 in PC3 and LNCaP were determined and radioligand binding studies confirmed DHA-EA as an agonist of both the CB receptors. Additionally, degradation of DHA-EA by FAAH was measured and the inhibition of this enzyme in LNCaP cells led to a potent increase in its anti-proliferative properties [(18)]. In other cancer cell types, such as breast cancer cells, DHA-EA mediated anti-proliferation effects through the PPARγ activation pathway [(50)]."

-Department of Comparative Biosciences, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Department of Biochemistry, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Division of Nutritional Sciences, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
-Beckman Institute for Advanced Science, Neuroscience Program, Center for Biophysics and Quantitative Biology, Department of Bioengineering, University of Illinois, Urbana-Champaign, Urbana, Illinois, United States
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6685292

Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production

"Background: Anandamide (ANA) is an endogenous lipid which acts as a cannabinoid receptor ligand and with potent anticarcinogenic activity in several cancer cell types.

Methods: The inhibitory effect of ANA on the epidermal growth factor receptor (EGFR) levels expressed on the EGF-stimulated prostatic cancer cells LNCaP, DU145, and PC3 was estimated by ELISA tests. The anti-proliferative and cytotoxic effects of ANA were also evaluated on these human prostatic cancer cell lines by growth tests, flow cytometric analyses, trypan blue dye exclusion assays combined with the Papanicolaou cytological staining method.

Results: ANA induced a decrease of EGFR levels on LNCaP, DU145, and PC3 prostatic cancer cells by acting through cannabinoid CB(1) receptor subtype and this leaded to an inhibition of the EGF-stimulated growth of these cells. Moreover, the G(1) arrest of metastatic DU145 and PC3 growth was accompanied by a massive cell death by apoptosis and/or necrosis while LNCaP cells were less sensitive to cytotoxic effects of ANA. The apoptotic/necrotic responses induced by ANA on these prostatic cancer cells were also potentiated by the acidic ceramidase inhibitor, N-oleoylethanolamine and partially inhibited by the specific ceramide synthetase inhibitor, fumonisin B1 indicating that these cytotoxic actions of ANA might be induced via the cellular ceramide production.

Conclusions: The potent anti-proliferative and cytotoxic effects of ANA on metastatic prostatic cancer cells might provide basis for the design of new therapeutic agents for effective treatment of recurrent and invasive prostatic cancers."

-Albert Lespagnol Institute of Pharmaceutical Chemistry, 3 Rue du Professeur Laguesse, BP83, Lille, France.
https://pubmed.ncbi.nlm.nih.gov/12746841/

Mechanisms of Omega-3 Polyunsaturated Fatty Acids in Prostate Cancer Prevention

"The health benefits of omega-3 polyunsaturated fatty acids (n-3 PUFA), mainly eicosapentaenoic acid (EPA 20:5) and docosahexaenoic acid (DHA, 22:6), have been long known. Epidemiologic studies dating back to the 1970s were among the first to suggest that dietary PUFA may be beneficial in preventing disease [1, 2]. Still today, studies continue to demonstrate the health benefits of n-3 PUFA; however, the mechanisms of action of n-3 PUFA are still not fully understood. Many new discoveries have advanced our understanding about the activities of n-3 PUFA against human disease. For example, DHA-receptor GPR120 has been demonstrated to

play a role in sensing and controlling obesity and metabolic syndrome [3]; the recently identified omega-3 mediators, resolvins, and protectins have been demonstrated to have anti-inflammatory and proresolving activities [4]. The purpose of this review is to highlight the recent advances in our understanding of the mechanisms by which n-3 PUFA modulate prostate cancer development."

-State Key Laboratory of Food Science and Technology, School of Food Science and Technology, Jiangnan University, Wuxi, China

-Department of Cancer Biology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3676993/

The role of cannabinoids in prostate cancer: Basic science perspective and potential clinical applications

"Prostate cancer is a global public health problem, and it is the most common cancer in American men and the second cause for cancer-related death. Experimental evidence shows that prostate tissue possesses cannabinoid receptors and their stimulation results in anti-androgenic effects. To review currently relevant findings related to effects of cannabinoid receptors in prostate cancer. PubMed search utilizing the terms "cannabis," "cannabinoids," "prostate cancer," and "cancer pain management," giving preference to most recent publications was done. Articles identified were screened for their relevance to the field of prostate cancer and interest to both urologist and pain specialists. Prostate cancer cells possess increased expression of both cannabinoid 1 and 2 receptors, and stimulation of these results in decrease in cell viability, increased apoptosis, and decreased androgen receptor expression and prostate-specific antigen excretion. It would be of interest to conduct clinical studies utilizing cannabinoids for patients with metastatic prostate cancer, taking advantage not only of its beneficial effects on prostate cancer but also of their analgesic properties for bone metastatic cancer pain."…

-Department of Urology, Columbia University, Mt Sinai Medical Center, Alton Rd, Miami Beach, FL 33129, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3339795

Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms

"**Background and purpose:** Cannabinoid receptor activation induces prostate carcinoma cell (PCC) apoptosis, but cannabinoids other than Δ(9) -tetrahydrocannabinol (THC), which lack potency at

cannabinoid receptors, have not been investigated. Some of these compounds antagonize transient receptor potential melastatin type-8 (TRPM8) channels, the expression of which is necessary for androgen receptor (AR)-dependent PCC survival.

Experimental approach: We tested pure cannabinoids and extracts from Cannabis strains enriched in particular cannabinoids (BDS), on AR-positive (LNCaP and 22RV1) and -negative (DU-145 and PC-3) cells, by evaluating cell viability (MTT test), cell cycle arrest and apoptosis induction, by FACS scans, caspase 3/7 assays, DNA fragmentation and TUNEL, and size of xenograft tumours induced by LNCaP and DU-145 cells.

Key results: Cannabidiol (CBD) significantly inhibited cell viability. Other compounds became effective in cells deprived of serum for 24 h. Several BDS were more potent than the pure compounds in the presence of serum. CBD-BDS (i.p.) potentiated the effects of bicalutamide and docetaxel against LNCaP and DU-145 xenograft tumours and, given alone, reduced LNCaP xenograft size. CBD (1-10 μM) induced apoptosis and induced markers of intrinsic apoptotic pathways (PUMA and CHOP expression and intracellular Ca(2+)). In LNCaP cells, the pro-apoptotic effect of CBD was only partly due to TRPM8 antagonism and was accompanied by down-regulation of AR, p53 activation and elevation of reactive oxygen species. LNCaP cells differentiated to androgen-insensitive neuroendocrine-like cells were more sensitive to CBD-induced apoptosis.

Conclusions and implications: These data support the clinical testing of CBD against prostate carcinoma."

-Institute of Cybernetics, Endocannabinoid Research Group, National Research Council, Pozzuoli, Italy.
https://pubmed.ncbi.nlm.nih.gov/22594963/

Cannabinoid receptor as a novel target for the treatment of prostate cancer

"Cannabinoids, the active components of Cannabis sativa Linnaeus (marijuana) and their derivatives have received renewed interest in recent years due to their diverse pharmacologic activities such as cell growth inhibition, anti-inflammatory effects and tumor regression. Here we show that expression levels of both cannabinoid receptors, CB1 and CB2, are significantly higher in CA-human papillomavirus-10 (virally transformed cells derived from adenocarcinoma of human prostate tissue), and other human prostate cells LNCaP, DUI45, PC3, and CWR22Rnu1 than in human prostate epithelial and PZ-HPV-7 (virally transformed cells derived from normal human prostate tissue) cells. WIN-55,212-2 (mixed CB1/CB2 agonist) treatment with androgen-responsive LNCaP cells resulted in a dose- (1-10 micromol/L) and time-dependent (24-48 hours) inhibition of cell growth, blocking of CB1 and CB2 receptors by their antagonists SR141716 (CB1)

and SR144528 (CB2) significantly prevented this effect. Extending this observation, we found that WIN-55,212-2 treatment with LNCaP resulted in a dose- (1-10 micromol/L) and time-dependent (24-72 hours) induction of apoptosis (a), decrease in protein and mRNA expression of androgen receptor (b), decrease in intracellular protein and mRNA expression of prostate-specific antigen (c), decrease in secreted prostate-specific antigen levels (d), and decrease in protein expression of proliferation cell nuclear antigen and vascular endothelial growth factor (e). Our results suggest that WIN-55,212-2 or other non-habit-forming cannabinoid receptor agonists could be developed as novel therapeutic agents for the treatment of prostate cancer."

-Department of Dermatology, University of Wisconsin, Madison, Wisconsin, USA
https://pubmed.ncbi.nlm.nih.gov/15753356/

Delta9-tetrahydrocannabinol [THC] induces apoptosis in human prostate PC-3 cells via a receptor-independent mechanism

"The effect of delta9-tetrahydrocannabinol (THC), the major psycho-active component of marijuana, in human prostate cancer cells PC-3 was investigated. THC caused apoptosis in a dose-dependent manner. Morphological and biochemical changes induced by THC in prostate PC-3 cells shared the characteristics of an apoptotic phenomenon. First, loss of plasma membrane asymmetry determined by fluorescent anexin V binding. Second, presence of apoptotic bodies and nuclear fragmentation observed by DNA staining with 4',6-diamino-2-phenylindole (DAPI). Third, presence of typical 'ladder-patterned' DNA fragmentation. Central cannabinoid receptor expression was observed in PC-3 cells by immunofluorescence studies. However, several results indicated that the apoptotic effect was cannabinoid receptor-independent, such as lack of an effect of the potent cannabinoid agonist WIN 55,212-2, inability of cannabinoid antagonist AM 251 to prevent cellular death caused by THC and absence of an effect of pertussis toxin pre-treatment."

-Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Alcalá, Alcalá de Henares, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/10570948/

delta(9)-Tetrahydrocannabinol [THC] increases nerve growth factor production by prostate PC-3 cells. Involvement of CB1 cannabinoid receptor and Raf-1

"Cannabinoids, the active components of marihuana, exert a variety of effects in humans. Many of these effects are mediated by binding to two types of cannabinoid receptor, CB1 and CB2.

Although CB1 is located mainly in the central nervous system, it may also be found in peripheral tissues. Here, we study the effect of cannabinoids in the production of nerve growth factor by the prostate tumor cell line PC-3. We show that addition of Delta(9)-tetrahydrocannabinol to PC-3 cells stimulated nerve growth factor production in a dose-dependent and time-dependent manner. Maximal effect was observed at 0.1 microM Delta(9)-tetrahydrocannabinol and 72 h of treatment. Stimulation was reversed by the CB1 antagonists AM 251 and SR 1411716A. Pre-treatment of cells with pertussis toxin also prevented the effect promoted by Delta(9)-tetrahydrocannabinol. These results indicate that Delta(9)-tetrahydrocannabinol stimulation of nerve growth factor production in these cells was mediated by the cannabinoid CB1 receptor. The implication of Raf-1 activation in the mode of action of Delta(9)-tetrahydrocannabinol is also suggested."

-Department of Biochemistry and Molecular Biology, University of Alcalá, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/11168391/

Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: Involvement of CB2

Background:

"We have previously shown that cannabinoids induce growth inhibition and apoptosis in prostate cancer PC-3 cells, which express high levels of cannabinoid receptor types 1 and 2 (CB1 and CB2). In this study, we investigated the role of CB2 receptor in the anti-proliferative action of cannabinoids and the signal transduction triggered by receptor ligation.

Methods:

The human prostate cancer cell lines, namely PC-3, DU-145 and LNCaP, were used for this study. Cell proliferation was measured using MTT proliferation assay, [3H]-thymidine incorporation assay and cell-cycle study by flow cytometry. Ceramide quantification was performed using the DAG kinase method. The CB2 receptor was silenced with specific small interfering RNA, and was blocked pharmacologically with SR 144528. In vivo studies were conducted by the induction of prostate xenograft tumours in nude mice.

Results:

We found that the anandamide analogue, R(+)-Methanandamide (MET), as well as JWH-015, a synthetic CB2 agonist, exerted anti-proliferative effects in PC-3 cells. R(+)-Methanandamide- and JWH-015-induced cell death was rescued by treatment with the CB2 receptor antagonist, SR 144528. Downregulation of CB2 expression reversed the effects of JWH-015, confirming the involvement of CB2 in the pro-apoptotic effect of cannabinoids. Further analysing the

mechanism of JWH-015-induced cell growth inhibition, we found that JWH-015 triggered a de novo synthesis of ceramide, which was involved in cannabinoid-induced cell death, insofar as blocking ceramide synthesis with Fumonisin B1 reduced cell death. Signalling pathways activated by JWH-015 included JNK (c-Jun N-terminal kinase) activation and Akt inhibition. In vivo treatment with JWH-015 caused a significant reduction in tumour growth in mice.

Conclusions:

This study defines the involvement of CB2-mediated signalling in the in vivo and in vitro growth inhibition of prostate cancer cells and suggests that CB2 agonists have potential therapeutic interest and deserve to be explored in the management of prostate cancer."

-Department of Biochemistry and Molecular Biology, School of Medicine, University of Alcalá, Alcalá de Henares, 28871 Madrid, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2743360/

Psoriasis

"Psoriasis-- is a chronic, autoimmune skin disease that is characterized by epidermal hyperproliferation and skin inflammation."

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary

-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ, USA

-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck, Germany

-School of Translational Medicine, University of Manchester, Manchester, UK

-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

Omega-3 fatty acids as pharmacotherapeutics in psoriasis: current status and scope of nanomedicine in its effective delivery

"Psoriasis is a multifactorial autoimmune skin disorder based on irregularities of the T- cell function. The abnormal keratinocyte hyper proliferation in psoriasis arises due to the activation of T-cells which produces rich amount of arachidonic acid leads to generation of various proinflammatory mediators like PGs, LTs, cytokines and adhesion molecules via MAPK/AP-1, EARK1/2 and protein kinase-C (PKCs) activation pathways. Incorporation of naturally occuring bioactives like, omega (ω)-3 fatty acids (i.e., EPA and DHA) in a dose dependent manner results in inhibition of various pro-inflammatory mediators and metabolization of EPA and DHA leads to

dampening of inflammation and higher resolution of the skin abnromalities. These all due to the promotion of the synthesis of ω-3 PUFA-derived lipid mediators viz namely resolvins and protectins. These have been widely used alone or in combination with other drugs in the treatment of psoriasis. Despite of their meritorious visages, the use of these bioactives is associated with several hiccups like higher unstability and vulnerable to degradation due to lipid peroxidation, poor and incosistent bioavilability by oral and topical administration. The potential use of nanomedicines in the delivery of such bioactives has gained wider attention owing to their promising bioavailability enhancement characteristics, improved stability and better efficacy. The present review gives an extensive account on ω-3 fatty acids (EPA and DHA) starting from seedling to apex, including biosynthesis, metabolites, and its mechanism of action in psoriasis. Moreover, barriers in the effective delivery of ω-3 fatty acids and how nanomedicines can be fit in the scope of its therapeutic delivery in psoriasis have also been addressed. Despite numerous advantages, application of EPA-DHA as ω-3 fatty acids therapeutics in the management of psoriasis are still at an initial stage. Nanomedicines approach to achieve high bioavailable delivery with safety and stability of ω-3 fatty acids showing the promising area for the future in psoriasis management."

-Department of Pharmaceutics, Dreamz College of Pharmacy, India.
https://pubmed.ncbi.nlm.nih.gov/23531113

Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, multicenter trial

"Background: Profound changes in the metabolism of eicosanoids with increased concentrations of free arachidonic acid (AA) and its proinflammatory metabolites have been observed in psoriatic lesions. Free eicosapentaenoic acid (EPA) may compete with liberated AA and result in an antiinflammatory effect."…

"Conclusion: Intravenous omega-3-fatty acid administration is effective in the treatment of chronic plaque-type psoriasis. This effect may be related to changes in inflammatory eicosanoid generation."

-Department of Dermatology and Andrology, Justus Liebig University Giessen, Germany.
https://pubmed.ncbi.nlm.nih.gov/9555791/

Psoriasis and skin tumors: aiming to increase ECS tone

…"Data showing that the cutaneous ECS tonically inhibits cell growth and angiogenesis and

induces apoptosis in most of the skin cell types, and that both human non-melanoma and melanoma tumors express considerable amounts of CB1 and CB2 [36,39,41,42,45,53], now warrant proof-of-principle studies to test the therapeutic value of cannabinoid agonists in the clinical management of hyperproliferative skin disease (e.g. psoriasis, which is characterized by a highly accelerated turnover of epidermal keratinocyte proliferation) and skin tumors of various cutaneous cell origins. Furthermore, these interventions (as detailed later) might also suppress skin inflammation seen in psoriasis."…

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ, USA
-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck, Germany
-School of Translational Medicine, University of Manchester, Manchester, UK
-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

A double-blind, randomized, placebo-controlled trial of n-3 fatty acid based lipid infusion in acute, extended guttate psoriasis. Rapid improvement of clinical manifestations and changes in neutrophil leukotriene profile

"Twenty patients hospitalized for acute psoriasis guttata with a minimum 10% of body surface area involvement (range 10-90%) completed a 10-day trial in which they were randomly allocated to receive daily infusions with either an n-3 fatty acid based lipid emulsion [100 ml/day with 2.1 g eicosapentaenoic (EPA) and 21 g docosahexaenoic acid (DHA)] or a conventional n-6 lipid emulsion (EPA + DHA < 0.1 g/100 ml). The severity of disease was evaluated by scoring daily erythema, infiltration, and desquamation and by a subjective scoring of clinical manifestations offered by the patients. Leukotriene (LT) and platelet-activating factor (PAF) generation were investigated in ionophore-stimulated neutrophils obtained on days 0, 1, 3, 5, 10, and 40. Moderate improvement in clinical manifestations was noted in the n-6 group (changes in score systems between 16-25% from baseline within 10 days). In contrast, the severity of disease markedly decreased in all patients of the n-3 group, with improvements in all score systems ranging between 45% and 76% within 10 days ($P < 0.05$ for each variable). The difference in response to the two regimens was evident within 4-7 days after onset of lipid infusion. A more than ten fold increase in neutrophil EPA-derived 5-lipoxygenase product formation (LTB5, its omega-oxidation products, non-enzymatic degradation products of LTA5 and 5-hydroxyeicosapentaenoic acid) was noted in the n-3 group but not in the n-6 group. Neutrophil PAF generation increased in the n-6 group but decreased in the n-3 group. In conclusion, modulation of eicosanoid metabolism by intravenous n-3 fatty acid supplementation appears to

exert a rapid beneficial effect on inflammatory skin lesions in acute guttate psoriasis."

-Center for Internal Medicine, Justus Liebig University Giessen.
https://pubmed.ncbi.nlm.nih.gov/8219661/

Psoriasis and the arachidonic acid cascade

"Arachidonic acid [omega-6] (5.8,11,14-eicosatetraenoic acid C20:4, n-6) is released from the cell membrane by the action of phospholipases on membrane phospholipids. Metabolites of arachidonic acid, which are generically termed eicosanoids, including prostaglandins, thromboxane, leukotrienes and hydroxyeicosatetraenoic acids, have been implicated as mediators or modulators of a number of physiological functions and pathological conditions in both normal and diseased human skin. Particularly, eicosanoids have been suspected to play an important role in the pathogenesis of psoriasis, because a number of phenomena observed in psoriasis can be explained, at least in part, by the action of eicosanoids. This review will focus on recent progress regarding the significance of eicosanoids in the pathogenesis of psoriasis. Recent developments in the molecular biology in the eicosanoids have renewed interest in the role of eicosanoids in psoriasis. New understanding of the etiology of psoriasis and advances in its treatment due to recent progress in eicosanoid biology will also be presented."

- Department of Dermatology, Kyoto University, Graduate School of Medicine, Japan.

https://pubmed.ncbi.nlm.nih.gov/10527374

See also Skin

Psychiatric Disorders

Microglial Cells as a Link between Cannabinoids and the Immune Hypothesis of Psychiatric Disorders

"Psychiatric disorders are one of the leading causes of disability worldwide. Although several therapeutic options are available, the exact mechanisms responsible for the genesis of these disorders remain to be fully elucidated. In the last decade, a body of evidence has supported the involvement of the immune system in the pathophysiology of these conditions. Microglial cells play a significant role in maintaining brain homeostasis and surveillance. Dysregulation of microglial functions has been associated with several psychiatric conditions. Cannabinoids regulate the brain–immune axis and inhibit microglial cell activation. Here, we summarized

evidence supporting the hypothesis that microglial cells could be a target for cannabinoid influence on psychiatric disorders, such as anxiety, depression, schizophrenia, and stress-related disorders."….

Conclusion

"A large body of evidence supports the involvement of neuroinflammatory mechanisms, including microglial activation, in the pathophysiology of psychiatric disorders. Drugs that interfere with these mechanisms, such as cannabinoids, could be a novel and important new pathway for the treatment of these disorders (Figure 1). Despite these pieces of evidence, few studies have yet directly investigated if interference with microglial cell activation is essential for the therapeutic effects of cannabinoids in psychiatric disorders. Additional studies, therefore, are needed to test this hypothesis."

-Department of Pharmacology, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

-Center of Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Ribeirão Preto, Brazil

-Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA

-Edited by: Frank Kirchhoff, University of Saarland, Germany

-Reviewed by: Eng-Ang Ling, National University of Singapore, Singapore;

-Aviva Jane Symes

-Uniformed Services University of the Health Sciences, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4729885/

Long chain n-3 [omega-3] polyunsaturated fatty acids decrease feelings of anger in substance abusers

…"Deficiencies in n-3 [omega-3] PUFAs have been reported in a wide range of psychiatric disorders that have included (but are not limited to) depression, suicidal tendencies and aggressive disorders (Alessandri et al., 2004; Young and Conquer, 2005)."…

-VA New York Harbor Healthcare System – Brooklyn Campus, 800 Poly Place, Brooklyn, NY, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225526/

Phytocannabinoids

Phytocannabinoids beyond the Cannabis plant – do they exist?

"It is intriguing that during human cultural evolution man has detected plant natural products that appear to target key protein receptors of important physiological systems rather selectively. Plants containing such secondary metabolites usually belong to unique chemotaxa, induce

potent pharmacological effects and have typically been used for recreational and medicinal purposes or as poisons. Cannabis sativa L. has a long history as a medicinal plant and was fundamental in the discovery of the endocannabinoid system. The major psychoactive Cannabis constituent Δ9-tetrahydrocannabinol (Δ9-THC) potently activates the G-protein-coupled cannabinoid receptor CB1 and also modulates the cannabinoid receptor CB2. In the last few years, several other non-cannabinoid plant constituents have been reported to bind to and functionally interact with CB receptors. Moreover, certain plant natural products, from both Cannabis and other plants, also target other proteins of the endocannabinoid system, such as hydrolytic enzymes that control endocannabinoid levels. In this commentary we summarize and critically discuss recent findings."

-Institute of Biochemistry and Molecular Medicine, University of Bern, Bern, Switzerland
-School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK
-Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931553

Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System

Herbal remedies

…"Some plants besides Cannabis produce vaguely cannabimimetic effects. Copal incense, extracted from Protium species (same plant family as Boswellia) contains a pentacyclic triterpene with high affinity for CB1 and CB2 [156]. Absinthe contains thujone, a constituent of wormwood, Artemisia absinthium. Thujone has weak affinity for CB1 [157]. Pristimerin, an alkaloid found in khat, Catha edulis, acts as a potent inhibitor of MAGL (IC50 = 93 nM) and causes an elevation of 2-AG levels in rat cortical neurons [158]. Salvinorin A in Salvia divinorum produces CB1-mediated effects in the gastrointestinal tract of rodents. Salvinorin A primarily acts as a kappa-opioid receptor agonist and is inactive as a ligand for CB1 and CB2 [159]; it may interact with a putative CB1-kappa-opioid receptor heterodimer [160].

Flavonoids such as biochanin A (from red clover, Trifolium pratense), genistein (from soybean, Glycine max), and kaempferol (from tea, Camelia sinensis, and many other plants) exert modest inhibition of FAAH in the low micromolar range [161]. Cyanidin and delphinidin, two anthocyanidins found in a wide range of plants, have micromolar affinities for CB1 [162]. Epigallocatechin-3-O-gallate, the most abundant catechin in tea, also has micromolar affinities for CB1 [163].

Yangonin, a kavalactone extracted from kava, Piper methysticum, exhibits affinity for CB1 with a

K i = 0.72 μM [164]. Curcumin, extracted from curry powders, elevates eCB levels and brain nerve growth factor (NGF) in a brain region-specific fashion, and pretreatment with CB1 antagonist AM4113 blocks this effect [165]. A study suggested that curcumin and resveratrol could bind to CB1, but the study was retracted [166].

Compounds with phytocannabinoid-like moieties have been extracted from legumes [167], [168], Helichrysum [169], Rhododendron sp. [170], liverworts [171], [172], and fungi [173]–[175].”..

- GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom,

- Department of Family Medicine, University of Vermont, Burlington, Vermont, United States of America,

- Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei, Pozzuoli, Napoli, Italy,

-St. Joseph's Hospital and Medical Center, United States of America,

https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24622769

■■■

“Phytocannabinoids from the plant Cannabis sativa induce a variety of physiological and pharmacological responses in living systems, including anti-inflammatory, antinociceptive, anti-ulcer and antitumor activities. The discovery of the cannabinoid receptors CB1 and CB2 led to the development of agonists and antagonists of these receptors for the treatment of a variety of diseases. Nabilone, a synthetic derivative of Delta9-tetrahydrocannabinol (Delta9-THC), which is the main natural psychotropic constituent of C sativa, was approved by the US FDA for the treatment of nausea and as an anti-emetic for patients undergoing chemotherapy. Delta9-THC and related cannabinoids are involved in a variety of signal transduction pathways; thus, reducing or removing the psychotropic effects of these compounds would enhance their therapeutic spectra. Compound synthesis and qualitative SAR studies are time-consuming activities; however, microbes are effectively the most inventive synthetic chemists because of their metabolic plasticity. This review discusses the potential of C sativa mycoflora, which is pathogenic as well as endophytic, to remove the psychotropic effects of Delta9-THC and related cannabinoids, and describes the development of a model system for the rapid and cost-effective commercial production of cannabinoids through fermentation pathways.”

-Natural Products and Drug Discovery, Department of Biotechnology and Environmental Sciences, Thapar University, Thapar Technology Campus, Patiala, Punjab 147004, India.

https://pubmed.ncbi.nlm.nih.gov/19333876/

Quercetin

Anti Proliferative and Pro Apoptotic Effects of Flavonoid Quercetin Are Mediated by CB1 Receptor in Human Colon Cancer Cell Lines

"Quercetin, the major constituent of flavonoid and widely present in fruits and vegetables, is an attractive compound for cancer prevention due to its beneficial anti proliferative effects, showing a crucial role in the regulation of apoptosis and cell cycle signaling. In vitro studies have demonstrated that quercetin specifically influences colon cancer cell proliferation. Our experiments, using human colon adenocarcinoma cells, confirmed the anti proliferative effect of quercetin and gave intriguing new insight in to the knowledge of the mechanisms involved. We observed a significant increase in the expression of the endocannabinoids receptor (CB1-R) after quercetin treatment. CB1-R can be considered an estrogen responsive receptor and quercetin, having a structure similar to that of the estrogens, can interact with CB1-R leading to the regulation of cell growth. In order to clarify the contribution of the CB1-R to the quercetin action, we investigated some of the principal molecular pathways that are inhibited or activated by this natural compound. In particular we detected the inhibition of the major survival signals like the PI3K/Akt/mTOR and an induction of the pro apoptotic JNK/JUN pathways. Interestingly, the metabolism of β-catenin was modified by flavonoid both directly and through activated CB1-R. In all the experiments done, the quercetin action has proven to be reinforced by anandamide (Met-F-AEA), a CB1-R agonist, and partially counteracted by SR141716, a CB1-R antagonist. These findings open new perspectives for anticancer therapeutic strategies."

-Laboratory of Cellular and Molecular Biology, National Institute for Digestive Diseases S. de Bellis, Bari, Italy.
-Nutritional Biochemistry, National Institute for Digestive Diseases S. de Bellis, Bari, Italy.
-Institute of Endocrinology and Experimental Oncology-CNR, Napoli, Italy.
-Department of Biology and Cellular Pathology, University Federico II, Napoli, Italy.
-Department of Medicine and Surgery, University of Salerno, Baronissi, Salerno, Italy.
https://pubmed.ncbi.nlm.nih.gov/25893829

■■■

…"Quercetin is a well-known polyphenol which is widely distributed in many fruits and plants like apples, onion, green tea, etc. [109]. Quercetin undergoes extensive phase II metabolism in the intestine and liver and presents as different forms of its metabolites [110]. Moreover, quercetin is claimed to exert many biological functions against allergies, inflammation, microbes, ulcers, hepatotoxin, viruses and tumors [111]. Torras et al. demonstrated that plant extraction may have some nonspecific involvement with proteins in bacteria cell walls, which inactivated enzymes and affect proteins transport [112]. Kamil Sierzant's studies indicated that the feeding of broilers

with a mixture of quercetin and other plants led to a reduction of microorganisms in the intestine, which showed that the quercetin extraction contributes to the prevention of diverticular disease [39]. Although most in vitro studies suggests that quercetin has anti-inflammation and immunological effect, the results from a double-blinded, placebo-controlled, randomized trial demonstrated that quercetin supplementation did not have effect on the innate immune system in community-dwelling adult females at 500 and 1000 mg/day for 12 weeks."…

-College of Laboratory Medicine, Jilin Medical University, China;
-Department of Pharmacological and Pharmaceutical Science, College of Pharmacy, University of Houston, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7084955

R

Reactive Oxygen Species (ROS)

…"The cannabinoid system can reduce oxidative load besides reducing the amount of ROS by influencing the removal of damaged macromolecules. "…

-Andras Bilkei-Gorzo
-Institute of Molecular Psychiatry, University of Bonn, Bonn 53127, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481530

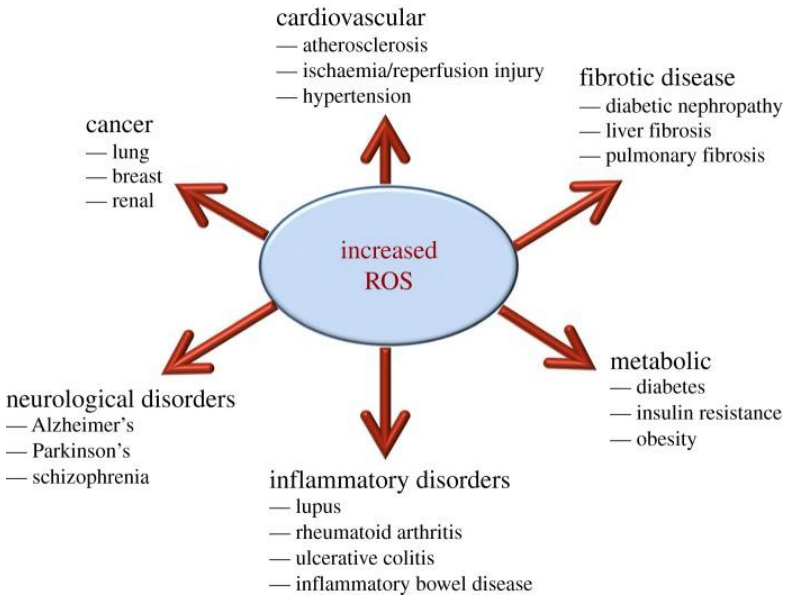
CB1 and CB2 cannabinoid receptors differentially regulate the production of reactive oxygen species by macrophages

…"CB1 promotes pro-inflammatory responses of macrophages through ROS production, which is negatively regulated by CB2 through Rap1 activation. Blocking CB1 together with selective activation of CB2 may suppress pro-inflammatory responses of macrophages."

-Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Songpa-gu, Seoul, Republic of Korea.
https://pubmed.ncbi.nlm.nih.gov/19596672/

Modulation of cellular redox homeostasis by the endocannabinoid system

"The endocannabinoid system (ECS) and reactive oxygen species (ROS) constitute two key



cellular signalling systems that participate in the modulation of diverse cellular functions. Importantly, growing evidence suggests that cross-talk between these two prominent signalling systems acts to modulate functionality of the ECS as well as redox homeostasis in different cell types. Herein, we review and discuss evidence pertaining to ECS-induced regulation of ROS generating and scavenging mechanisms, as well as highlighting emerging work that supports redox modulation of ECS function. Functionally, the studies outlined reveal that interactions between the ECS and ROS signalling systems can be both stimulatory and inhibitory in nature, depending on cell stimulus, the source of ROS species and cell context. Importantly, such cross-talk may act to maintain cell function, whereas abnormalities in either system may propagate and undermine the stability of both systems, thereby contributing to various pathologies associated with their dysregulation."…

"The cellular redox environment constitutes a delicate balance between the production of reactive oxygen species (ROS) and their removal by antioxidant enzymes and small-molecular-weight antioxidants. At low concentrations, ROS are involved in regulating numerous physiological events, including their ability to mediate signal transduction from membrane receptors, thereby facilitating the activation of multiple proteins and enzymes [1,2]. However, excess accumulation of intracellular ROS causes oxidative stress, which can damage cellular membranes, promote mitochondrial injury and induce cell death, thereby negatively impacting upon cell function and survival [3–5]. Notably, this is largely owing to the damaging effects that free radicals convey upon cellular lipids, proteins and DNA, thus impairing their normal function. Accordingly, the dysregulation of redox homeostasis has been linked with the development of various pathologies, including those associated with metabolic disorders such as type 2 diabetes and obesity, cardiovascular disease, as well as various neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease and multiple sclerosis; figure 1) [6–11]. Consequently, there is growing interest in identifying cellular pathways and/or processes that can regulate ROS levels, for example by altering the balance between pro-oxidants and free radical scavenging molecules. In this review, we explore experimental evidence supporting a role for the

endocannabinoid system (ECS) in the modulation of redox homeostasis and provide examples of how this relationship may impact upon cellular function."

"There is accumulating evidence that supports a key role for the ECS in the modulation of ROS production in different cell types. For example, extensive work carried out investigating the neuroprotective properties of cannabinoid ligands has revealed a crucial link between the ECS and redox homeostasis [57–60]. For example, anandamide has been reported to attenuate neurotoxicity in response to oxidative stress [58,61]. In accord with this, the mixed CB1R/CB2R agonist WIN-55,212-2 and the plant-derived cannabinoid tetrahydrocannabinol (THC) have both been shown to protect serum-deprived astrocytes against H2O2-induced apoptosis [57]. Notably, this protective action was found to be prevented by the selective CB1R blocker SR141716, suggesting the involvement of CB1R in mediating these anti-apoptotic and/or antioxidant actions. However, it is noteworthy that the protective effect of THC may be cell specific as judged by the finding that activation of CB1R by THC increases cellular susceptibility of C6 glioblastoma cells to oxidative damage [62].

Notably, as well as responses mediated through CB1R, there is evidence to suggest that stimulation of CB2R may also convey beneficial free radical scavenging effects. Indeed, in a study by Ribeiro et al. [60], and co-workers, the selective CB2R agonist AM1241 was shown to almost completely block ROS generation in response to lipopolysaccharide (LPS) in BV-2 cells. Consistent with this, CB2R activation has also been reported to attenuate oxidative stress damage in various tissue types, including brain [59], kidney [63], heart [64] and liver [65]. Moreover, previous work using CB2R agonists and/or knockout mice indicates that activation of CB2R confers protection against hepatic ischaemia–reperfusion (I/R) injury, concomitant with its ability to alleviate tissue free radical damage [66–68]. Allied to this, further evidence supporting a protective role for the ECS was provided in a study by Cao et al. [65], who demonstrated that pharmacological inhibition of monoacylglycerol lipase, the enzyme which catalyses the hydrolysis of 2-AG, led to the suppression of oxidative stress and associated inflammation in liver tissue following hepatic I/R injury in mice [65]. Notably, the protective effects of MAGL inhibition against hepatic I/R injury involved increased endocannabinoid signalling via CB2R [65].

Conversely, stimulation of the ECS has also been demonstrated to induce the production of ROS in certain cell types [69–71]. For example, 2-AG stimulation has been shown to promote an increase in cellular ROS in BeWo trophoblasts [71]. Moreover, increased ROS and concomitant TNF-α cytokine production have been reported in human macrophages following CB1R activation, with both responses being attenuated by pharmacological inhibition of CB1R [69]. Moreover, CB1R inhibition using SR141716 has been found to ameliorate diabetes-induced retinal oxidative stress and inflammation, as well as improving oxidative stress in mice with non-alcoholic fatty liver

disease [72]. In accord with this, evidence from a number of studies indicates that CB1R stimulation can either promote and/or facilitate oxidative stress and associated inflammation and/or cell death in human coronary artery endothelial cells [70], as well as in various models of cardiomyopathy [28,73,74], and nephropathy [75]. In addition, work by Dando et al. [76] showed that activation of CB1R or CB2R promotes oxidative stress in Panc1 pancreatic cancer cells resulting in the AMP-activated protein kinase (AMPK)-dependent induction of autophagy, which may, at least in part, account for the observed inhibitory effects of cannabinoid receptor ligands upon tumour cell growth [77–79]. Importantly, such findings are often supported by data demonstrating the beneficial effects on ROS-related inflammation and/or cell death following genetic deletion or pharmacological inhibition of CB1R [72,74,75,77,78].

Intriguingly, CB1R and CB2R have also been reported to differentially regulate ROS production within the same cell type. For example, a study by Han et al. [69] demonstrated that CB1R activation led to the upregulation of ROS levels in RAW264.7 macrophages, whereas CB2R stimulation in the same cells acted to suppress CB1R-stimulated ROS production through a pathway involving the small G protein Rap1. Therefore, modulation of these distinct cannabinoid receptors can promote differential responses with respect to cellular redox homeostasis, even within one specific cell type."

-Division of Cell Signalling and Immunology, Sir James Black Centre, School of Life Sciences, University of Dundee, Dundee, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4852457/

■■■

…"A large amount of data indicates that inflammation is closely connected to oxidative stress. Reactive oxygen species (ROS) are continuously produced by our cells as a by-product of oxidative metabolism and are essential for several physiological functions and signalling pathways. However, an excessive accumulation of ROS may cause cellular oxidative damage to nucleic acids and proteins in cells of several systems including the endocrine and the immune systems [26,50]. We have recently hypothesised that most of the deleterious effects of excessive oxidative stress in tissues and organs can be mediated by the induction of unwanted inflammatory reactions [50]."…

-Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Italy;
-Interdepartmental Centre "L. Galvani" (CIG) University of Bologna, Bologna, Italy;
-IRCCS, Institute of Neurological Sciences, Italy
-National Research Council of Italy, CNR, Institute for Organic Synthesis and Photoreactivity (ISOF), Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425163

Lipids Damage by Reactive Oxygen Species

…"One of the consequences of uncontrolled oxidative stress (imbalance between the prooxidant and antioxidant levels in favor of prooxidants) is cells, tissues, and organs injury caused by oxidative damage. It has long been recognized that high levels of free radicals or reactive oxygen species (ROS) can inflict direct damage to lipids. The primary sources of endogenous ROS production are the mitochondria, plasma membrane, endoplasmic reticulum, and peroxisomes [20] through a variety of mechanisms including enzymatic reactions and/or autooxidation of several compounds, such as catecholamines and hydroquinone. Different exogenous stimuli, such as the ionizing radiation, ultraviolet rays, tobacco smoke, pathogen infections, environmental toxins, and exposure to herbicide/insecticides, are sources of in vivo ROS production."….

-Lipid Peroxidation Products in Human Health and Disease 2014
https://www.hindawi.com/journals/omcl/2014/360438

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…"During inflammation, an increase in the levels of macrophages and neutrophils leads to increased levels of RONS [reactive oxygen and nitrogen species] [18]. RONS in turn induce base lesions including eA, 8oxoG and Hx, which have been observed at sites of inflammation [18,19]."…

- Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
- Singapore–MIT Alliance for Research and Technology, Singapore,
-Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA-University of Washington, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4372043/

Respiratory Diseases

"Inflammation, which is induced and perpetuated by microorganism pathogens or from the damage or death of host cells, is an essential component of various common respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, and acute respiratory distress syndrome (ARDS), as well as of less common ones, for example, sarcoidosis. Although different diseases express distinct inflammatory responses, there are some shared common features. For example, the Th2-related eosinophilic inflammation, which is typically present in asthma, is also characteristic of eosinophilic phenotype of COPD. On the other hand, the innate neutrophilic inflammation shared by a number of diseases, including COPD and ARDS,

could be demonstrated in some patients with severe asthma. In this special issue, common inflammation was dissected in diverse ways by the authors to better understand the related respiratory diseases, from the clinical to the underlying mechanisms, pointing to future therapeutic prospect."

-Division of Pulmonary Medicine, Shuang Ho Hospital and Division of Pulmonary Medicine, School of Medicine, College of Medicine, Taipei Medical University,Taipei, Taiwan

-Airway Disease, National Heart and Lung Institute, Imperial College London, UK

-Faculty of Medicine Siriraj Hospital, Mahidol University, Wanglang Street, Bangkok, Thailand

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4884796/

The potential of cannabinoids and inhibitors of endocannabinoid degradation in respiratory diseases

"The global incidence of respiratory diseases and complications is increasing. Therefore, new methods of treatment, as well as prevention, need to be investigated. A group of compounds that should be considered for use in respiratory diseases is cannabinoids. There are three groups of cannabinoids - plant-derived phytocannabinoids, synthetic cannabinoids, and endogenous endocannabinoids including the enzymes responsible for their synthesis and degradation. All cannabinoids exert their biological effects through either type 1 cannabinoid receptors (CB1) and/or type 2 cannabinoid receptors (CB2). In numerous studies (in vitro and in vivo), cannabinoids and inhibitors of endocannabinoid degradation have shown beneficial anti-inflammatory, antioxidant, anti-cancer, and anti-fibrotic properties. Although in the respiratory system, most of the studies have focused on the positive properties of cannabinoids and inhibitors of endocannabinoid degradation. There are few research reports discussing the negative impact of these compounds. This review summarizes the properties and mechanisms of action of cannabinoids and inhibitors of endocannabinoid degradation in various models of respiratory diseases. A short description of the effects selected cannabinoids have on the human respiratory system and their possible use in the fight against COVID-19 is also presented. Additionally, a brief summary is provided of cannabinoid receptors properties and their expression in the respiratory system and cells of the immune system."

-Department of Experimental Physiology and Pathophysiology, Medical University of Białystok, Białystok, Poland.

https://pubmed.ncbi.nlm.nih.gov/34648805/

Respiration

CB1 [cannabinoid type 1] receptor-mediated respiratory depression by endocannabinoids.

"Our results imply that the EC [endocannabinoid] system has an important role in the physiological control of respiration by modulating the respiratory rate and consequently influencing arterial oxygen saturation. Furthermore, this mechanism is entirely dependent on CB1 receptors."

-Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary;
-Max-Planck Institute for Heart and Lung Research, Department of Pharmacology, Bad Nauheim, Germany.
-Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary.
-Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary.
https://www.ncbi.nlm.nih.gov/pubmed/28254562

Reproductive Health

Effect of different dietary omega-3/omega-6 fatty acid ratios on reproduction in male rats

…"These findings demonstrated that a balanced n-3/n-6 ratio was important in male rat reproduction. Therefore there is a necessity to determine an appropriate n-3/n-6 PUFA ratio in man and different male animals in the future."…

The results of this study showed that different ratios of n-3/n-6 PUFAs had no effects on the testis index, but improved sperm quality. With an increasing n-3/n-6 PUFA ratio, sperm density and motility were increased, and the sperm deformity rate tended to decrease. Additionally, better histological and ultra-structural changes of testis and sperm were observed in the group consuming a n-3/n-6 PUFA ratio of 1.52. It was reported that boar diets supplemented with 30 g/kg of tuna oil or fish oil (rich in long chain n-3 fatty acids) increased sperm motility and the content of normal acrosome and sperm cell morphology [1], improving the total number of sperm per ejaculation, and the membrane integrity of sperm [6]. More recently, it was found that boar diets fortified with n-3 rich fatty acid additives enhanced the sperm total number of average ejaculations, and the morphological integrity of sperm was improved [7]. Furthermore, the ratio of n-3/n-6 PUFAs in boar sperm were positively correlated with sperm motility, viability, normal morphology, and normal plasma membranes [10], and excessive n-3 PUFA supplementation decreased the sperm density and motility in our experiment, which indicated the importance of

the n-6/n-3 PUFA ratio in sperm quality.

Research has shown that diets containing distinct lipid sources differentially modified the lipid contents of the sperm head and body membranes, resulting in significant improvement in semen quality [23,24]. Al-Daraji et al. [23] found the proportion of n-3 fatty acids in spermatozoa from Japanese male quail fed fish oil compared with corn oil was higher (9.6% vs. 4.3%) and that of n-6 fatty acids was lower (22.4% vs. 33.3%). The sperm of flaxseed-fed rabbits had an n-3/n-6 ratio two times higher compared with the control because of the increasing dietary n-3/n-6 ratio [25]. In addition, it was reported that diets containing different lipid sources changed the lipid contents of sperm, mainly affecting the sperm head and body membranes [24]. It is worth noting that the dietary n-3/n-6 PUFA ratio affected the lipid composition of perch semen. However, no significant effects of changes in the n-3/n-6 ratios were observed in the sperm volume density and spermatozoa motility when the n-3/n-6 ratios were 0.2 and 7.0 respectively [26], indicating high correlations between these changes in dietary lipid content and sperm lipid concentration, and that an appropriate n-3/n-6 PUFA ratio was important for sperm quality. Therefore, we speculate that a possible reason for improving sperm quality in our experiment should be related to the changes in sperm composition induced by different fatty acid compositions in the diets.

In fact, very few studies have been conducted to examine the effects of the ratio of n-3/n-6 PUFAs on male reproduction. It is known that both n-6 and n-3 PUFAs can influence reproductive processes. In this study, we found that litter size and birth weight increased with increasing n-3/n-6 PUFA ratios; lower or higher n-3/n-6 ratios have adverse effects on reproduction, which was consistent with the results of sperm quality and sperm morphology. Blesbois [27] found that increasing the ratio of n-3/n-6 PUFAs in the diet can enhance the hatching rates of male turkeys at 48–58 weeks by nearly 2 points. Higher rates of embryonic and larval survival were observed in male European sea bass fed PUFA-enriched diets [28]. Similarly, studies conducted in females also have observed positive effects of diets rich in n-3 PUFA on reproductive performance. It was demonstrated that supplementing n-3 fatty acids from fish oil in the diet of sows improved early embryo survival [29], thereby increased piglet litter sizes [30,31]. Meanwhile, the content and variety of the maternal intake of PUFAs were shown to be associated with weight gain and growth of infants, particularly in preterm infants [32,33]. Therefore, these results confirmed that maintaining an appropriate n-3/n-6 PUFA ratio was very important for reproductive performance in males and females.”…

-Key Laboratory for Animal Disease Resistance Nutrition of the Ministry of Education, and Animal Nutrition Institute of Sichuan Agricultural University, Ya’an, 625014, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3627632/

Polyunsaturated fatty acids in male and female reproduction

"In Westernized societies, average consumption of n-6 polyunsaturated fatty acids (PUFAs) far exceeds nutritional requirements. The ratio of n-6 to n-3 PUFAs is generally >10:1 whereas on a primitive human diet it was closer to 1:1. Diets fed to intensively farmed livestock have followed a similar trend. Both n-6 and n-3 PUFAs can influence reproductive processes through a variety of mechanisms. They provide the precursors for prostaglandin synthesis and can modulate the expression patterns of many key enzymes involved in both prostaglandin and steroid metabolism. They are essential components of all cell membranes. The proportions of different PUFAs in tissues of the reproductive tract reflect dietary consumption. PUFA supplements (particularly n-3 PUFAs in fish oil) are promoted for general health reasons. Fish oils may also benefit fertility in cattle and reduce the risk of preterm labor in women, but in both cases current evidence to support this is inconclusive. Gamma-linolenic acid containing oils can alter the types of prostaglandins produced by cells in vitro, but published data to support claims relating to effects on reproductive health are lacking. Spermatozoa require a high PUFA content to provide the plasma membrane with the fluidity essential at fertilization. However, this makes spermatozoa particularly vulnerable to attack by reactive oxygen species, and lifestyle factors promoting oxidative stress have clear associations with reduced fertility. Adequately powered trials that control for the ratios of different PUFAs consumed are required to determine the extent to which this aspect of our diets does influence our fertility."

-Department of Veterinary Basic Sciences, Royal Veterinary College
https://pubmed.ncbi.nlm.nih.gov/17442851

Effects of altering dietary fatty acid composition on prostaglandin synthesis and fertility

"Several studies over the past 20 years have demonstrated that subjects on diets composed of substances with high levels of n-3 polyunsaturated fatty acids (PUFAs) (e.g. fish) have a decreased incidence of heart disease. On this basis, a recent report from the Department of Health has advised UK consumers to decrease the proportion of saturated as opposed to unsaturated fats in their diet and to increase the ratio of n-3 to n-6 PUFAs. This could be achieved by altering the amounts of these constituents in milk and meat. n-3 Fatty acids can most easily be added to animal feed as either fish oil or linseed oil and can be increased in the blood and milk of ruminants following protection to avoid hydrogenation in the rumen. In western countries the ratio of consumption of n-6 to n-3 PUFAs is greater than 10 and current evidence tends to suggest that a ratio nearer 5 would be more desirable and compatible with

cardiovascular well being. As fertility in the UK dairy herd is already poor, it is important to establish whether alterations in dietary n-3 and n-6 PUFAs affects herd fertility before widespread changes in animal diets are recommended. Therefore, this review considers the role played by PUFAs and eicosanoids in fertility, with particular reference to the implications for farm livestock production. The evidence reviewed shows that alteration of the concentration and ratio of n-6 and n-3 PUFAs in feeds can influence prostaglandin synthesis/metabolism in a number of mammalian systems. The changed patterns of prostaglandin synthesis can as a consequence, affect the diverse functions (e.g. hormone secretion) that are normally mediated via prostaglandins. Similarly, changes in prostaglandin synthesis effected through manipulation of PUFAs has a major bearing on fertility (as PGs affect many reproductive parameters, e.g. ovulation). Several studies in cattle and other mammals, show that feeding or infusing different types of fat with varying PUFA content to females can alter: the number and size of ovarian follicles, the ovulation rate, progesterone production by the corpus luteum, the timing of luteolysis and gestational length. In the male most recent work has focussed on sperm production and experiments in fowl have demonstrated clear effects of dietary PUFAs on both the sperm membrane phospholipid composition and on fertilizing ability."

-Reproduction and Development Group, Department of Veterinary Basic Sciences, Royal Veterinary College, London, UK.

https://pubmed.ncbi.nlm.nih.gov/10670689

Polyunsaturated fatty acids modulate prostaglandin synthesis by ovine amnion cells in vitro

"Diets or supplements high in n-3 and n-6 polyunsaturated fatty acids (PUFAs) have been shown to influence the timing of parturition. PUFAs are substrates for prostaglandin (PG) synthesis, and PGs play central roles in parturition. Hence, the effects of altering PUFA composition may be mediated through alterations in the type and relative quantities of PGs synthesised. Therefore, we have investigated the effects of a range of n-3 and n-6 PUFAs in vitro on PG synthesis by amnion cells of late gestation ewes. The n-6 PUFA, arachidonic acid (20:4, n-6), increased synthesis of two-series PGs. Degree of stimulation induced by the n-6 PUFAs was dependent on the position of the PUFA in the PG synthetic pathway, i.e. PG production of the two-series (principally prostaglandin E(2):PGE(2)) increased progressively with longer chain PUFAs. Effects of n-3 PUFAs on output of PGE(2) were more modest and variable. The two shorter chain n-3 PUFAs, α-linolenic acid (18:3, n-3) and stearidonic acid (18:4, n-3), induced a small but significant increase in PGE(2) output, while the longest chain n-3 PUFA docosahexaenoic acid (22:6, n-3) inhibited PGE(2) synthesis. Dihomo-γ-linolenic acid (20:3, n-6), the PUFA substrate for synthesis

of one-series PGs, induced an increase in PGE(1) generation and a decrease in PGE(2) and PGE(3) outputs. Hence, we have demonstrated that PUFA supplementation of ovine amnion cells in vitro affects the type and quantity of PGs synthesised."

-Endocrinology, Development, Genomics and Reproduction Group, Department of Veterinary Basic Sciences, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, UK

https://pubmed.ncbi.nlm.nih.gov/20826537

Low fatty acid amide hydrolase and high anandamide levels are associated with failure to achieve an ongoing pregnancy after IVF and embryo transfer

…"Taken together with the reported negative effects of AEA on embryo implantation, this study indicates that low FAAH activity and subsequent increased AEA levels in blood might be one of the causes of implantation failure or pregnancy loss, thereby leading to a better understanding of the pathophysiological and therapeutic implications of endocannabinoids in human fertility."

-Department of Experimental Medicine and Biochemical Sciences, University of Rome Tor Vergata, I-00133 Rome, Italy.

https://pubmed.ncbi.nlm.nih.gov/11818522

Endocannabinoids, hormone-cytokine networks and human fertility

"**Anandamide (N -arachidonoylethanolamine, AEA) is a major endocannabinoid, shown to impair mouse pregnancy and embryo development and to induce apoptosis in blastocysts.** Here, we review the roles of AEA, of the AEA-binding cannabinoid (CB) receptors, of the selective AEA membrane transporter (AMT), and of the AEA-hydrolyzing enzyme fatty acid amide hydrolase (FAAH), in human gestation. In particular, we discuss the interplay between the endocannabinoid system and the hormone-cytokine array involved in the control of human pregnancy, showing that the endocannabinoids take part in the immunological adaptation occurring during early pregnancy. In this line, we discuss the critical role of FAAH in human peripheral lymphocytes, showing that the expression of this enzyme is regulated by progesterone, Th1 and Th2 cytokines, which also regulate fertility. **Moreover, we show that AEA and the other endocannabinoid, 2-arachidonoylglycerol, inhibit the release of the fertility-promoting cytokine leukemia inhibitory factor from human lymphocytes.** Taken together, low FAAH and consistently high blood levels of AEA, but not CB receptors or AMT, can be early (<8 weeks of gestation) markers of spontaneous abortion, potentially useful as diagnostic tools for large-scale, routine monitoring of gestation in humans."

-Department of Experimental Medicine and Biochemical Sciences, University of Rome Tor Vergata, Via Montpellier 1,

I-00133 Rome, Italy.
https://pubmed.ncbi.nlm.nih.gov/12052045

Inflammatory responses and inflammation-associated diseases in organs

…"The hallmarks of inflammation are observed during many normal reproductive processes, including menstruation, ovulation, implantation, and parturition [156]. Injury and healing caused by menstruation, ovulation, and parturition trigger the inflammatory cascade. However, initiation and maintenance of inflammatory processes are also important components of many reproductive tract diseases. Damaged tissues locally release inflammatory interleukins, growth factors, cytokines, and prostaglandins, which activate signaling pathways and recruit immune cells (e.g. neutrophils and macrophages) to the site of injury. This process synergistically controls tissue remodeling and repair, but can also induce inflammatory diseases [7]. Inflammatory cytokines, including IL-6, are the primary mediators of inflammation-related reproductive tract diseases, and act via signal transduction pathways such as the MAPK pathway [157, 158]."…

- College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, China
- Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, China
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805548

Respiratory Syncytial Virus (RSV)

"Respiratory syncytial virus (RSV) causes infections of the lungs and respiratory tract. It's so common that most children have been infected with the virus by age 2. Respiratory syncytial (sin-SISH-ul) virus can also infect adults.

In adults and older, healthy children, RSV symptoms are mild and typically mimic the common cold. Self-care measures are usually all that's needed to relieve any discomfort.

RSV can cause severe infection in some people, including babies 12 months and younger (infants), especially premature infants, older adults, people with heart and lung disease, or anyone with a weak immune system (immunocompromised)."

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/respiratory-syncytial-virus/symptoms-causes/syc-20353098

The Role of Cannabinoid Receptor 1 in the Immunopathology of Respiratory Syncytial Virus

"Endocannabinoid system plays an important role in pathophysiologic processes such as immune functions and impacts on disease severity. Our previous study showed that cannabinoid receptor 2 (CB2) affects clinical course of respiratory syncytial virus (RSV) infection. In this study, we investigated the role of cannabinoid receptor 1 (CB1) in RSV immunopathology and its therapeutic potential in mice model. To study the role of CB1 receptors in the immunopathology of RSV, CB1 was blocked daily with AM281 as a selective antagonist in Balb/c mice and were infected by intranasal inoculation of RSV-A2 24 h following the first dose of antagonist administration. The potential pharmacological therapeutic effects of cannabinoid receptor activation during RSV infection were studied using JZL184 as a selective indirect agonist, 24 h after infection. Mice were sacrificed on day 5 after infection and experimental analyses were performed to study the CB1 receptor expression, airway immune cell influx, cytokine/chemokine secretion, lung histopathology, and viral load. RSV infection of airways significantly induced the expression of CB1 receptors in lung cells of mice. Blockade of CB1 receptors using AM281 enhanced immune cell influx and cytokine/chemokine production, and aggravated lung pathology. Activation of cannabinoid receptors using JZL184 decreased immune cell influx and cytokine/chemokine production, and alleviated lung pathology. This study and our previous finding indicated that endocannabinoid signaling regulates the inflammatory response to RSV infection, and is a potential therapeutic candidate for alleviation of RSV-associated immunopathology."

-Department of Virology, School of Public Health, Tehran University of Medical Sciences , Tehran, Iran .
-Infectious Diseases Research Center, Golestan University of Medical Sciences , Gorgan, Iran .
-Department of Biochemistry, School of Medicine, Iran University of Medical Sciences , Tehran, Iran .
-Department of Immunology, School of Public Health, Tehran University of Medical Sciences , Tehran, Iran
https://pubmed.ncbi.nlm.nih.gov/29461930

Retina

Expression and Function of the Endocannabinoid System in the Retina and the Visual Brain

…"The purpose of this review is to characterize the expression and physiological functions of the endocannabinoid system in the visual system, from the retina to the primary visual cortex, with a main interest regarding the retina, which is the best-described area in this system so far. It will show that the endocannabinoid system is widely present in the retina, mostly in the through

pathway where it can modulate neurotransmitter release and ion channel activity, although some evidence also indicates possible mechanisms via amacrine, horizontal, and Müller cells. The presence of multiple endocannabinoid ligands, synthesizing and catabolizing enzymes, and receptors highlights various pharmacological targets for novel therapeutic application to retinal diseases."….

"**Conclusion:** Endocannabinoids constitute one of the newest neuromodulators found in neural and nonneural tissues throughout the body. Their wide expression in the nervous system and peripheral organ systems highlights the range of their actions and their potential in therapeutic applications. Strong evidence now suggests a wide distribution of eCBs, receptors, and enzymatic machinery in key structures of the visual system, including a strong presence in the retina. Although no clear picture can ascertain the specific effects cannabinoids can have in the retina itself, or the visual system as a whole, various mechanisms in specific cellular structures of the retina have now been reported. The cannabinoid system also appears to have several roles in neuronal survival and apoptosis in the retina and could be linked with many other ocular disorders. However, their specific mechanisms in retinal development, neuroplasticity, and neuroprotection need to be more thoroughly investigated."

-Laboratoire de Neuropharmacologie, École d'optométrie, Université de Montréal, C.P. Succursale Centre-Ville, Montréal, QC, Canada H3C 3J7

https://www.hindawi.com/journals/np/2016/9247057/

The Endocannabinoid System in the Retina: From Physiology to Practical and Therapeutic Applications

…"In the last decade, there has been a growing interest for endocannabinoids in the retina and their role in visual processing. This review gives an overview of the distribution of the cannabinoid system in the retina together with its involvement in the regulation of retinal neurotransmission, neuroplasticity, and neuroprotection. These suggest potential alterations of structural and functional retinal properties by exogenous cannabinoids, especially THC and cannabidiol contained in joints. As cannabis is widely spread worldwide, it is now critical to explore the effects of cannabis on the human retina. Based on experimental studies in animals, this review also aims to provide several retinal methods to correlate the cellular and molecular changes induced by cannabinoids to potential functional retinal deficits in cannabis users. **However, considering the neuroprotective role of the cannabinoid system in the retina, this review also argues for therapeutic uses of synthetic* cannabinoids in the treatment and the prevention of retinal diseases.**"

-Pôle Hospitalo-Universitaire de Psychiatrie, Centre Psychothérapique de Nancy, Laxou, France

-EA7298, INGRES, Université de Lorraine, Vandœuvre-lès-Nancy, France

-INSERM U1114, Fédération de Médecine Translationnelle de Strasbourg, Département de Psychiatrie, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France

-Maison des Addictions, CHU Nancy, Nancy, France

-Service d'Ophtalmologie, CHU Nancy, Nancy, France

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4736597/

Immune regulation in the aging retina

"The retina is an immune privileged tissue, which is protected from external and internal insults by its blood-retinal barriers and immune suppressive microenvironment. Apart from the avoidance and tolerance strategies, the retina is also protected by its own defense system, i.e., microglia and the complement system. The immune privilege and defense mechanisms work together to maintain retinal homeostasis. During aging, the retina is at an increased risk of developing various degenerative diseases such as age-related macular degeneration, diabetic retinopathy, and glaucomatous retinopathy. Previously, we have shown that aging induces a para-inflammatory response in the retina. In this review, we explore the impact of aging on retinal immune regulation and the connection between homeostatic control of retinal immune privilege and para-inflammation under aging conditions and present a view that may explain why aging puts the retina at risk of developing degenerative diseases."…

-Centre for Experimental Medicine, School of Medicine, Dentistry & Biomedical Sciences, Queen's University Belfast, UK

-Aier Eye Institute, Aier School of Ophthalmology, Central South University of China

-Infection and Immunity, School of Medicine, University of Aberdeen, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6373845

Retinol

"Retinol is important for the human body; however the body itself cannot synthesize it. Retinol, a fat-soluble unsaturated isoprenoid like its two important metabolites retinaldehyde and retinoic acid, is essential for growth, differentiation and maintenance of epithelial tissues and influences reproduction. In human skin two retinoid receptors are expressed, which can be activated by retinol and its metabolites.[49]

Retinaldehyde, additionally being important for vision, is created by in vivo oxidation of retinol in a reversible process. The normal plasma concentration of vitamin A in humans is 0.35–0.75 µg/ml.[50,51]

Retinol must derive from diet. Natural retinol and retinol ester are contained in liver, milk, egg yolk, cheese and fatty fish etc. Naturally occurring and synthetic vitamin A (retinol) show similar biological activities. Different retinol products, both for cosmetic (topical) and pharmaceutical (topical, systemic) use can be found on the market.

In a review of topical methods to counteract skin wrinkling and irregular pigmentation of aging skin, Bayerl evaluates the effects of vitamin A acid derivatives, chemical peeling and bleaching agents. Also, the effects of UV protection by using sunscreens and topical antioxidants are reviewed.[52] The topical retinoid treatments inhibit the UV-induced, MMP-mediated breakdown of collagen and protect against UV-induced decreases in procollagen expression.[53-55]"

-Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center; Dessau, Germany
-Laboratory for Biogerontology, Dermato-Pharmacology and Dermato-Endocrinology; Institute of Clinical Pharmacology and Toxicology; Charité Universitaetsmedizin Berlin; Berlin, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3583891

Rheumatoid Arthritis

…"A rheumatoid factor test is one of a group of blood tests primarily used to help pinpoint a diagnosis of rheumatoid arthritis. These other tests may include:

- Anti-nuclear antibody (ANA)
- Anti-cyclic citrullinated peptide (anti-CCP) antibodies
- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR, or sed rate)"…

-Mayo Clinic
https://www.mayoclinic.org/tests-procedures/rheumatoid-factor/about/pac-20384800

Dietary Intake of Polyunsaturated Fatty Acids and Pain in Spite of Inflammatory Control Among Methotrexate-Treated Early Rheumatoid Arthritis Patients

"This study is to our knowledge the first to examine the association between dietary intake of

polyunsaturated FAs [fatty acids] and pain patterns in early RA [Rheumatoid Arthritis] patients. We found that higher intake of omega-3 FA [fatty acid] was inversely associated with both unacceptable pain and refractory pain. **A higher omega-6:omega-3 FA ratio was directly associated with unacceptable pain and refractory pain.**"…

-Karolinska Institutet, Stockholm, Sweden

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5817233/

■■■

"A person with RA should avoid omega-6 fatty acids from corn, safflower, soybean, and sunflower oils as they can increase the risk of joint inflammation and obesity. Some foods that are associated with making inflammation worse include hamburgers, chicken, and meats that have been grilled or fried at high temperature."

-MeicalNewsToday

https://www.medicalnewstoday.com/articles/315580.php

Managing Rheumatoid Arthritis with Dietary Interventions

…"The [Rheumatoid Arthritis] patient should avoid any processed food, high salt (185), oils, butter, sugar, and animal products (186)."…

-Disease Biology Laboratory, School of Biotechnology, KIIT University, Bhubaneswar, Odisha, India

-Edited by: Marilia Seelaender, University of São Paulo, Brazil

-Reviewed by: Dario Coletti, Sapienza Università di Roma, Italy; Emanuele Rinninella, Agostino Gemelli University Polyclinic, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5682732/

Polyunsaturated fatty acids: any role in rheumatoid arthritis?

"Polyunsaturated fatty acids (PUFAs) [aka omegas] are members of the family of fatty acids and are included in the diet. Particularly, western diet is usually low in n-3 [omega-3] PUFAs and high in n-6 PUFAs. PUFAs play a central role in the homeostasis of immune system: n-6 [omega-6] PUFAs have predominantly pro-inflammatory features, while n-3 PUFAs seem to exert anti-inflammatory and pro-resolving properties. Rheumatoid arthritis (RA) is a chronic inflammatory arthritis in which many inflammatory pathways contribute to joint and systemic inflammation, disease activity, and structural damage. Research on PUFAs could represent an important opportunity to better understand the pathogenesis and to improve the management of RA patients."

-Unit of Allergology, Immunology, Rheumatology, Department of Medicine, Università Campus Bio-Medico di Roma
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634864/

Joints for joints: cannabinoids in the treatment of rheumatoid arthritis.

…"Cannabinoids might be a suitable treatment for RA, but it is important to target the right receptors in the right place. For clinical studies, we propose a combination of a CB2 [cannabinoid type 2 receptor] agonist to decrease cytokine production, a peripheral CB1 [cannabinoid type 1 receptor] antagonist to prevent detrimental CB1 signaling and to support anti-inflammatory effects of CB2 via activation of β2-adrenergic receptors and CBD to induce cannabinoid-receptor-independent anti-inflammatory effects."

-Poliklinik, Funktionsbereich & Hiller Forschungszentrum für Rheumatologie, University Hospital Duesseldorf, Duesseldorf, Germany.
https://www.ncbi.nlm.nih.gov/pubmed/30920973

The endocannabinoid system and its therapeutic implications in rheumatoid arthritis.

"Since the discovery of the endogenous receptor for Δ(9)-tetrahydrocannabinol, a main constituent of marijuana, the endocannabinoid system (comprising cannabinoid receptors and their endogenous ligands, as well as the enzymes involved in their metabolic processes) has been implicated as having multiple regulatory functions in many central and peripheral conditions, including rheumatoid arthritis (RA). RA is an immune-mediated inflammatory disease that is associated with the involvement of many kinds of cells (such as fibroblastlike synoviocytes [FLSs], osteoclasts, T cells, B cells, and macrophages) and molecules (such as interleukin-1β, tumor necrosis factor-α, interleukin-6, matrix metalloproteinases [MMPs], and chemokines). Increasing evidence suggests that the endocannabinoid system, especially cannabinoid receptor 2 (CB2), has an important role in the pathophysiology of RA. Many members of the endocannabinoid system are reported to inhibit synovial inflammation, hyperplasia, and cartilage destruction in RA. In particular, specific activation of CB2 may relieve RA by inhibiting not only the production of autoantibodies, proinflammatory cytokines, and MMPs, but also bone erosion, immune response mediated by T cells, and the proliferation of FLSs. In this review, we will discuss the possible functions of the endocannabinoid system in the modulation of RA, which may be a potential target for treatment."

-Department of Pharmacy, Children's Hospital of Soochow University, Suzhou, China; Department of Rheumatology & Immunology, Changhai Hospital, Second Military Medical University, Shanghai, China.
-Department of Rheumatology & Immunology, Changhai Hospital, Second Military Medical University, Shanghai,

China.

-Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, USA; Division of Pain Medicine, Mayo Clinic, Rochester, MN, USA.

-Department of Pharmacy, Children's Hospital of Soochow University, Suzhou, China.

-Department of Rheumatology & Immunology, Changhai Hospital, Second Military Medical University, Shanghai, China.

https://www.ncbi.nlm.nih.gov/pubmed/25791728

Effects of dietary omega-3 and omega-6 lipids and vitamin E on serum cytokines, lipid mediators and anti-DNA antibodies in a mouse model for rheumatoid arthritis.

"Omega-3 (omega-3) fatty acid rich-fish oil (FO) and vitamin E (vit-E) may delay the progress of certain autoimmune diseases. The present study examined the mechanism of action of omega-3 and omega-6 lipids and vit-E on the serum cytokines and lipid mediators in autoimmune-prone MRL/lpr mice (a model for rheumatoid arthritis, RA). The lpr (lymphoproliferative) gene is overexpressed in these mice causing extensive lymphoproliferation, lupus-like symptoms and accelerated aging."

…"It is clear from our observations that the beneficial effects of FO can be enhanced by the addition of 500 IU of vit-E in the diet. The FO diet containing 500 IU of vit-E may specifically modulate the levels of IL-6, IL-10, IL-12 and TNF-alpha and thereby may delay the onset of autoimmunity in the MRL/lpr mouse model. The observations from this study may form a basis for selective nutrition intervention based on specific fatty acids and antioxidants in delaying the progress of RA."

-Department of Physical Therapy, Exercise and Nutrition Sciences, State University of New York at Buffalo, USA.

https://www.ncbi.nlm.nih.gov/pubmed/10613412

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…"The arachidonic acid cascade has become a starting point for a dietary approach based on n-3 PUFA supplementation and dietary modification of patients with rheumatoid arthritis (RA). The concern is based primarily on the contention that a diet rich in linoleic acid (18:2n-6, LA) would promote tissue AA accumulation, enhance the production of pro-inflammatory eicosanoids derived from AA, and/or inhibit the conversion of α-linolenic acid (18:3n-3, ALA) to EPA and DHA and their subsequent metabolism to predominantly anti-inflammatory compounds [6, 7]. Some studies indicated that manipulation in dietary fatty acids can reduce a number of swollen and tender joints in patients with RA [8, 9], but others do not confirm these findings [10]."…

See supplements to understand the research inconsistencies with omega-3 supplementation. Omega-3s should be mostly acquired from diet due to conversion problems with various omega-3 supplements.

-Third Department and Clinic of Paediatrics, Immunology and Rheumatology of Developmental Age, Wroclaw Medical University, Wroclaw, Poland

-First Department of Paediatrics Pulmonology and Rheumatology, University of Medicine in Lublin, Lublin, Poland

-Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw, Poland

-Department of Food Science and Dietetics, Wroclaw Medical University, Wroclaw, Poland

-Department of Paediatric Rheumatology, John Paul II Paediatric Centre, Sosnowiec, Poland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5486496/

Omega-3 fatty acids are associated with a lower prevalence of autoantibodies in shared epitope-positive subjects at risk for rheumatoid arthritis

"Previously, we found that omega-3 fatty acids (n-3 FAs) were inversely associated with anti-cyclic citrullinated peptide (anti-CCP) positivity in participants at risk for future rheumatoid arthritis (RA). We investigated whether n-3 FAs were also associated with rheumatoid factor (RF) positivity and whether these associations were modified by shared epitope (SE) positivity."

…"The potential protective effect of n-3 FAs on RA-related autoimmunity may be most pronounced in those who exhibit HLA class II genetic susceptibility to RA."

-Department of Epidemiology, Colorado School of Public Health, Aurora, Colorado, USA

-Division of Rheumatology, University of Colorado, Aurora, Colorado, USA

-Cedars-Sinai Medical Center, Los Angeles, California, USA

-Benaroya Research Institute at Virginia Mason, Seattle, Washington, USA

-Feinstein Institute for Medical Research and North Shore-Long Island Jewish Health System, Manhasset, New York, USA

-Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, Nebraska, USA

-Scripps Health, La Jolla, California, USA

-National Jewish Health, Denver, Colorado, USA

-Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, Colorado, USA

-Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, Florida, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5371398/

Lower omega-3 fatty acids are associated with the presence of anti-cyclic citrullinated peptide autoantibodies in a population at risk for future rheumatoid arthritis: a nested case-control study

"The aim of this study was to investigate omega-3 fatty acid (FA) supplement use and omega-3 FAs in erythrocyte membranes [omega-3 FA % in erythrocyte membranes (RBC)] and their association with anti-CCP autoantibodies in a population without RA, but who are at genetic risk for RA."

…"Anti-CCP2 positive cases were less likely than controls to report omega-3 FA supplement use (odds ratio: 0.14; 95% CI 0.03, 0.68). In addition, the likelihood of anti-CCP2 positivity was inversely associated with total omega-3 FA % in RBCs (odds ratio: 0.47; 95% CI 0.24, 0.92, for a s.d. increase)."

…"The inverse association between anti-CCP2 positivity and self-reported omega-3 FA supplement use and omega-3 FA % in RBCs suggests that omega-3 FAs may protect against the development of RA-related autoimmunity in pre-clinical RA."

-Colorado School of Public Health, Department of Epidemiology, Aurora,
-Colorado School of Public Health, Department of Biostatistics and Informatics,
-University of Colorado, Division of Rheumatology, Aurora, CO,
-Cedars-Sinai Medical Center, Los Angeles, CA,
-Benaroya Research Institute at Virginia Mason, Seattle, WA,
-Feinstein Institute for Medical Research and North Shore – Long Island Jewish Health System, Manhasset, NY,
-Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE,
-Scripps Health, La Jolla and
-Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5009416/

Marine ω-3, vitamin D levels, disease outcome and periodontal status in rheumatoid arthritis outpatients

"Marine ω-3 fatty acids (FAs) and Vitamin D (VitD) are reportedly capable of down-regulating inflammation in rheumatoid arthritis (RA) and periodontal disease [PD]. This study was undertaken to relate marine FA and VitD status to RA disease status and periodontal conditions."

"Seropositive RA patients had a higher prevalence of periodontitis than seronegative patients. An ω-3 index >8 was related to ω-3 supplementation and more desirable VAS [visual analog scale] and lower PD. VitD status was satisfactory for most patients and was not associated with differences in RA severity or periodontal diagnosis."…

Highlights

- Periodontitis was most prevalent in patients with rheumatoid arthritis (RA) who were seropositive for rheumatoid factor and/or anticitrullinated protein antibody.
- Seafood intake in accordance with the recommendation was related to lower RA symptoms (modified health assessment questionnaire [MHAQ], visual analog scale [VAS]).
- A favorable ω-3 index (>8) was associated with the use of ω-3 supplements.
- An ω-3 index >8 was also related to a more desirable VAS score and lower probing depth.
- Overall vitamin D status was good and did not differ for RA and periodontal measurements.

-Faculty of Medicine, Department of Clinical Dentistry, University of Bergen, Bergen, Norway
-Institute of Marine Research, Bergen, Norway
-Department of Rheumatology, Haukeland University Hospital, Bergen, Norway
-Department of Clinical Science, University of Bergen, Bergen, Norway
https://www.sciencedirect.com/science/article/pii/S0899900718301849

Clinical Benefits of n-3 PUFA and ɤ-Linolenic Acid in Patients with Rheumatoid Arthritis

…"The combination of n-3 PUFA and GLA (group II) increased ɤ-linolenic acid (0.00 ± 0.00 to 0.13 ± 0.11, $p < 0.001$), which was undetectable in all groups before the treatments; (4) Conclusion: Daily supplementation with n-3 fatty acids alone or in combination with GLA exerted significant clinical benefits and certain changes in disease activity."…

-Department of Internal medicine, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia;
-Department of Hygiene, Institute for Public Health, Faculty of Medical Sciences, University of Kragujevac, Kragujevac , Serbia;
-Centre of Research Excellence in Nutrition and Metabolism, Institute for Medical Research, University of Belgrade, Beograd, Serbia;
-Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac, Kragujevac , Serbia;
-Faculty of Hotel Management and Tourism, Department of Natural Sciences and medicine, University of Kragujevac, Kragujevac, Serbia;
-Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia;
-Faculty of Medical Sciences, University of Kragujevac, Physiology, Kragujevac, Serbia
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5409664/

The endocannabinoid system in pain and inflammation: Its relevance to rheumatic disease

…"There is increasing and exciting evidence showing that endocannabinoids regulate the immune response at both the innate (monocytes, macrophages, neutrophils, NK cells,

eosinophils, basophils, mast cells) and adaptive immune level [55]. Immune cells are not only able to be influenced, but are also able to generate and secrete endocannabinoids that lead to changes in immune-cell behavior as well as the production of other inflammatory factors that subsequently influence tissue inflammation [56, 57]."

The Role of Endocannabinoids in Joint Inflammation

"Chinese healers, who have known about the healing properties of endocannabinoids since 2000 BC, have claimed that cannabis "undoes rheumatism" [58]. Evidence supporting the anti-inflammatory effects of endocannabinoids come from preclinical studies that have shown that all classes of cannabinoids including phytocannabinoids (tetrahydrocannabinol, cannabidiol) and synthetic analogs such as Ajulemic acid, "Nabilone," and elmiric acid possess anti-inflammatory effects [18]. These anti-inflammatory effects may be due to direct action on participating immune cells, or by changes in the local endocannabinoid concentrations that then carry out anti-inflammatory actions. In arthritis, persistent inflammation results in the infiltration of immune cells and the subsequent development of hypersensitivity. Synovial serum samples from patients with RA consistently express elevated cytokine levels such as TNF-α, interleukin-6 (IL-6), and IL-1β, which act directly to sensitize joint nociceptors and stimulate the release of prostaglandins [59, 60]. In an elegant study by Sancho et al. it was shown that AEA can inhibit TNF-α-induced NF-κβ activation by direct inhibition of the IκB kinase [60]. The protective effects of endocannabinoids have been noted in other inflammatory conditions such as multiple sclerosis, celiac disease, and periodontitis [18].

Malfait et al. [61] have shown that endocannabinoids can block progression of joint inflammation in rodent models of arthritis. The anti-inflammatory potential of CB2 has been confirmed in mouse models of arthritis [61, 62]. The protective CB2 effects include the suppression of pro-inflammatory cytokine and damaging proteinases secretion; as well as regulating immune cell adhesion and migration to the inflamed joint. Together, this helps slow the perpetuation of disease and alleviate associated arthritic pain primarily derived from localized inflammation [36]. Further to this, elevated levels AEA and 2-AG are detected in the synovial fluid of RA and OA patients, but absent in healthy controls, suggest that local endocannabinoid secretion may assist in minimising inflammation in the arthritic joints [4, 60]."… With both cannabinoid receptors and endogenous ligands present in inflamed human joints, targeting this system may hold therapeutic promise for both inflammatory, as well as degenerative arthritis [60]. Administration of cannabinoid agonists, WIN55212 [synthetic cannabinoid] and CP55940 [synthetic cannabinoid], have shown the ability to reduce inflammatory IL-6 and interleukin-8 (IL-8) cytokine production by fibroblast like synoviocytes cells, ameliorating acute inflammation and associated pain in arthritic joints [2, 63]. Similarly, systemic administration of the CB2 agonist,

JWH133, suppressed pain and corrected deviation in circulating pro- and anti-inflammatory cytokines in the rat MIA model [43]. These anti-inflammatory effects are limited by the rapid cellular uptake and degradation of endocannabinoid metabolites but can be overcome through the inhibition of the catabolic enzyme FAAH allowing longer physiological effects [35]. "…

-Department of Rheumatology, University of Sydney, Westmead Hospital, Sydney, Australia

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5685274/

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…"An intriguing finding has been an inverse relationship between the presence of RA-related autoantibodies in At-Risk populations and intake of omega-3 fatty acids as well as lipid biomarkers that measure levels of these key anti-inflammatory molecules. Because of the potential relationship of this exposure to the chronic local inflammation that underlies the mucosal origins hypothesis, these findings are reviewed in more depth. Notably, there is both established and emerging evidence that poly-unsaturated fatty acids (PUFAs) derived from the omega-3 FA biosynthesis pathway may play an important role in RA treatment and prevention. Omega-3 PUFA supplementation in patients with classified RA has been shown to reduce signs and symptoms of inflammation and lead to decreased use of other therapeutic agents[82,83]. Population-based approaches have demonstrated that increased intake of fish rich in omega-3 PUFAs or direct supplementation with PUFAs are associated with a reduced risk for developing RA[84]. With regard to At-Risk subjects, it has recently been shown that increased omega-3 FA intake as well as higher levels of the red blood cell (RBC) omega-3 FA pathway eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are associated with a decreased risk of RA-related autoantibody positivity[85]. Specifically, in those studies the likelihood of anti-CCP2 positivity in subjects was inversely associated with total omega-3 FA% in RBCs (odds ratio: 0.47; 95% CI 0.24, 0.92, for a one standard deviation increase), and anti-CCP2 positive cases were less likely than controls to report omega-3 FA supplement use (odds ratio: 0.14; 95% CI 0.03, 0.68). Intriguingly, the strongest effect was found in SE+ individuals[86]. In further observational studies of ACPA+ subjects without synovitis at baseline, lower levels of RBC omega-3 FAs were associated with increased risk for progression to IA[87]."…

…"Finally, one could ask how chronic inflammation might relate mechanistically to epidemiologic factors such as smoking or lower levels of omega-3 PUFA. Prior studies have suggested that smoking is associated with increased citrullinated proteins in the lung[151]. With regard to the omega-3 PUFA levels and exposures, recent studies have shown that molecules derived from this

pathway, especially bioactive lipid mediators including resolvins and maresins that are biosynthesized in vivo from EPA and DHA, are key factors in resolving or reducing inflammation[152]. The observation that RBC levels of omega-3 fatty acids are lower in those progressing to IA suggest that these factors are either present in insufficient quantities or are consumed as part of the excessive mucosal inflammation that is present, and that these two processes, local inflammation and a lack of appropriate levels of omega3 fatty acids, may be both necessary for continued evolution of disease. These anti-inflammatory compounds decrease inflammation through mechanisms including blocking neutrophil and other cell chemotaxis/recruitment, increasing neutrophil apoptosis, and promoting cellular immune switching to regulatory phenotypes (reviewed in[153]). Furthermore, the actions of agents such as resolvins have been shown to reduce inflammation at mucosal surfaces in the lung as well as elsewhere (e.g. gut)[154,155], and to reduce cell activation and immune-complex mediated inflammation in a variety of diseases including IgA nephropathy[153,156,157]. Importantly, as described above, all of these are pathways may be critical to the initiation and propagation of autoimmunity and the ultimate development of arthritis."…

-University of Colorado Denver, Division of Rheumatology, Aurora, CO, USA
-Benaroya Research Institute, Seattle, WA, USA
-Stanford University, Division of Immunology and Rheumatology, Stanford, CA, USA
-Colorado School of Public Health, Department of Epidemiology, Aurora, CO, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6704378/

Modulation of C-reactive protein and plasma omega-6 fatty acid levels by phospholipase A2 gene polymorphisms following a 6-week supplementation with fish oil.

"This clinical trial investigated the impact of a six-week supplementation with fish oil and single nucleotide polymorphisms (SNPs) in PLA2G4A and PLA2G6 genes on total omega-6 fatty acid (n-6 FA) levels in plasma phospholipids (PL) and plasma C-reactive protein (CRP) levels in 191 subjects. Interaction effects between SNPs and supplementation modulated total n-6 FAs and CRP levels in both men and women. Associations between SNPs and total n-6 FA levels and between SNPs and CRP levels were identified in men, independently of supplementation. Supplementation decreased total n-6 FAs without affecting plasma CRP levels. Changes in CRP levels correlated positively with changes in total n-6 FAs in men (r=0.25 p=0.01), but not in women. In conclusion, total n-6 FA levels in plasma PL and plasma CRP levels are modulated by SNPs within PLA2G4A and PLA2G6 genes alone or in combination with fish oil supplementation."

-Institute of Nutrition and Functional Foods (INAF), Laval University, 2440 Hochelaga Blvd, Quebec, Qc, Canada
-CHU de Québec Research Center - Endocrinology and Nephrology, 2705 Laurier Blvd, Quebec, Qc, Canada G1V 4G2.
-Institute of Nutrition and Functional Foods (INAF), Laval University, 2440 Hochelaga Blvd, Quebec, Qc, Canada
-Prostaglandins Leukot Essential Fatty Acids (2015).
https://www.ncbi.nlm.nih.gov/pubmed/26525102

Low omega-6/omega-3 polyunsaturated fatty acid ratios reduce hepatic C-reactive protein expression in apolipoprotein E-null mice.

"Expression characteristics of C-reactive protein (CRP) for the omega-6/omega-3 polyunsaturated fatty acid (PUFA) ratios have not been evaluated in the well-qualified experimental atherosclerotic mouse model. This work focused on characteristics of CRP expression in the liver of apolipoprotein E-null (apoE(-/-)) mice influenced by omega-6/omega-3 PUFA ratios."

…"As the dietary ratio of omega-6/omega-3 fatty acids ascended, so did the expression of hepatic and aortic CRP and hepatic IL-6 protein. However, peroxisome proliferator-activated receptor-gamma mRNA level had a tendency to decrease. Serum IL-1beta, IL-6, and tumor necrosis factor-alpha levels did not show a statistical difference among the mice fed the four ratios of the omega-6/omega-3 PUFA diet. The group 4 mice developed a significant increase in atherosclerotic lesions compared with the other groups."

…"The results indicated that low ratios of omega-6/omega-3 PUFAs (1.28-9.98) downregulated the hepatic and aortic CRP expressions and reduced aortic en face lesions in apoE(-/-) mice compared with the high ratio of the omega-6/omega-3 PUFA diet."

-The Key Laboratory of Animal Resistance Biology of Shandong, College of Life Sciences, Shandong Normal University, Jinan, People's Republic of China.
https://www.ncbi.nlm.nih.gov/pubmed/20004083

Polyunsaturated Fatty Acids and Serum C-Reactive Protein: The Rotterdam Study

…"Both n-3 [omega-3] PUFAs and n-6 [omega-6] PUFAs inhibit the activities of δ-6 desaturase, δ-5 desaturase, and cyclooxygenase, all of which are involved in fatty acid regulation that influences pro- and antiinflammatory mediators [32–34]. Therefore, high intake of both n-3 and n-6 PUFAs could lead to a reduction in inflammation. Additionally, PUFAs can modify the activity of transcription factors, such as peroxisome proliferator-activated receptors and nuclear factor κB. Peroxisome proliferator-activated receptors can interfere with the activation of nuclear factor κB

by inhibiting signaling molecules and therefore impeding the production of proinflammatory cytokines [35]."…

-American Journal of Epidemiology, Volume 181, Issue 11, 1 June 2015, Pages 846–856
https://academic.oup.com/aje/article/181/11/846/87496

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…"The inflammatory biomarkers, erythrocyte sedimentation rate, and interleukin-8 decreased after supplementation with n-3 [omega-3] FA and erythrocyte sedimentation rate increased after supplementation with n-6 [omega-6] FA."…

-Departments of Pediatrics, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.
https://www.ncbi.nlm.nih.gov/pubmed/20639712

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…"It has been noted that rheumatoid arthritis and autoimmune inflammatory disease are associated with an increased risk for cardiovascular Disease.[1] "…

-Dr Joseph Lamb, M.D
-Director of Intramural Clinical Research, Metagenics
-Anti-Aging Medical News - The Future of Medicine Today (2014)
https://www.a4m.com/assets/pdf/medical-news/medical-news-winter-2014.pdf

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"Prostaglandin E2 (PGE2) acts via its EP4 receptor as a cytokine amplifier (e.g., interleukin [IL]-6) and induces the differentiation and expansion of inflammatory T-helper (Th) lymphocytes. These mechanisms play a key role in the onset and progression of rheumatoid arthritis (RA). "....

-Rottapharm Biotech, Via Valosa di Sopra 9, I-20900, Monza, MB, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/29490676

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"There is evidence to support the use of supplementation with long-chain omega-3 polyunsaturated fatty acids (LCn-3PUFA) from oily fish or fish oil for the treatment of various inflammatory diseases such as rheumatoid arthritis."…

The anti-inflammatory properties of LCn-3PUFA [omega-3] have been beneficial in other inflammatory diseases with recent systematic reviews in rheumatoid arthritis and cardiovascular

disease concluding that the benefits of LCn-3PUFA are modest but clinically relevant [65,66]. In people with rheumatoid arthritis all included studies showed some clinical benefit with LCn-3PUFA supplementation [66]"…

-Nutritional Physiology Research Centre, Sansom Institute for Health Research, School of Health Sciences, University of South Australia, City East Campus, Frome Road, Adelaide, South Australia, Australia

-Clinical Nutrition Research Centre, School of Biomedical Sciences & Pharmacy, University of Newcastle, University Drive, Callaghan, New South Wales, Australia

-Respiratory Medicine, Flinders University, Faculty of Health Sciences, Repatriation General Hospital, Daws Road, Daw Park, South Australia, Australia

-School of Population Health, University of South Australia, City East Campus, Frome Road, Adelaide, South Australia , Australia

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3748832/

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…"Omega-3 fatty acid intake is associated with the improvement of rheumatoid arthritis, as omega-3 metabolites inhibit the production of inflammatory cytokines responsible for arthritic pain (Zainal et al. 2009). Supplementation with EPA and DHA is effective against arthritic pain as well as other symptoms, including joint stiffness (Goldberg and Katz 2007)."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

The Effect of Omega-3 Fatty Acids in Patients With Active Rheumatoid Arthritis Receiving DMARDs Therapy: Double-Blind Randomized Controlled Trial

"**Background**: Rheumatoid arthritis is a symmetric peripheral polyarthritis of unknown etiology that, untreated or if unresponsive the therapy, typically leads to deformity and destruction of joints due to erosion of cartilage and bone. Omega-3 fatty acids have been shown to reduce morning stiffness, the number of tender joints and swollen joints in patients with rheumatoid arthritis. This study is designed for evaluation of omega-3 effects on disease activity and remission of rheumatoid arthritis in DMARDs treated patients and on weight changes and reduction of analgesic drugs consumption versus placebo."…

"**Results**: Significant improvement in the patient's global evaluation and in the physician's assessment of disease was observed in those taking omega-3. The proportions of patients who improved and of those who were able to reduce their concomitant analgesic medication were

significantly greater with omega-3 consumption. There were no weight changes.

Conclusion: Daily supplementation with omega-3 results has significant clinical benefit and may reduce the need for concomitant analgesic consumption without weight changes."

-Department of Rheumatology, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
https://pubmed.ncbi.nlm.nih.gov/26925896

Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis. A 12-month, double-blind, controlled study

"Results: Significant improvement in the patient's global evaluation and in the physician's assessment of pain was observed only in those taking 2.6 gm/day of omega 3. The proportions of patients who improved and of those who were able to reduce their concomitant antirheumatic medications were significantly greater with 2.6 gm/day of omega 3.

Conclusion: Daily supplementation with 2.6 gm of omega 3 results in significant clinical benefit and may reduce the need for concomitant antirheumatic medication."

-Arthritis and Metabolic Bone Disease Research Unit, K. U. Leuven, U. Z. Pellenberg, Belgium.
https://pubmed.ncbi.nlm.nih.gov/8003055

The Effect of Omega-3 Fatty Acids on Rheumatoid Arthritis

"Omega-3 fatty acids are unsaturated fatty acids thought to play a role in health and disease. They are known as essential fatty acids, as they cannot be synthesized in mammals. Omega-3 fatty acids have a beneficial effect on the secondary prevention of coronary artery disease and stroke and are essential for the development and function of the nervous system and the retina in man. Omega-3 fatty acids are thought to have immunomodulatory properties as they act as precursors to lipid mediators of inflammation which may limit or modulate the inflammatory response. Omega-3 fatty acids seem to prevent or attenuate experimental arthritis. They may have a beneficial effect in the treatment of rheumatoid arthritis. Clinical studies have shown that omega-3 fatty acids may have a modulatory effect on disease activity, namely on the number of swollen and tender joints. It appears that omega-3 fatty acids may modulate disease activity in rheumatoid arthritis."…

"Omega-3 fatty acids are polyunsaturated fatty acids which have an impact in health and disease. They act as precursors to lipid mediators of inflammation and may attenuate and modulate the autoimmune inflammatory response. They have been shown to ameliorate or prevent experimental arthritis and may decrease disease activity in rheumatoid arthritis."

-Department of Endocrinology, Asclepeion Hospital, Voula, Athens, Greece
-First Department of Medicine, Asclepeion Hospital, Voula, Athens, Greece
-Department of Rheumatology, St. Paul's Hospital, Thessaloniki, Greece
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7362115

See also Ginger , Prostaglandins , Synovial Membrane

Rheumatic Diseases

Omega-3 Fatty Acids in Rheumatic Diseases: A Critical Review.

"Many clinical trials of omega-3 fatty acids, supplied as fish oil supplements, have been carried out in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), lupus nephritis, and osteoarthritis (OA) over the past 3 decades. This review attempts to summarize the highlights of these studies to evaluate the clinical efficacy for omega-3 fatty acids to be added alongside existing treatment regimens. A total of 20 clinical trials have been carried out in RA, of which 16 exhibited significant improvements in multiple disease clinical outcomes. Nine clinical trials have been completed in SLE and lupus nephritis, of which 6 exhibited significant improvements in 1 or more clinical outcomes. A total of 4 clinical trials have been conducted in OA, of which 3 exhibited significant improvements in at least 1 clinical parameter. Multiple mechanisms for the clinical effects of omega-3 fatty acids have been implicated, including the modulation of eicosanoid synthesis toward a more anti-inflammatory profile and suppressed production of proinflammatory cytokines. Overall, fish oil supplements appear to be a safe and effective agent that could be added to the current treatment regimens in RA. Longer-term trials with larger patient cohort sizes are warranted to establish any long-term benefits of fish oil supplements in SLE, lupus nephritis, and OA."

-Department of Biomedical Engineering, University of Houston, Houston, TX.
https://www.ncbi.nlm.nih.gov/pubmed/28816722

Rimonabant

Also known as SR 141716A

"Rimonabant is an anorectic anti-obesity drug produced and marketed by Sanofi-Aventis. It is an

inverse agonist for the cannabinoid receptor CB1. Its main avenue of effect is reduction in appetite. Rimonabant is the first selective CB1 receptor blocker to be approved for use anywhere in the world. Rimonabant is approved in 38 countries including the E.U., Mexico, and Brazil. It was rejected for approval for use in the United States. This decision was made after a U.S. advisory panel recommended the medicine not be approved because it may increase suicidal thinking and depression."

-National Library of Medicine
https://pubchem.ncbi.nlm.nih.gov/compound/Rimonabant

■■■

"The endocannabinoid system (ECS) is known to exert regulatory control on essentially every aspect related to the search for, and the intake, metabolism and storage of calories, and consequently it represents a potential pharmacotherapeutic target for obesity, diabetes and eating disorders. While the clinical use of the first generation of cannabinoid type 1 (CB(1)) receptor blockers has been halted due to the psychiatric side effects that their use occasioned, recent research in animals and humans has provided new knowledge on the mechanisms of actions of the ECS in the regulation of eating behavior, energy balance, and metabolism. In this review, we discuss these recent advances and how they may allow targeting the ECS in a more specific and selective manner for the future development of therapies against obesity, metabolic syndrome, and eating disorders."

-INSERM, Neurocentre Magendie, Physiopathologie de la Plasticité Neuronale, France.-University of Bordeaux, Neurocentre Magendie, Physiopathologie de la Plasticité Neuronale, Bordeaux, France.
-Endocrinology Department, Haut-Lévêque Hospital, Pessac, France.
-INSERM, Neurocentre Magendie, Physiopathologie de la Plasticité Neuronale, Bordeaux, France.
-University of Bordeaux, Neurocentre Magendie, Physiopathologie de la Plasticité Neuronale, Bordeaux, France.
https://pubmed.ncbi.nlm.nih.gov/26408168

S

Scaring (Fibrosis)

Cannabinoid CB2 receptors are involved in the regulation of fibrogenesis during skin wound repair in mice

"The endocannabinoid system is composed of endogenous ligands, cannabinoid receptors, and synthesizing and degrading enzymes of endogenous ligands. The most extensively investigated cannabinoid receptors are cannabinoid CB1 and cannabinoid CB2 receptors [(1)]. Increasing evidence has demonstrated that cannabinoid CB2 receptor activation decreases fibrosis in mice exhibiting hepatic fibrosis [(2)], abates skin fibrosis in a mouse model of scleroderma (3), and reduces fibroblast proliferation, and prevents the development of skin and lung fibrosis in a systemic sclerosis mouse model [(4)]. In addition, our previous study demonstrated that cannabinoid CB2 receptors are expressed in a time-dependent manner in neutrophils, macrophages and myofibroblasts during skin wound healing in mice [(5)]. These findings suggest a potential role of cannabinoids in alleviating, or even reversing, skin fibrosis following traumatic damage to the skin."

-Department of Forensic Pathology, School of Forensic Medicine, China Medical University, Shenyang, Liaoning , P.R. China

-Department of Forensic Medicine, Xuzhou Medical College, Xuzhou, Jiangsu, P.R. China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4805070/

See also Skin

Schizophrenia

Differences in omega-3 and omega-6 polyunsaturated fatty acid consumption in people at ultra-high risk of psychosis, first-episode schizophrenia, and in healthy controls.

"AIM: Supplementation with omega-3 PUFA showed efficacy in reducing the risk of transition into psychosis in UHR [Universal Health Record] individuals. It is uncertain whether dietary patterns can be partly responsible for n-3 deficiencies observed in susceptible participants before the diagnosis of schizophrenia. The study was designed to assess differences in omega-3 and omega-6 PUFA consumption in healthy controls (HC), UHR participants and FES patients as well as to verify the hypothesis that dietary changes in PUFA consumption are present before active psychosis develops, that is, in UHR individuals."....

"RESULTS: Significant differences in omega-3 and omega-6 PUFA intake were observed between

study groups. UHR and FES groups reported significantly higher consumption of omega-6 PUFA in comparison with HC. FES patients also reported a higher consumption of alpha-linolenic acid (omega-3) in comparison with HC. No significant differences were seen in consumption of long-chain marine PUFA.

CONCLUSIONS: Differences in omega-6 and omega-3 PUFA consumption exist before development of psychotic symptoms, fulfilling the criteria of schizophrenia."

-Department of Affective and Psychotic Disorders, Medical University of Lodz, Lodz, Poland.
-Nutrition Hygiene and Epidemiology, Medical University of Lodz, Lodz, Poland.
https://www.ncbi.nlm.nih.gov/pubmed/26279283

■■■

"A 2013 meta-analysis of 18 studies compared the PUFA composition of red blood cell membranes in patients with schizophrenia to individuals without the disorder [198]. The majority of studies investigated medicated patients, though the authors separated the analysis into three groups of patients at time of measurement in order to account for possible confounding from pharmacologic agents: antipsychotic-medicated, antipsychotic-naïve, and antipsychotic-free. Overall, decreased concentrations of DPA, DHA, and AA in red blood cell membranes were associated with the schizophrenic state. Several mechanisms may account for PUFA abnormalities in schizophrenia, such as altered lipid metabolism, increased oxidative stress, or changes in diet consequent to disease-related behavior.

The use of long-chain omega-3 fatty acid supplements to alleviate symptoms of schizophrenia or to mitigate adverse effects of antipsychotic medications has been investigated in a number of clinical trials [194, 199]. In a recent randomized, placebo-controlled trial in 50 subjects with recent onset of schizophrenia who were medicated, daily supplementation with EPA (740 mg) and DHA (400 mg) reduced psychotic symptoms (assessed with the Brief Psychiatric Rating Scale) only in those who were not taking the anxiolytic, lorazepam (Ativan) [200]. Overall, however, there was no effect of long-chain PUFA supplements on schizophrenia symptoms. Yet, given the high safety profile of fish oil supplements and some evidence of a positive effect of EPA supplementation in a subset of trials, some clinicians may consider EPA a useful adjunct to antipsychotic therapy in patients with schizophrenia."…

- Oregon State University
https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids#neuropsychiatric-disorders-treatment

See also Social Functioning , Mental Health

Scleroderma

See also Systemic Sclerosis

Seizures

Seizing an Opportunity for the Endocannabinoid System

"Exogenous cannabinoids can limit seizures and neurodegeneration, and their actions are largely mimicked by endogenous cannabinoids (endocannabinoids). Endocannabinoids are mobilized by epileptiform activity and in turn influence this activity by inhibiting synaptic transmission; both excitatory and some inhibitory synapses can be suppressed, leading to potentially complex outcomes. Moreover, the endocannabinoid system is not a fixed entity, and its strength can be enhanced or reduced. Endocannabinoids and their receptors are altered by epileptic seizures in ways that can reduce the efficacy of both exogenous and endogenous cannabinoids in sometimes unexpected ways."…

-Bradley E. Alger, PhD, Departments of Physiology and Psychiatry, Program in Neuroscience, University of Maryland School of Medicine, Baltimore, MD

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4189640/

The endocannabinoid system controls key epileptogenic circuits in the hippocampus

"Balanced control of neuronal activity is central in maintaining function and viability of neuronal circuits. The endocannabinoid system tightly controls neuronal excitability. Here, we show that endocannabinoids directly target hippocampal glutamatergic neurons to provide protection against acute epileptiform seizures in mice. Functional CB1 cannabinoid receptors are present on glutamatergic terminals of the hippocampal formation, colocalizing with vesicular glutamate transporter 1 (VGluT1). Conditional deletion of the CB1 gene either in cortical glutamatergic neurons or in forebrain GABAergic neurons, as well as virally induced deletion of the CB1 gene in the hippocampus, demonstrate that the presence of CB1 receptors in glutamatergic hippocampal neurons is both necessary and sufficient to provide substantial endogenous protection against kainic acid (KA)-induced seizures. The direct endocannabinoid-mediated control of hippocampal glutamatergic neurotransmission may constitute a promising therapeutic target for the treatment of disorders associated with excessive excitatory neuronal activity."

-Department of Physiological Chemistry, Johannes Gutenberg University, Duesbergweg 6, 55099 Mainz, Germany.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1769341/

Senses

"a faculty by which the body perceives an external stimulus; one of the faculties of sight, smell, hearing, taste, and touch." - *Oxford Languages / Google*

■■■

"The body also produces its own cannabinoid chemicals. They play a role in regulating pleasure, memory, thinking, concentration, body movement, awareness of time, appetite, pain, and the senses (taste, touch, smell, hearing and sight)."

- National Institute of Health / National Institute on Drug Abuse
bit.do/nih-cannabinoid (The original document was removed from NIH)

Cannabinoid Control of Olfactory Processes: The Where Matters

"Olfaction has a direct influence on behavior and cognitive processes. There are different neuromodulatory systems in olfactory circuits that control the sensory information flowing through the rest of the brain. The presence of the cannabinoid type-1 (CB1) receptor, (the main cannabinoid receptor in the brain), has been shown for more than 20 years in different brain olfactory areas. However, only over the last decade have we started to know the specific cellular mechanisms that link cannabinoid signaling to olfactory processing and the control of behavior. In this review, we aim to summarize and discuss our current knowledge about the presence of CB1 receptors, and the function of the endocannabinoid system in the regulation of different olfactory brain circuits and related behaviors."…

"CB1 receptors are widely expressed in the central nervous system and likely represent the most abundant GPCR in the brain [15]. Given its ubiquitous expression in multiple brain areas, CB1 receptors modulate a variety of functions, from sensory perception to more complex cognitive processes such as learning and memory [16,17,18]."….

"Growing evidence has revealed that the ECS modulates direct olfactory processes such as odor sensitivity or olfactory learning and memory. Across different brain olfactory areas, the ECS appears to play an essential role in the control of synaptic transmission and plasticity, but also in the regulation of vital behaviors that depend on olfaction, such as the feeding state of the

individual (Figure 1; [59]).”

-INSERM, U1215 NeuroCentre Magendie, 146 rue Léo Saignat, CEDEX, 33077 Bordeaux, France; moc.liamg@larretyerffoeg (G.T.); rf.mresni@onacisram.innavoig (G.M.)

-University of Bordeaux, 146 rue Léo Saignat, 33000 Bordeaux, France

-Interdisciplinary Institute for Neuroscience, CNRS, UMR 5297, 33000 Bordeaux, France

-Department of Neurosciences, University of the Basque Country UPV/EHU, Barrio Sarriena s\n, 48940 Leioa, Spain; sue.uhe@sednarg.ordep

-Achucarro Basque Center for Neuroscience, Science Park of the UPV/EHU, 48940 Leioa, Spain

-IKERBASQUE, Basque Foundation for Science, Maria Diaz de Haro 3, 48013 Bilbao, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7230191/

Sensory Disorders

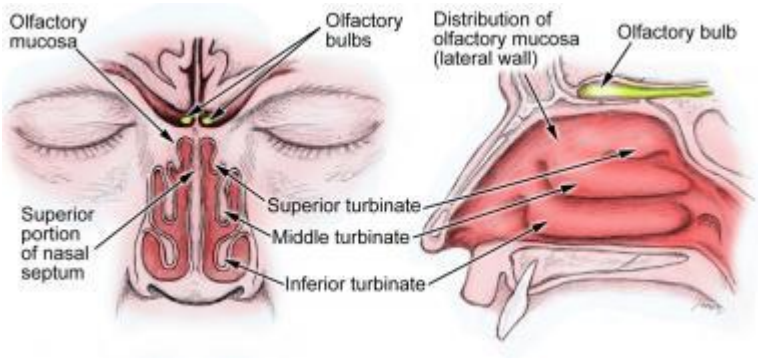
“Historically, disorders of taste and smell have been difficult to diagnose and treat, often because of a lack of knowledge and understanding of these senses and their disease states. An alteration in taste or smell may be a secondary process in various disease states, or it may be the primary symptom.

The prevalence of disorders of taste and smell in the US general population has been estimated from the US National Health and Nutrition Examination Survey (NHANES) 2011-2014 protocol. A total of 3519 men and women aged 40 and older were tested with a scratch-and-sniff olfactory test; smell, taste, and combined smell and taste impairment had estimated prevalences of 13.5%, 17.3%, and 2.2%, respectively. [1]

It is also known that chemosensory dysfunction deteriorates with age starting in the fifth decade of life. [2] Given the aging of the US population, therefore, it stands to reason that a significant and increasing number of individuals will experience age-related sensory loss. [3] A 2002 study showed that the prevalence of objective olfactory impairment in adults older than 53 years is 24.5% and grows more prevalent with age, reaching 62.5 % in those aged 80-97 years. Extrapolating from these values, there are currently 14 million older adults with some degree of olfactory impairment. Self-reported impairment in this study was only 9.5%, which supports the need for more accurate data based on objective measures. [4]

Loss of smell and/or taste has been linked to inadequate nutritional intake, reduced social pleasure, and decreased psychological well-being. It may even be life threatening, impairing the detection of smoke in a fire or the ability to identify spoiled food. Because approximately 80% of taste disorders are truly smell disorders, much of this article focuses on the sense of smell and its

dysfunction, with additional discussion of taste and related disorders. See the image below."



Head anatomy with olfactory nerve.

Terminology

"The disorders of smell are classified as "-osmias" and those of taste as "-geusias."

- Anosmia - Inability to detect odors [5]
- Hyposmia - Decreased ability to detect odors
- Dysosmia - Any smell alteration
  - Parosmia - Altered perception of smell in the presence of an odor, usually unpleasant
  - Phantosmia – Perception of smell without an odor present
  - Agnosia - Inability to classify or contrast odors, although able to detect odors
- Ageusia - Inability to taste
- Hypogeusia - Decreased ability to taste
- Dysgeusia – Distorted ability to taste

Smell and taste disorders can be total (all odors or tastes), partial (affecting several odors or tastes), or specific (only one or a select few odors or tastes)."

-Dr. Eric H Holbrook, MD Associate Professor, Department of Otolaryngology, Harvard Medical School; Chief of Rhinology Division, Massachusetts Eye and Ear Infirmary

-Dr. Donald Leopold, MD Professor of Otorhinolaryngology, University of Vermont College of Medicine

https://emedicine.medscape.com/article/861242-overview

Sepsis

…“Sepsis is a dysregulated inflammatory response syndrome that leads to life-threatening organ dysfunction.[1] The current definition of sepsis identifies a heterogeneous population of individuals with diverse patterns of immune response, organ dysfunction and clinical outcomes.1 Current sepsis biomarkers may be helpful in determining organ failure and evaluating the patient's clinical course; however, the use of a single biomarker is insufficient to reflect the complexity of the sepsis pathophysiology,[2] which is multifactorial and rapidly changing.3 Therefore, molecular analysis of sepsis including cytokines and circulating mediators is essential to understand the complexity of cell-to-cell communication in multiple organs,[3, 4] which is a decisive response to stressors.”…

- Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul Republic of Korea,

- Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul Republic of Korea,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7417686/

Anti-inflammatory effects of cannabinoid CB2 receptor activation in endotoxin-induced uveitis

“Recently, several studies have reported that modulating CB2 receptors in experimental models of sepsis decreased inflammation (Lehmann et al., 2011; 2012), and deleting these receptors reduced survival (Tschop et al., 2009). Attenuation of the inflammatory response by activation of CB2 receptors has also been reported in the brain.“

-Department of Pharmacology, Dalhousie University, Halifax, NS, Canada

-Department of Microbiology and Immunology, Dalhousie University, Halifax, NS, Canada

-Department of Anesthesia, Dalhousie University, Halifax, NS, Canada

-Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3954484/

…“Moreover, patients with increased risk of sepsis (IL-6/IL-10 ratio >8) showed a tendency to shorter ICU stay (18 hr) under omega-3 PUFA treatment.”…

-Department of Anesthesiology and Critical Care Medicine, University Hospital Carl Gustav Carus, University of Technology, Dresden, Germany.

https://pubmed.ncbi.nlm.nih.gov/15239141

...“The dysregulation of apoptosis in immune and nonimmune cells plays a critical role in the pathogenesis of sepsis [70,71].”..

-Liver Cancer Prevention Research Unit, RIKEN Cluster for Pioneering Research, Japan;

-Department of Intensive Care Unit, The Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7918628/

Apoptosis in sepsis

“Sepsis demonstrates a marked dysregulation of the immune system in its ability to fight infection. Previous models have focused on the mechanisms which upregulate and sustain the heightened immune response without addressing the role of down-regulation effectors. Attention has been drawn to these down-regulating mechanisms and their precise role in the pathophysiology of sepsis. Apoptosis is an evolutionarily conserved, energy-dependent mode of cell death requiring the initiation and regulation of complex genetic programs. It is the body's main method of getting rid of cells which are in excess, damaged, or no longer needed in a controlled manner. The role of this cellular phenomenon in physiology and pathophysiology has been the subject of intense scrutiny over the last decade. Much work has demonstrated that dysregulation of apoptosis does occur in immune and nonimmune cells in in vitro and in vivo models of sepsis. The difficulty has been in tying the phenomenology of apoptosis into the pathophysiology of sepsis. Further work is needed to make these connections to elucidate rational approaches for clinical applications of immunomodulation in sepsis.”

-Department of Surgery, University of Pittsburgh School of Medicine, PA, USA.

https://pubmed.ncbi.nlm.nih.gov/10807323/

Exosomes in Sepsis

“Sepsis is a severe state of infection with high mortality. Pathogen-associated molecular patterns and damage-associated molecular patterns (DAMPs) initiate dysregulated systemic inflammation upon binding to pattern recognition receptors. Exosomes are endosome-derived vesicles, which carry proteins, lipids and nucleic acids, and facilitate intercellular communications. Studies have shown altered contents and function of exosomes during sepsis. In sepsis, exosomes carry increased levels of cytokines and DAMPs to induce inflammation. Exosomal DAMPs include, but are not limited to, high mobility group box 1, heat shock proteins, histones, adenosine triphosphate, and extracellular RNA. Exosomes released during sepsis have impact on multiple

organs, including the lungs, kidneys, liver, cardiovascular system, and central nervous system. Here, we review the mechanisms of inflammation caused by exosomes, and their contribution to multiple organ dysfunction in sepsis."

-Center for Immunology and Inflammation, The Feinstein Institutes for Medical Research, Manhasset, NY, United States

-Department of Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY, United States

-Department of Surgery, Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY, United States

https://www.frontiersin.org/articles/10.3389/fimmu.2020.02140/full

Exosomes in Sepsis and Inflammatory Tissue Injury

"Sepsis is the leading cause of death in medical intensive care units, and thus represents a serious healthcare problem worldwide. Sepsis is often caused by the aberrant host responses to infection, which induce dysregulated inflammation that leads to life-threatening multiple organ failures. Mediators such as proinflammatory cytokines that drive the sepsis pathogenesis have been extensively studied. Exosomes, biological lipid bilayer nanoparticles secreted via the endosomal pathway of cells, have recently emerged as important cargos that carry multiple mediators critical for the pathogenesis of sepsis-associated organ dysfunctions. Here we will review current knowledge on the exosomes in sepsis and relevant inflammatory tissue injuries."

-Dept. of Molecular Pathobiology and Cell Adhesion Biology, Mie University Graduate School of Medicine, Japan.

-Dept. of Emergency and Disaster Medicine, Mie University Graduate School of Medicine, Japan.

https://pubmed.ncbi.nlm.nih.gov/31738129/

Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans

"Patients with sepsis have impaired host defenses that contribute to the lethality of the disorder. Recent work implicates lymphocyte apoptosis as a potential factor in the immunosuppression of sepsis. If lymphocyte apoptosis is an important mechanism, specific subsets of lymphocytes may be more vulnerable. A prospective study of lymphocyte cell typing and apoptosis was conducted in spleens from 27 patients with sepsis and 25 patients with trauma. Spleens from 16 critically ill nonseptic (3 prospective and 13 retrospective) patients were also evaluated. Immunohistochemical staining showed a caspase-9-mediated profound progressive loss of B and CD4 T helper cells in sepsis. Interestingly, sepsis did not decrease CD8 T or NK cells. Although there was no overall effect on lymphocytes from critically ill nonseptic patients (considered as a group), certain individual patients did exhibit significant loss of B and CD4 T cells. The loss of B

and CD4 T cells in sepsis is especially significant because it occurs during life-threatening infection, a state in which massive lymphocyte clonal expansion should exist. Mitochondria-dependent lymphocyte apoptosis may contribute to the immunosuppression in sepsis by decreasing the number of immune effector cells. Similar loss of lymphocytes may be occurring in critically ill patients with other disorders."

-Department of Anesthesiology, Washington University School of Medicine, USA.
https://pubmed.ncbi.nlm.nih.gov/11359857

How are sepsis and systemic inflammatory response syndrome (SIRS) differentiated?

"Sepsis is a systemic response to infection. It is identical to SIRS, except that it must result specifically from infection rather than from any of the noninfectious insults that may also cause SIRS (see the image below). That sepsis and SIRS are phenotypically similar underscores a common inflammatory pathway causing both."…

-Medscape
https://www.medscape.com/answers/169640-99167/how-are-sepsis-and-systemic-inflammatory-response-syndrome-sirs-differentiated

Resolution of inflammation and sepsis survival are improved by dietary Ω-3 fatty acids

"Critical conditions such as sepsis following infection or traumatic injury disturb the complex state of homeostasis that may lead to uncontrolled inflammation resulting in organ failure, shock and death. They are associated with endogenous mediators that control the onset of acute inflammatory response, but the central problem remains the complete resolution of inflammation. Omega-3 enriched lipid emulsions (Ω-3+ LEs) were used in experimental studies and clinical trials to establish homeostasis, yet with little understanding about their role on the resolution of inflammation and tissue regeneration. Here, we demonstrate that Ω-3 lipid emulsions (LEs) orchestrate inflammation-resolution/regeneration mechanism during sterile peritonitis and murine polymicrobial sepsis. Ω-3+ LEs recessed neutrophil infiltration, reduced pro-inflammatory mediators, reduced the classical monocyte and enhanced the non-classical monocytes/macrophages recruitment and finally increased the efferocytosis in sepsis. The actions of Ω-3+ LE were 5-lipoxygenase (5-LOX) and 12/15-lipoxygenase (12/15-LOX) dependent. Ω-3+ LEs shortened the resolution interval by 56%, stimulated the endogenous biosynthesis of resolution mediators lipoxin A4, protectin DX and maresin 1 and contributed to tissue

regeneration. Ω-3+ LEs protected against hypothermia and weight loss and enhanced survival in murine polymicrobial sepsis. We highlighted a role of Ω-3+ LEs in regulating key mechanisms within the resolution terrain during murine sepsis. This might form the basis for a rational design of sepsis specific clinical nutrition."…

"The initiation and resolution of inflammation are complex processes characterized by the release of mediators that control the migration and the function of immune cells. This process is essential to exert successful protection against injury and/or infection. If particularly the resolution process fails, inflammation can become chronic leading to collateral tissue destruction and loss of functional organ integrity. Newly identified bioactive resolution phase lipid mediators such as arachidonic acid (AA)-derived lipoxins, eicosapentaenoic acid (EPA)-derived resolvins and docosahexaenoic derived resolvins, protectins (PDs) and maresins (MaRs) and their bioactive peptide-conjugate pathways are biosynthesized during the resolution phase. These so-called specialized pro-resolving lipid mediators (SPMs) actively stimulate cardinal signs of resolution, namely limitation of neutrophil influx, the counterregulation of pro-inflammatory mediators, apoptosis of PMN and the active clearance of apoptotic cells and invading microorganisms.1

Sepsis, a syndrome that is particularly marked by failed resolution of inflammation predisposes to metabolic and immunological dysfunction that causes high morbidity and mortality worldwide.2, 3 To date, however treatment for sepsis is nonspecific, focused primarily on symptomatic therapy. In recent years lipid emulsions have been tested in experimental and clinical trials in critically ill to evaluate a possible beneficial influence on inflammation. This showed a controversial beneficial role for Ω-3 supplementation in critically ill,4, 5, 6 meaning that so far, treatment strategies with reduced load of Ω-6 fatty acids such as fish oil-based, olive oil-based or medium-chain triglycerid-based LEs have not been recommended for critically ill because of the insufficient data.7 Discrepancies are still considered in the methodological bias including the optimum composition, dose and timeframes, and indication for parenteral LEs. In particular little information is available about the mechanism of LEs during the onset and the resolution of acute inflammation and the tissue regeneration.

In this report, we show that administration of Ω-3+ LEs control inflammation-resolution mechanisms. Using a self-limited acute inflammation model and a murine polymicrobial sepsis model we found dietary Ω-3+ LEs to stop neutrophil infiltration, to reduce pro-inflammatory cytokines and to enhance anti-inflammatory mediators. This was associated with a strong reduction of classical monocytes and an increase of non-classical monocyte/macrophage (MΦ) recruitment. Moreover, Ω-3+ LEs enhanced efferocytosis, whereas this phagocyte responses were lost in 12/15-LOX−/− mice, suggesting that the actions of Ω-3+ LEs were 5-LOX and 12/15-LOX dependent. Ω-3+ LEs shortened the resolution interval, stimulated the local endogenous

biosynthesis of SPMs and enhanced the tissue regeneration during peritonitis compared with vehicle control or the administration of Ω-3− LEs. Moreover, Ω-3+ LEs protected against hypothermia and weight loss enhancing survival in murine polymicrobial sepsis. Together, these results demonstrate that Ω-3+ LEs control key innate protective mechanism during the onset and resolution of acute inflammation and promote to tissue repair and regeneration."

-Department of Anesthesiology and Intensive Care Medicine, University Hospital Tübingen, Eberhard-Karls University, Tübingen, Germany

-Center for Proteomics and Metabolomics, Leiden University Medical Center (LUMC), Leiden, The Netherlands

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5762854/

Serotonin System

Modulation of the Serotonin System by Endocannabinoid Signaling

"The cannabinoid CB1 receptors and their endogenous agonists, endocannabinoids (eCBs), are ubiquitously distributed throughout the central nervous system (CNS), where they play a key role in the regulation of neuronal excitability. As such, CB signaling has been implicated in the regulation of a myriad of physiological functions ranging from feeding homoeostasis to emotional and motivational processes. Ample evidence from behavioral studies also suggests that eCBs are important regulators of stress responses and a deficit in eCB signaling contributes to stress-related disorders such as anxiety and depression. The eCB-induced modulation of stress-related behaviors appears to be mediated, at least in part, through the regulation of the serotoninergic system. In this article, we review the role of eCB signaling in the regulation of the serotoninergic system with special emphasis on the cellular mechanisms by which cannabinoid CB1 receptors modulate the excitability of dorsal raphe serotonin neurons."…

-Research Institute on Addictions, University at Buffalo, State University of New York, 1021 Main Street, Buffalo, New York

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110547/

Sexual Dysfunction

Endocannabinoid system in sexual motivational processes: Is it a novel therapeutic horizon?

"The endocannabinoid system (ECS), which is composed of the cannabinoid receptors types 1 and 2 (CB1 and CB2) for marijuana's psychoactive ingredient Δ9-tetrahydrocannabinol (Δ9-THC),

the endogenous ligands (AEA and 2-AG) and the enzymatic systems involved in their biosynthesis and degradation, recently emerged as important modulator of emotional and non-emotional behaviors. For centuries, in addition to its recreational actions, several contradictory claims regarding the effects of Cannabis use in sexual functioning and behavior (e.g. aphrodisiac vs anti-aphrodisiac) of both sexes have been accumulated. The identification of Δ9-THC and later on, the discovery of the ECS have opened a potential therapeutic target for sexual dysfunctions, given the partial efficacy of current pharmacological treatment. In agreement with the bidirectional modulation induced by cannabinoids on several behavioral responses, the endogenous cannabinoid AEA elicited biphasic effects on sexual behavior as well. The present article reviews current available knowledge on herbal, synthetic and endogenous cannabinoids with respect to the modulation of several aspects of sexuality in preclinical and human studies, highlighting their therapeutic potential."

-National Institute of Mental Health, Klecany, Czech Republic; 3rd Faculty of Medicine, Charles University, Prague, Czech Republic.

-Dept. of Pharmacology, Faculty of Medicine, Masaryk University, Brno, Czech Republic.

-Dept. of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy.

-Dept. of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy;

https://www.ncbi.nlm.nih.gov/pubmed/27884725

Circulating Endocannabinoid Concentrations and Sexual Arousal in Women

"Several lines of evidence point to the potential role of the endocannabinoid system in female sexual functioning. These include results from studies describing the subjective effects of exogenous cannabinoids on sexual functioning in humans and the observable effects of exogenous cannabinoids on sexual functioning in other species, as well as results from studies investigating the location of cannabinoid receptors in the brain and periphery, and the effects of cannabinoid receptor activation on neurotransmitters implicated in sexual functioning. While these lines of research suggest a role for the endocannabinoid system in female sexual functioning, no studies investigating the relationship between concentrations of endogenous cannabinoids (i.e., arachidonoylethanolamide [AEA] and 2-arachidonoylglycerol [2-AG]) and sexual functioning have been conducted in any species."

-University of British Columbia, Dept. of Psychology, Vancouver, BC, Canada

-The University of Calgary, Hotchkiss Brain Institute, Calgary, AB, Canada

-Medical College of Wisconsin, Dept. of Pharmacology and Toxicology, Milwaukee, WI, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856894/

Sickness Behavior

"It is of considerable translational importance whether depression is a form or a consequence of sickness behavior. Sickness behavior is a behavioral complex induced by infections and immune trauma and mediated by pro-inflammatory cytokines. It is an adaptive response that enhances recovery by conserving energy to combat acute inflammation. There are considerable phenomenological similarities between sickness behavior and depression, for example, behavioral inhibition, anorexia and weight loss, and melancholic (anhedonia), physio-somatic (fatigue, hyperalgesia, malaise), anxiety and neurocognitive symptoms. In clinical depression, however, a transition occurs to sensitization of immuno-inflammatory pathways, progressive damage by oxidative and nitrosative stress to lipids, proteins, and DNA, and autoimmune responses directed against self-epitopes. The latter mechanisms are the substrate of a neuroprogressive process, whereby multiple depressive episodes cause neural tissue damage and consequent functional and cognitive sequelae. Thus, shared immuno-inflammatory pathways underpin the physiology of sickness behavior and the pathophysiology of clinical depression explaining their partially overlapping phenomenology. Inflammation may provoke a Janus-faced response with a good, acute side, generating protective inflammation through sickness behavior and a bad, chronic side, for example, clinical depression, a lifelong disorder with positive feedback loops between (neuro)inflammation and (neuro)degenerative processes following less well defined triggers."

-Maes Clinics @ TRIA, Piyavate Hospital, Thailand

-School of Medicine, Deakin University, Australia

-Orygen Youth Health Research Centre, Centre for Youth Mental Health, Australia

-The Mental Health Research Institute of Victoria, Australia

-Department of Psychiatry, Melbourne University, Level 1, North Block Main Building Royal Melbourne Hospital, Australia

-Center for the Study of Complementary and Alternative Therapies, School of Nursing, University of Virginia, USA

-Department of Psychology and Neurosciences, Dalhousie University, Canada

-Department of Pharmacology, Chinese Academy Engineering Instit ute for the Development of Endangered Medicinal Resources in Southwest China 189 Changgang Road, Xing Ning District, Nanning, Guangxi Post Code, P. R. China

-CRC, Rm 30, 57 Laurel street, Glasgow G11 7QT, Scotland, UK

-Department of Adult Psychiatry, Medical University of Łóź, Poland

-Department of Pharmacology, Galway University, University Road, Galway, Co.Galway, Ireland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3391987

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..."Excessive peripheral and cerebral inflammatory cytokine response is associated with clinical

complications among which cognitive dysfunction (Heyser et al., 1997), prolonged sickness behaviour (Combrinck et al., 2002), and depressive-like behaviour (Capuron et al., 2003), that are detrimental for the infected host. Based on these data, limiting the over-expression of brain proinflammatory cytokines seems crucial for protection against the adverse effects of cytokines in the brain. Dietary essential polyunsaturated fatty acids (PUFA) of the n-3 and n-6 series are potent regulators of cytokine production on which they exert opposing actions (Yaqoob, 2004; Calder, 2006). In particular, n-3 long-chain derivatives eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) down-regulate cytokine production in macrophages and microglia (Connor et al., 2007; Liuzzi et al., 2007; De Smedt-Peyrusse et al., 2008), while n-6 long-chain derivative arachidonic acid (AA, 20:4n-6) displays proinflammatory properties, particularly through the synthesis of eicosanoids (Tilley et al., 2001). Interestingly, it was demonstrated that anti-inflammatory properties of DHA targets proinflammatory cytokine signalling pathways in monocytes (Lee et al., 2004), T cells (Denys et al., 2001), and microglia (De Smedt-Peyrusse et al., 2008)"…

-Psychoneuroimmunologie, Nutrition et Genetique, PsyNuGen, INRA 1286, CNRS 5226, Université Bordeaux 2, 146 rue Leo Saignat, France

-Integrative Immunology and Behavior program, University of Illinois at Urbana-Champaign, Illinois 61801, USA

-Unité de Nutrition et Régulation Lipidique des Fonctions Cérébrales NuReLiCe, France

-Corresponding author: Sophie Layé, PhD, PsyNuGen, Université Bordeaux 2

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769572/

Silent Inflammation

Dietary Origin of Silent Inflammation: The Perfect Nutritional Storm

"There has not been one dietary change alone in past 30 years that has increased the levels of silent inflammation. However, there has been a convergence of three distinct dietary changes that can be termed as "The Perfect Nutritional Storm" [9]. These dietary factors include increased consumption of refined carbohydrates, increased consumption of refined vegetable oils rich in omega-6 fatty acids, decreased consumption of long-chain omega-3 fatty acids.

The first of these dietary changes is the increased consumption of refined carbohydrates that has significantly increased the glycemic load of the diet. The glycemic load of a meal is defined as the amount of a particular carbohydrate that is consumed at a meal multiplied by its glycemic index [16, 17]. Today high glycemic-index carbohydrates are not only the major components in virtually all processed foods, but also in potato, rice, and white bread products. As the cost of production of refined carbohydrates has dramatically decreased in the past 25 years, the availability of products made from these ingredients has dramatically increased [18]. Increased

consumption of refined food products generates meals with a high glycemic load. This results in the increased secretion of the insulin necessary to lower the resulting postprandial rise in blood glucose [17].

However, increased insulin production alone is not sufficient to explain the rapid increase in silent inflammation. This requires the presence of another recent dietary component: the increased consumption of refined vegetable oils rich in omega-6 fatty acids. The primary fatty acid in the most common vegetable oils is the omega-6 fatty acid known as linoleic acid. Until the last 50 years linoleic acid has been a relatively minor component of the human diet. As an example, traditional cooking fats such as butter, lard, and olive oil contain less than 10% linoleic acid. Common vegetable oils such as corn, soy, sunflower, and safflower contain 50%–75% linoleic acid. The usage of these vegetable oils has increased by more than 400% since 1980 [19]. Since refined carbohydrates and vegetable oils are now the cheapest source of calories [18, 20–22], it is not surprising that the combination of these two dietary trends has increased the production of AA thus leading to an epidemic increase in silent inflammation.

There is epidemiological evidence that suggests that high intake of omega-6 fatty acids may have a potential cardiovascular benefit [23, 24]. However, this epidemiological hypothesis was tested in a carefully controlled secondary prevention trial [25, 26]. This study, known as the Lyon Diet Heart Study, placed patients who already had a previous heart attack into one of two intervention groups. The first group followed a diet rich in omega-6 fatty acids following the American Heart Association dietary guidelines. The other group followed a diet that was low in omega-6 fatty acids. After 3.5 years the group with the low omega-6 fatty acid intake had 70% fewer fatal and nonfatal heart attacks and a complete elimination of sudden cardiac death compared to the group following the high omega-6 fatty acid diet.

The impact of a high omega-6 fatty acid diet can be understood from the metabolic pathway of linoleic acid conversion to AA as shown in Figure 1."…

"The two rate-limiting steps in this metabolic cascade of linoleic acid to arachidonic acid are the enzymes delta-6 and delta-5 desaturase. These enzymes insert cis-double bonds into unique positions in the omega-6 fatty acid molecule. Normally, these steps are very slow, thus limiting the production of AA. However, insulin is a strong activator of each of these enzymes [27–30]. This means that a high glycemic-load diet coupled with increased intake of vegetable oils rich in linoleic acid will lead to increased production of AA and a corresponding increase in silent inflammation.

Finally, there is the role of the omega-3 fatty acid EPA in this metabolic cascade and its effect on silent inflammation. In high enough concentrations, EPA can partially inhibit the activity of the delta-5-desaturase enzyme thus reducing AA formation by acting as a weak feedback inhibitor as

both fatty acids use the same enzyme for their production. More importantly, an increased EPA content in the membrane phospholipids decreases the release of AA that is necessary to make pro-inflammatory eicosanoids. In this regard, increased consumption of EPA dilutes out existing AA, thus decreasing the production of pro-inflammatory eicosanoids. Finally, EPA is the molecular building block to powerful anti-inflammatory eicosanoids known as resolvins [31–34].

Unfortunately, the consumption of long-chain omega-3 fatty acids, such as EPA, has dramatically decreased over the past century [35]. With that decrease in EPA intake coupled with the increased consumption of refined carbohydrates and vegetable oils, the dietary stage was set for a dramatic increase in silent inflammation."…

-Inflammation Research Foundation, USA

-Diabetes Research Institute, University of Miami, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952901/

Singing

An Analysis of Endocannabinoid Concentrations and Mood Following Singing and Exercise in Healthy Volunteers

…"Singing increased plasma levels of anandamide (AEA) by 42% ($P < 0.05$), palmitoylethanolamine (PEA) by 53% ($P < 0.01$) and oleoylethanolamine (OEA) by 34% ($P < 0.05$) and improved positive mood and emotions ($P < 0.01$), without affecting hunger scores."…

-Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Nottingham, United Kingdom

-Centre for Analytical Bioscience, Advanced Materials and Healthcare Division, School of Pharmacy, University of Nottingham, Nottingham, United Kingdom

-BBC Studios "Trust Me I'm a Doctor", BBC Scotland, Glasgow, United Kingdom

-Edited by: Walter Adriani, Istituto Superiore di Sanità (ISS), Italy

-Reviewed by: Maria Morena, University of Calgary, Canada; Antonia Manduca, Aix-Marseille Université, France

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6275239

Sjogren's Syndrome

"Sjögren's syndrome occurs when a person's normally protective immune system attacks her/his body and damages moisture-producing glands, including salivary (saliva-producing) glands and lacrimal (tear-producing) glands. The lungs, bowel, and other organs may rarely be affected."

-Cleveland Clinic

https://my.clevelandclinic.org/health/diseases/4929-sj%C3%B6grens-syndrome

Skeletal Muscle

"Skeletal muscle performance is usually determined by the use of standard measurements such as the rate of muscle protein synthesis, muscle mass, maximum voluntary contraction, rate of torque development, and the markers of muscle damage.

Researchers saw a positive effect of n-3 PUFAs on muscle anabolism and catabolism [24] not only in cancer cachexia [34] but also in healthy volunteers, with a positive impact on the maintenance of muscle. Both in vivo [35] and in vitro [36] studies show a significant increased muscle protein synthesis in both young and older subjects after eight weeks of 4 g n-3 PUFAs daily administration [37]. Similarly, six months of supplementation (3.36 g/day) resulted in an increased muscle mass (+3.6%) and strength (+4%) in older people [24]. Another study concerning muscle recovery and soreness after performing eccentric biceps curls displayed that seven days of 3 g/day n-3 PUFA supplementation decreased post-exercise muscle damage and soreness [38].

Positive findings in muscle recovery and, subsequently, training adaptation, were reported in other similar studies [39,40,41,42]. N-3 PUFAs attenuated the loss of muscle strength and range of motion, blood markers of inflammation such as TNF-α, and markers of muscle damage, such as myoglobin, creatine kinase, and skeletal muscle slow troponin I [43]. In addition, DHA seems to increase lipid oxidation and insulin sensitivity in skeletal muscle and it can stimulate glycolytic capacity in myocytes. N-3 PUFAs can probably improve athletic performances, through a modulation on cell membranes' permeability and on insulin sensitivity, which makes the muscle cells more permeable with regard to necessary nutrients, such as glucose and amino acids [44,45]. This is supported by an up-regulation of the glucose transporter type 4 (GLUT4). Based on these studies, n-3 PUFAs appears to be a potent stimulator of metabolism in muscle cells and a potential ergogenic aid [44,45]. An interesting study in older adults showed that n-3 PUFAs supplementation augments the hyper-aminoacidemia-hyperinsulinemia induced an increase in the rate of muscle protein synthesis in older adults. Omega-3 fatty acids, therefore, likely attenuate the anabolic resistance and may potentially be useful as a therapeutic agent against catabolic processes."

-Human and Clinical Nutrition Unit, Dept. of Medical, Oral and Biotechnological Sciences, University G. D'Annunzio, 66100 Chieti, Italy;

-Cardiology Unit, Cardiology Dept. , San Camillo De Lellis Hospital, Manfredonia, Foggia, Italy

-Department of Internal and Specialistic Medicine DIBIMIS, University of Palermo, Palermo, Italy;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6357022/

Omega-3 Fatty Acids and Skeletal Muscle Health

"Skeletal muscle is a plastic tissue capable of adapting and mal-adapting to physical activity and diet. The response of skeletal muscle to adaptive stimuli, such as exercise, can be modified by the prior nutritional status of the muscle. The influence of nutrition on skeletal muscle has the potential to substantially impact physical function and whole body metabolism. Animal and cell based models show that omega-3 fatty acids, in particular those of marine origin, can influence skeletal muscle metabolism. Furthermore, recent human studies demonstrate that omega-3 fatty acids of marine origin can influence the exercise and nutritional response of skeletal muscle. These studies show that the prior omega-3 status influences not only the metabolic response of muscle to nutrition, but also the functional response to a period of exercise training. Omega-3 fatty acids of marine origin therefore have the potential to alter the trajectory of a number of human diseases including the physical decline associated with aging. We explore the potential molecular mechanisms by which omega-3 fatty acids may act in skeletal muscle, considering the n-3/n-6 ratio, inflammation and lipidomic remodelling as possible mechanisms of action. Finally, we suggest some avenues for further research to clarify how omega-3 fatty acids may be exerting their biological action in skeletal muscle."…

"As previously mentioned, skeletal muscle is highly adaptable or mal-adaptable to changes in diet composition. In particular, diets high in saturated fat have been linked with the onset of both obesity and T2D [12,13]. However, diets high in polyunsaturated fatty acids such as the Mediterranean diet have been linked to beneficial outcomes, such as improved cardiovascular health [14,15]. Furthermore, the traditional diet of Inuit populations which is high in omega-3 PUFAs and low in omega-6 fatty acids is associated with a lowered risk of cardiovascular disease and improved insulin sensitivity despite being a diet very high in fat [16,17]. Therefore, the amount and type of fat in the diet can play an important role in regulating whole body metabolic health."…

EPA vs DHA

"Omega-3 PUFAs consist of a heterogeneous mixture of fatty acids, of which eicosapentaenoic acid (EPA, 20:5) and docosapentaenoic acid (DHA, 22:6) are currently thought to be the most bioactive of the omega-3 species, however, docosapentaenoic acid (DPA, 22:5), an intermediary of EPA and DHA, may also have beneficial health effects [49]. Despite being very similar in structure and sharing some metabolic effects there is emerging evidence that different omega-3 PUFAs independently alter metabolic functions. The role of DPA in skeletal muscle metabolism remains unclear due to the only relatively recent availability in pure form. Yet, studies have

observed that DPA has similar, and in some cases more potent, actions as EPA and DHA although to date the knowledge of DPA's effect on skeletal muscle health is limited [50,51,52]. There is also evidence to suggest that EPA has a more potent effect on skeletal muscle protein metabolism compared with DHA [53]. The typical western diet, however, is deficient in omega-3 PUFAs and abundant in omega-6 fatty acids [54]. This n-6/n-3 ratio is linked to an increased state of chronic inflammation, which has been linked to diseases such as T2D and obesity [55]. There is now growing evidence to assert that, concurrent with CV and anti-inflammatory effects, omega-3 PUFAs play a beneficial role in skeletal muscle metabolism and function [10,11]. Although the mechanisms of action that underpin these changes remain to be fully characterised. We will discuss some of the studies demonstrating the mechanisms of omega-3 PUFAs and where applicable the potential differential effects of EPA and DHA."

-Health and Exercise Sciences Research Group, School of Sport, University of Stirling, Scotland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4663562/

Skin

The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities

"The newly discovered endocannabinoid system (ECS; comprising the endogenous lipid mediators endocannabinoids present in virtually all tissues, their G-protein-coupled cannabinoid receptors, biosynthetic pathways and metabolizing enzymes) has been implicated in multiple regulatory functions both in health and disease. Recent studies have intriguingly suggested the existence of a functional ECS in the skin and implicated it in various biological processes (e.g. proliferation, growth, differentiation, apoptosis and cytokine, mediator or hormone production of various cell types of the skin and appendages, such as the hair follicle and sebaceous gland). It seems that the main physiological function of the cutaneous ECS is to constitutively control the proper and well-balanced proliferation, differentiation and survival, as well as immune competence and/or tolerance, of skin cells. The disruption of this delicate balance might facilitate the development of multiple pathological conditions and diseases of the skin (e.g. acne, seborrhea, allergic dermatitis, itch and pain, psoriasis, hair growth disorders, systemic sclerosis and cancer)."

…"Recent intriguing data suggest that the cutaneous ECS is fully functional (Figure 1). Indeed, as described later, the ECS has been implicated in the regulation of skin cell proliferation, survival and differentiation, the delicate balance of which is a key determinant of proper cutaneous

homeostasis. Furthermore, fine-tuning of the endocannabinoid tone appears to be a key factor in modulating cutaneous growth and differentiation [Table 1]."

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School
-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck
-School of Translational Medicine, University of Manchester, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

Cannabinoid Signaling in the Skin: Therapeutic Potential of the "C(ut)annabinoid" System

"The endocannabinoid system (ECS) has lately been proven to be an important, multifaceted homeostatic regulator, which influences a wide-variety of physiological processes all over the body. Its members, the endocannabinoids (eCBs; e.g., anandamide), the eCB-responsive receptors (e.g., CB1, CB2), as well as the complex enzyme and transporter apparatus involved in the metabolism of the ligands were shown to be expressed in several tissues, including the skin. Although the best studied functions over the ECS are related to the central nervous system and to immune processes, experimental efforts over the last two decades have unambiguously confirmed that cutaneous cannabinoid ("c[ut]annabinoid") signaling is deeply involved in the maintenance of skin homeostasis, barrier formation and regeneration, and its dysregulation was implicated to contribute to several highly prevalent diseases and disorders, e.g., atopic dermatitis, psoriasis, scleroderma, acne, hair growth and pigmentation disorders, keratin diseases, various tumors, and itch. The current review aims to give an overview of the available skin-relevant endo- and phytocannabinoid literature with a special emphasis on the putative translational potential, and to highlight promising future research directions as well as existing challenges."…

"The fundamental role of homeostatic eCB-signaling in controlling epidermal inflammatory responses was further supported by a recent study demonstrating that activation of TLR2 by lipoteichoic acid (LTA; 10 μg/mL; 24 h) led to the up-regulation of FAAH-activity as well as expression at the protein (but intriguingly, not at the mRNA) level in human keratinocytes [144]. Moreover, FAAH-inhibitors could prevent the LTA-induced pro-inflammatory response in a CB1/CB2 receptor-dependent manner. Co-administration of the CB1 and CB2 antagonists/inverse agonists AM251 and AM630 (both at 1 μM) prevented the action; however, the compounds were only tested in combination, leaving the individual roles of CB1 and CB2 unexplored. Moreover, following topical application, the FAAH-inhibitors alleviated dust mite-induced cutaneous inflammation of NC/Tnd mice with the same efficiency as the positive control

tacrolimus . Likewise, topical administration of sulfur mustard and nitrogen mustard at concentrations that induced tissue injury in mice led to up-regulation of FAAH (as well as of CB1, CB2, and PPARα). These alterations persisted throughout the wound healing process, and FAAH-inhibitors were found to be highly effective in suppressing vesicant-induced cutaneous inflammation in this study too [187]. Collectively, these data highlight the possibility that by regulating homeostatic eCB signaling, FAAH may be an important regulator of the initiation and maintenance of cutaneous inflammatory processes. Thus, restoration of the homeostatic eCB tone by e.g., FAAH-inhibitors may be a promising tool in alleviating skin inflammation [93].""

-Department of Physiology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-Department of Immunology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-HCEMM Nonprofit Ltd., Szeged, Hungary
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429381/

The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities

"The newly discovered endocannabinoid system (ECS; comprising the endogenous lipid mediators endocannabinoids present in virtually all tissues, their G-protein-coupled cannabinoid receptors, biosynthetic pathways and metabolizing enzymes) has been implicated in multiple regulatory functions both in health and disease. Recent studies have intriguingly suggested the existence of a functional ECS in the skin and implicated it in various biological processes (e.g. proliferation, growth, differentiation, apoptosis and cytokine, mediator or hormone production of various cell types of the skin and appendages, such as the hair follicle and sebaceous gland). It seems that the main physiological function of the cutaneous ECS is to constitutively control the proper and well-balanced proliferation, differentiation and survival, as well as immune competence and/or tolerance, of skin cells. The disruption of this delicate balance might facilitate the development of multiple pathological conditions and diseases of the skin (e.g. acne, seborrhea, allergic dermatitis, itch and pain, psoriasis, hair growth disorders, systemic sclerosis and cancer)."…

-Department of Physiology, University of Debrecen, Research Center for Molecular Medicine, Debrecen, Hungary
-University of Medicine and Dentistry, Department of Surgery, New Jersey Medical School, Newark, NJ 07103, USA
-Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck 23538, Germany
-School of Translational Medicine, University of Manchester, Manchester, M13 9PL, UK
-Section on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, Rockville, MD, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757311/

■■■

“The endocannabinoid system (ECS) regulates multiple physiological processes, including cutaneous cell growth and differentiation.”…

-DE-MTA “Lendület” Cellular Physiology Research Group, Department of Physiology, University of Debrecen, Debrecen, Hungary.

-Laboratory for Ion Channel Research and TRP Research Platform Leuven, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium.

-Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan.

-Department of Dermatology, University of Lübeck, Lübeck, Germany.

-Neurobiology Research Group, Department of Physiology, University of Debrecen, Debrecen, Hungary.

-Laboratory of Cutaneous Physiopathology and Integrated Center of Metabolomics Research, San Gallicano Dermatologic Institute, IRCCS, Rome, Italy.

-Departments of Dermatology, Venereology, and Allergology and Immunology, Dessau Medical Center, Dessau, Germany.

-School of Translational Medicine, University of Manchester, Manchester, United Kingdom.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151231/

cutaneous - relating to or affecting the skin.

- Oxford / Google

Omega-3 Versus Omega-6 Polyunsaturated Fatty Acids in the Prevention and Treatment of Inflammatory Skin Diseases

“Omega-3 (ω-3) and omega-6 (ω-6) polyunsaturated fatty acids (PUFAs) are nowadays desirable components of oils with special dietary and functional properties. Their therapeutic and health-promoting effects have already been established in various chronic inflammatory and autoimmune diseases through various mechanisms, including modifications in cell membrane lipid composition, gene expression, cellular metabolism, and signal transduction. The application of ω-3 and ω-6 PUFAs in most common skin diseases has been examined in numerous studies, but their results and conclusions were mostly opposing and inconclusive. It seems that combined ω-6, gamma-linolenic acid (GLA), and ω-3 long-chain PUFAs supplementation exhibits the highest potential in diminishing inflammatory processes, which could be beneficial for the management of inflammatory skin diseases, such as atopic dermatitis, psoriasis, and acne. Due to significant population and individually-based genetic variations that impact PUFAs metabolism and associated metabolites, gene expression, and subsequent inflammatory responses, at this point, we could not recommend strict dietary and supplementation strategies for disease prevention and treatment that will be appropriate for all. Well-balanced nutrition and additional anti-inflammatory PUFA-based supplementation should be encouraged in a targeted manner for individuals in need to provide better management of skin diseases but, most importantly, to

maintain and improve overall skin health."

- Department of Dermatology and Venereology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb

- Department of Ophtalmology and Optometry, General Hospital Dubrovnik

- School of Medicine, University of Zagreb,

https://www.mdpi.com/1422-0067/21/3/741/pdf

Skin Carotenoids in Public Health and Nutricosmetics: The Emerging Roles and Applications of the UV Radiation-Absorbing Colourless Carotenoids Phytoene and Phytofluene

…"The protection of skin is important in the context of health as a means of preventing disorders that eventually lead to harmful conditions. Additionally, the appearance of the skin, notably the face, is an attribute of great relevance in signalling, since it conveys information with impacts at the socioeconomic level.

The role of nutrition in skin health and appearance is undeniable and long-known, hence the efforts of the industry to innovate in cosmetics, cosmeceuticals, nutricosmetics, functional foods, or nutraceuticals.

Carotenoids are natural dietary products that have been shown to intervene in health-promoting actions and whose value in the context of nutricosmetics continues to grow. From the literature it can be inferred that a diet rich in carotenoid-containing products and the avoidance of stress factors have a beneficial impact on skin health and appearance, with other likely beneficial systemic effects.

Excellent recent original studies and reviews point to the fact that the positive perceivable effects that dietary carotenoids cause in the skin may be harnessed in the context of public health. For instance, they can be used to promote healthy dietary patterns rich in carotenoid containing products as a strategy to reduce the risk of developing serious diseases, including cancer, cardiovascular disease, eye disorders, osteoporosis, or metabolic diseases.

Among dietary carotenoids, the UVR-absorbing colourless carotenes phytoene and phytofluene have been largely overlooked, probably due to their lack of colour, which made their detection more challenging in the past compared to other carotenoids. Hence, the considerable lack of abundant data about their presence in foods and tissues, in contrast with the other major dietary carotenoids found in humans. However, it is well-established that they are major dietary carotenoids (found in products frequently consumed as tomatoes, carrots, citrus, and derivatives), present in plasma, human milk, skin, and other tissues, and involved in several

health-promoting actions, as revealed by studies of different nature. Notably, evidence is accumulating that they could be involved in the health benefits traditionally associated to lycopene, since the latter seems to always occur along with the colourless carotenoids in foods. Being the unique major dietary carotenoids absorbing maximally in the UV region and possessing other distinctive characteristics within the carotenoid family, research and applications in the use of these carotenoids in the promotion of health and cosmetics is a timely and expanding area recently featuring in the carotenoid field."…

-Food Colour & Quality Laboratory, Area of Nutrition & Food Science, Universidad de Sevilla
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6566388/

"**Carotenoids** are pigments in plants, algae, and photosynthetic bacteria. These pigments produce the bright yellow, red, and orange colors in plants, vegetables, and fruits. Carotenoids act as a type of antioxidant for humans. There are more than 600 different types of carotenoids."

-Healthline
https://www.healthline.com/health/carotenoids

Chia oil as skin curative

"A study was performed to determine the likely benefits of topical omega-3 fatty acids, topical products containing chia oil formulated. Five patients with pruritus affected by end stage renal disease and five health volunteers having xerotic pruritus were used in this investigation. A topical formulation was prepared by the addition of 4 % chia oil and applied for 8 weeks. Itching indications, trans-epidermal water loss and skin capacitance were measured on a 6 points scale. Application of topical formulation added with chia oil significantly improved the skin hydration, lichen simplex chronicus, and prurigo nodularis in all the patients. Healthy volunteers suffering from xerotic pruritus also revealed improvement in skin hydration followed by the trans epidermal water loss and capacitance of skin (Jeong et al. 2010)."

-Department of Dairy Technology, University of Veterinary and Animal Sciences Lahore, Lahore, Pakistan
-Department of Animal Nutrition, University of Veterinary and Animal Sciences Lahore, Lahore, Pakistan
-Department of Food Science, Nutrition & Home Economics Institute of Home and Food Sciences Faculty of Science and Technology Govt, College University Faisalabad, Faisalabad, Pakistan
-Department of Poultry Production, University of Veterinary and Animal Sciences Lahore, Lahore, Pakistan
-Department of Wildlife and Ecology, University of Veterinary and Animal Sciences Lahore, Lahore, Pakistan
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4926888

Cannabinoid system in the skin - a possible target for future therapies in dermatology

"Cannabinoids and their derivatives are group of more than 60 biologically active chemical agents, which have been used in natural medicine for centuries. The major agent of exogenous cannabinoids is Delta(9)-tetrahydrocannabinol (Delta(9)-THC), natural psychoactive ingredient of marijuana. However, psychoactive properties of these substances limited their use as approved medicines. Recent discoveries of endogenous cannabinoids (e.g. arachidonoylethanolamide, 2-arachidonoylglycerol or palmithyloethanolamide) and their receptors initiated discussion on the role of cannabinoid system in physiological conditions as well as in various diseases. Based on the current knowledge, it could be stated that cannabinoids are important mediators in the skin, however their role have not been well elucidated yet. In our review, we summarized the current knowledge about the significant role of the cannabinoid system in the cutaneous physiology and pathology, pointing out possible future therapeutic targets."

-Department of Clinical Immunology, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw, Poland.

https://pubmed.ncbi.nlm.nih.gov/19664006

Mechanisms of Cannabinoids and Potential Applicability to Skin Diseases

"The legalisation of cannabis in a growing number of jurisdictions has led to increasing interest in its potential therapeutic effects in a range of disorders, including cutaneous conditions. Cannabinoids have been used as natural medicines for centuries; however, their biological activity in the skin is a new area of study. Recent data suggest that cannabinoids are involved in neuro-immuno-endocrine modulation of skin functioning, yet their effect on the features of dermatologic conditions is unclear. This article sought to review the mechanisms by which cannabinoids regulate skin functioning through the lens of relevance to treatment of dermatologic diseases looking at the effects of cannabinoids on a range of cellular activities and dermatologic conditions both in vitro and in vivo. We identified studies demonstrating an inhibitory effect of cannabinoids on skin inflammation, proliferation, fibrosis, pain, and itch-biological mechanisms involved in the pathogenesis of many dermatologic conditions. Cannabinoids have the potential to expand the therapeutic repertoire of a wide spectrum of skin disorders. Given their widespread unregulated use by the general public, basic and clinical studies are required to elucidate the effectiveness and long-term effects of topical and systemic cannabinoids in cutaneous disorders."

-University of Toronto, Toronto, Canada.

-The Hospital for Sick Children and University of Toronto, 555 University Ave, Toronto, ON, M5G 1X8, Canada.

https://pubmed.ncbi.nlm.nih.gov/32060787

Cannabinoids in dermatology: a scoping review

"The therapeutic applications of cannabis and cannabinoids are an increasingly conspicuous topic as de-criminalization and legalization of these products continues to expand. A limited number of cannabinoid compounds have been approved for a specific set of conditions. However, the current role of cannabinoids for the treatment of dermatologic conditions remains to be defined. We conducted a review of the current literature to determine the applications of cannabinoids for the therapy of various skin diseases. After conducting our analysis, we found that cannabinoid products have the potential to treat a variety of skin conditions, including acne vulgaris, allergic contact dermatitis, asteatotic dermatitis, atopic dermatitis, hidradenitis suppurativa, Kaposi sarcoma, pruritus, psoriasis, skin cancer, and the cutaneous manifestations of systemic sclerosis. However, the majority of available data on these compounds are pre-clinical and there is a corresponding lack of high-quality randomized, controlled trials that evaluate their effects. Cannabinoids have shown some initial promise as therapy for a variety of skin diseases. However, there is a requirement for thorough pre-clinical research and large-scale, randomized, controlled trials before cannabinoids can be considered safe and effective treatments for these conditions."

-University of Colorado School of Medicine, Department of Dermatology, Aurora, Colorado Denver Veterans Affairs Medical Center (VAMC), Department of Dermatology, Denver, Colorado.

https://pubmed.ncbi.nlm.nih.gov/30142706/

The potential role of cannabinoids in dermatology

"Cannabis is increasingly being used world-wide to treat a variety of dermatological conditions. Medicinal cannabis is currently legalized in Canada, 31 states in America and 19 countries in Europe. The authors reviewed the literature on the pharmacology and use of cannabinoids in treating a variety of skin conditions including acne, atopic dermatitis, psoriasis, skin cancer, pruritus, and pain. Cannabinoids have demonstrated anti-inflammatory, antipruritic, anti-ageing, and antimalignancy properties by various mechanisms including interacting with the newly found endocannabinoid system of the skin thereby providing a promising alternative to traditional treatments."

-The Royal Prince Alfred Hospital, Sydney, Australia.

-Icahn School of Medicine at Mount Sinai, New York, NY, USA.

https://pubmed.ncbi.nlm.nih.gov/31599175

Omega-3 Versus Omega-6 Polyunsaturated Fatty Acids in the Prevention and Treatment of Inflammatory Skin Diseases

"While major changes have taken place in the human diet over the past 10,000 years, our genes have not changed that much. As humans are naturally used to food on which they evolved, and their genetic patterns were established—therefore, it is not surprising that newly established Western diets deficient in ω-3, and rich in ω-6 PUFAs promote the pathogenesis of many chronic inflammatory (skin) diseases. ω-3 PUFAs, DHA, and EPA, are associated with healthy aging and have a role in the prevention and treatment of numerous diseases by exerting their beneficial effects through inhibiting actions of multiple cytokines in disease progression. On the other side, ω-6 FAs, ARA with its eicosanoids, have opposing properties from those of ω-3 PUFAs and change the physiological state to pro-inflammatory with increased production of inflammatory LTs, PGs, and cytokines. As things are usually more gray than just black or white, we could not simply divide ω-3 and ω-6 FAs to ''good'' and ''bad'' omegas because there is a lot of scientific and clinical evidence of benefits of GLA supplementation in the treatment and prevention of chronic inflammatory diseases. "…

-Department of Dermatology and Venereology, University Hospital Centre Zagreb, School of Medicine University of Zagreb, Šalata 4, 10 000 Zagreb, Croatia

-Department of Ophtalmology and Optometry, General Hospital Dubrovnik, Ulica dr. Roka Mišetića 2, 20000 Dubrovnik, Croatia;

-School of Medicine, University of Zagreb, Šalata 3, 10000 Zagreb, Croatia;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7037798

See also Cancer & Inflammation , Chia Seeds

Skin Cancer

The potential of omega-3 fatty acids in the prevention of non-melanoma skin cancer

"In toto, there is strong circumstantial evidence from both experimental and clinical studies to support a role for omega-3 FA in the prevention of non-melanoma skin cancer (NMSC). In experimental animal studies there is direct evidence that dietary omega-3 FA inhibits ultraviolet radiation (UVR) carcinogenic expression, with regard to both increased tumor latent period and reduced tumor multiplicity. Equivalent levels of omega-6 FA increase UVR carcinogenic expression. Dietary omega-3 FA dramatically reduces the plasma and cutaneous pro-inflammatory and immunosuppressive PGE(2) levels in mice. Dietary omega-6 FA increases prostaglandin E synthase type 2 (PGE(2)) level. Dietary omega-3 FA significantly reduces the

inflammatory response and sustains, or enhances, the delayed type hypersensitivity immune response in mice when compared to an equivalent dietary level of omega-6 FA. Supplementary omega-3 FA significantly increases the UVR-mediated erythema threshold in humans. Supplementary omega-3 FA significantly reduces the level of pro-inflammatory and immunosuppressive PGE(2) levels in Ultraviolet B-irradiated human skin."

-Department of Dermatology, Baylor College of Medicine, Houston, TX , USA.
https://www.ncbi.nlm.nih.gov/pubmed/16872755

Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors

"Nonmelanoma skin cancer is one of the most common malignancies in humans. Different therapeutic strategies for the treatment of these tumors are currently being investigated. Given the growth-inhibiting effects of cannabinoids on gliomas and the wide tissue distribution of the two subtypes of cannabinoid receptors (CB1 and CB2), we studied the potential utility of these compounds in anti–skin tumor therapy. Here we show that the CB1 and the CB2 receptor are expressed in normal skin and skin tumors of mice and humans. In cell culture experiments pharmacological activation of cannabinoid receptors induced the apoptotic death of tumorigenic epidermal cells, whereas the viability of nontransformed epidermal cells remained unaffected. Local administration of the mixed CB1/CB2 agonist WIN-55,212-2 or the selective CB2 agonist JWH-133 induced a considerable growth inhibition of malignant tumors generated by inoculation of epidermal tumor cells into nude mice. Cannabinoid-treated tumors showed an increased number of apoptotic cells. This was accompanied by impairment of tumor vascularization, as determined by altered blood vessel morphology and decreased expression of proangiogenic factors (VEGF, placental growth factor, and angiopoietin 2). Abrogation of EGF-R function was also observed in cannabinoid-treated tumors. These results support a new therapeutic approach for the treatment of skin tumors."

-Project on Cellular and Molecular Biology and Gene Therapy, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas, Madrid, Spain

- Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain

-Department of Pathology, Hospital General de Móstoles, Madrid, Spain- Department of Chemistry, Clemson University, Clemson, South Carolina, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC151833/

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"Melanoma is responsible for the greatest number of skin cancer–related deaths worldwide. It

was reported that CB1 and the CB2 receptors are expressed in normal skin and skin tumors of mice and humans. In vitro studies showed that activation of cannabinoid receptors induced the apoptotic death of tumorigenic epidermal cells, without affecting the nontransformed epidermal cells. Administration of WIN-55,212-2 or the selective CB2 agonist JWH-133 was shown to result in growth inhibition of malignant tumors in nude mice (ref. 6 and references therein). Another study showed that activation of these receptors decreased tumor growth, angiogenesis and metastasis of melanomas in mice, and inhibited proliferation via inhibition of Akt pathway and hypophosphorylation of retinoblastoma in melanoma cells (6). These two studies offer an exciting opportunity to further explore the use of cannabinoids for the treatment and management of melanoma."

-Chemoprevention Program, Paul P. Carbone Comprehensive Cancer Center and Department of Dermatology, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin USA.
https://pubmed.ncbi.nlm.nih.gov/18199524/

The role of inflammation in skin cancer.

"Cancer is an environmental disease and skin cancer (melanoma and non-melanoma) is the most common of all cancers. Epidemiological and experimental evidence suggest "chronic inflammation" to be one of the hallmarks in solar ultraviolet radiation and several other environmental agent-mediated skin cancers."

…"Considering the potential role of inflammation in tumor initiation and its major role in promotion/progression, as well as tumor angiogenesis and metastasis; inflammatory pathways may become attractive targets for skin cancer prevention. Hence this review focuses on compiling available evidence and understanding the role of chronic inflammation in the development of skin cancer."

-Maru Lab, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre (TMC), Sector-22, Kharghar, Navi Mumbai
https://www.ncbi.nlm.nih.gov/pubmed/24818733

See also Cancer & Inflammation

Sleep

Endocannabinoid Signaling and the Hypothalamic-Pituitary-Adrenal Axis

"The eCB system should be considered as a part of the body's homeostatic processes. Activation of the CB1R promotes return of the HPA axis to nonstressed levels, together with other restorative effects, such as increased feeding and sleep."

-Department of Pharmacology and Toxicology, and Neuroscience Research Center, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

-Department of Medicine, and Neuroscience Research Center, Medical College of Wisconsin, Milwaukee, Wisconsin

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5871916/

The role of the CB1 [cannabinoid type 1] receptor in the regulation of sleep.

"During the 1990s, transmembranal proteins in the central nervous system (CNS) that recognize the principal compound of marijuana, the delta-9-tetrahydrocannabinol (Delta9-THC) were described. The receptors were classified as central or peripheral, CB1 and CB2, respectively. To this date, it has been documented the presence in the CNS of specific lipids that bind naturally to the CB1/CB2 receptors. The family of endogenous cannabinoids or endocannabinoids comprises oleamide, arachidonoylethanolamine, 2-arachidonylglycerol, virodhamine, noladin ether and N-arachidonyldopamine. Pharmacological experiments have shown that those compounds induce cannabimimetic effects. Endocannabinoids are fatty acid derivates that have a variety of biological actions, most notably via activation of the cannabinoid receptors. The endocannabinoids have an active role modulating diverse neurobiological functions, such as learning and memory, feeding, pain perception and sleep generation. Experimental evidence shows that the administration of Delta9-THC promotes sleep. The activation of the CB1 receptor leads to an induction of sleep, this effect is blocked via the selective antagonist. Since the system of the endogenous cannabinoids is present in several species, including humans, this leads to the speculation of the neurobiological role of the endocannabinoid system on diverse functions such as sleep modulation. This review discusses the evidence of the system of the endocannabinoids as well as their physiological role in diverse behaviours, including the modulation of sleep."

-Laboratory of Neurobiology, Faculty of Medicine, Autonomous University of Campeche, Campeche, Campeche. Mexico.

(Laboratorio de Neurobiología, Facultad de Medicina, Universidad Autónoma de Campeche, Campeche, Campeche. Mexico.)

https://www.ncbi.nlm.nih.gov/pubmed/18514375

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"However, in the present study, we also show that chronic loss of CB1 [cannabinoid type 1 receptor] reduces NREM delta rebound following TSD [total sleep deprivation]."

…"The findings that CB1 receptors are important in sleep are complemented by studies showing a hypnogenic role for AEA [anandamide] [63], [64], [70]. These data provide one potential mechanism through which the EC system may modulate NREM sleep. Future studies with cell-type specific, targeted deletion of CB1 (particularly in CCK+ interneurons) would be useful in testing some of the hypotheses that emerge from the present study."

-Department of Neurosciences and Center for Drug and Alcohol Programs, Medical University of South Carolina

-Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina, USA,

-Ralph H. Johnson VA Medical Center, Charleston, South Carolina, USA,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3919802/

Multiple sleep alterations in mice lacking cannabinoid type 1 receptors.

"Cannabinoid type 1 (CB1) receptors are highly expressed in the brain and play a role in behavior control. Endogenous cannabinoid signaling is modulated by high-fat diet (HFD). We investigated the consequences of congenital lack of CB1 receptors on sleep in mice fed standard diet (SD) and HFD. CB1 cannabinoid receptor knock-out (KO) and wild-type (WT) mice were fed SD or HFD for 4 months (n = 9-10 per group). Mice were instrumented with electroencephalographic (EEG) and electromyographic electrodes. Recordings were performed during baseline (48 hours), sleep deprivation (gentle handling, 6 hours), sleep recovery (18 hours), and after cage switch (insomnia model paradigm, 6 hours). We found multiple significant effects of genotype on sleep. In particular, KO spent more time awake and less time in non-rapid-eye-movement sleep (NREMS) and rapid-eye-movement sleep (REMS) than WT during the dark (active) period but not during the light (rest) period, enhancing the day-night variation of wake-sleep amounts. KO had slower EEG theta rhythm during REMS. REMS homeostasis after sleep deprivation was less effective in KO than in WT. Finally, KO habituated more rapidly to the arousing effect of the cage-switch test than WT. We did not find any significant effects of diet or of diet x genotype interaction on sleep. **The occurrence of multiple sleep alterations in KO indicates important roles of CB1 cannabinoid receptors in limiting arousal during the active period of the day, in sleep regulation, and in sleep EEG in mice.**"

-PRISM lab, Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum - University of Bologna, Bologna, Italy.

-Endocrinology Unit and Center for Applied Biomedical Research, Department of Medical and Surgical Sciences, S. Orsola University Hospital, Alma Mater Studiorum - University of Bologna, Bologna, Italy.

https://www.ncbi.nlm.nih.gov/pubmed/24586776

Knockout Mice (KO) - a mouse whose DNA has been genetically engineered so that it does not express particular proteins. (From Oxford/Google) *In the quote above they are referring to KO as mice lacking cannabinoid type 1 receptors in order to determine if it will affect sleep.*

Cannabinoids, Endocannabinoids and Sleep

…"It is becoming increasingly evident that endocannabinoids play a prominent role in sleep and sleep neurophysiology, and cannabinoid drugs alter these processes. There are clear overlaps between the brain eCB system and sleep-wake circuitry, and cannabinergic manipulations are capable of altering sleep on a large scale in terms of time spent in specific vigilance states, and fine-scale in terms of sleep architecture and spectral power of specific sleep-related brain rhythms. Given that a significant portion of the population suffers from poor sleep quality or sleep-related disorders (DSM-V; American Psychiatric Association, 2013), with an estimated 50–70 million individuals in the United States alone as of 2006 (Colten and Altevogt, 2006), understanding how eCBs are functioning under normal and pathological conditions can offer insight to these illnesses and potential treatments."

-Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Health (NIH), Bethesda, MD, United States

-Center on Compulsive Behaviors, Intramural Research Program, National Institute of Health (NIH), Bethesda, MD, United States

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7388834/

Higher levels of omega-3 in diet are associated with better sleep, study shows

"Source: University of Oxford

Summary: Higher levels of omega-3 DHA, the group of long-chain fatty acids found in algae and seafood, are associated with better sleep, shows a randomized, placebo-controlled study. The study finds that higher blood levels of the long-chain omega-3 DHA (the main omega-3 fatty acid found in the brain) are significantly associated with better sleep, including less bedtime resistance, parasomnias and total sleep disturbance. It adds that higher ratios of DHA in relation to the long-chain omega-6 fatty acid AA (arachidonic acid) are also associated with fewer sleep problems."

-ScienceDaily.com

-Centre for Evidence-Based Intervention, University of Oxford, Oxford, UK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4263155/

Social Behavior & Functioning

Endocannabinoid signaling in the control of social behavior

"Many mammalian species, including humans, exhibit social behavior and form complex social groups. Mechanistic studies in animal models have revealed important roles for the endocannabinoid signaling system—consisting of G protein-coupled cannabinoid receptors and their endogenous lipid-derived agonists—in the control of neural processes that underpin social anxiety and social reward, two key aspects of social behavior. An emergent insight from these studies is that endocannabinoid signaling in specific circuits of the brain is context-dependent and selectively recruited. These insights open new vistas on the neural basis of social behavior and social impairment."…

"A growing body of studies support a distinct role for endocannabinoid signaling in the control of social behavior. Cannabis and synthetic cannabinoid receptor agonists may have varied effects, particularly under certain conditions to reduce hostility and threat perception, or during critical developmental windows to potentially effect persistent dysfunction. In contrast, anandamide-mediated signaling appears to act more selectively in reducing social anxiety and enhancing social reward. Based on translational evidence, these actions of anandamide are postulated to be important in social impairment related to (i) schizophrenia, in which tempering social anxiety might be dysfunctional, as well as in (ii) ASD, where a primary deficit may be in nucleus accumbens-regulated social reward. fMRI studies in humans supports these possible roles of anandamide, as a single nucleotide polymorphism (C385A) in the human FAAH gene is associated with decreased threat-related amygdala reactivity and increased reward-related ventral striatal reactivity [86]. In contrast to the specificity demonstrated by anandamide, the actions of 2-AG appear to be more generalizable to other natural rewards. These ongoing developments inform the promising but limited research into cannabinoid-based pharmacotherapies for neuropsychiatric conditions (see [62] for review) at a time when the legal status and public perception of cannabis are dramatically changing.

The difference between global cannabinoid receptor activation and selective endocannabinoid enhancement may be rooted in the selectivity of recruiting circuit projections, such as those of the oxytocin system (Fig. 1). Endocannabinoid signaling in processes specific to social behavior might thus be mechanistically distinguished from endocannabinoid signaling in processes that overlap with the social sphere (e.g. non-social anxiety or reward). This hypothesis addresses a

core question in social neuroscience – whether a distinction can be made between social and non-social signaling [11]. The hypothesis also opens several directions for future investigations, which will be crucial to define the circuits of normal social-information processing and fluent social behavior (see Outstanding Questions). Such investigations will help us understand the contributory social factors and the social-impairment consequences of neuropsychiatric-disease states, such as schizophrenia, ASD, and drug addiction. They are also likely to provide mechanistic insights into the therapeutic actions of social bonding on mental and physical health, a key finding of social neuroscience."

-Dept. of Anatomy and Neurobiology, University of California, Irvine
-School of Medicine, University of California, Irvine
-Dept. of Brain and Cognitive Sciences, Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA, USA
-Harvard Medical School, Harvard University, Boston, MA, USA
*-*Author for correspondence: Daniele Piomelli, Department of Anatomy and Neurobiology,*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5699224

Endocannabinoid signaling in social functioning: an RDoC perspective

…"The empirical evidence reviewed strongly supports the role for dysregulated cannabinoid signaling in the pathophysiology of social functioning deficits observed in brain disorders, such as autism spectrum disorder, schizophrenia, major depressive disorder, posttraumatic stress disorder and bipolar disorder. Moreover, these findings indicate that the endogenous cannabinoid system holds exceptional promise as a biological marker of, and potential treatment target for, neuropsychiatric and neurodevelopmental disorders characterized by impairments in social functioning."…

-Center for Interdisciplinary Brain Sciences Research, Department of Psychiatry and Behavioral Sciences
-Division of Child and Adolescent Psychiatry, Department of Psychiatry and Behavioral Sciences
-Stanford University School of Medicine
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5048207/

Endocannabinoids in Amygdala and Nucleus Accumbens Mediate Social Play Reward in Adolescent Rats

"The brain endocannabinoid system plays a crucial role in emotional processes. We have previously identified an important role for endocannabinoids in social play behavior, a highly rewarding form of social interaction in adolescent rats. Here, we tested the hypothesis that endocannabinoid modulation of social play behavior occurs in brain regions implicated in

emotion and motivation. Social play increased levels of the endocannabinoid anandamide in the amygdala and nucleus accumbens (NAc), but not in prefrontal cortex or hippocampus of 4- to 5-week-old male Wistar rats. Furthermore, social play increased phosphorylation of CB1 cannabinoid receptors in the amygdala. Systemic administration of the anandamide hydrolysis inhibitor URB597 increased social play behavior, and augmented the associated elevation in anandamide levels in the amygdala, but not the NAc. Infusion of URB597 into the basolateral amygdala (BLA) increased social play behavior, and blockade of BLA CB1 cannabinoid receptors with the antagonist/inverse agonist SR141716A prevented the play-enhancing effects of systemic administration of URB597. Infusion of URB597 into the NAc also increased social play, but blockade of NAc CB1 cannabinoid receptors did not antagonize the play-enhancing effects of systemic URB597 treatment. Last, SR141716A did not affect social play after infusion into the core and shell subregions of the NAc, while it reduced social play when infused into the BLA. These data show that increased anandamide signaling in the amygdala and NAc augments social play, and identify the BLA as a prominent site of action for endocannabinoids to modulate the rewarding properties of social interactions in adolescent rats."

-Rudolf Magnus Institute of Neuroscience, Department of Neuroscience and Pharmacology, University Medical Center Utrecht, The Netherlands;

-Department of Animals in Science and Society, Division of Behavioural Neuroscience, Faculty of Veterinary Medicine, Utrecht University, The Netherlands;

-Department of Biology, University "Roma Tre," Italy;

-Endocannabinoid Research Group, Consiglio Nazionale delle Ricerche, Pozzuoli, Italy; and

-Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3496852/

Spices

See also Beta-caryophyllene (β-caryophyllene) ,
Ethylene Oxide (EtO)

Spicy Foods

…"Transient receptor potential vanilloids 1 (TRPV1) channels are activated by vanilloids such as capsaicin as well as by heat, protons, and various lipids, including endocannabinoids, anandamide, and N-arachidonoyl dopamine [79]. The multi-ligand sensing TRPV1 contributes to the detection of acute pain generated by heat and certain chemicals. The surface expression of

TRPV1 in sensory neurons, particularly in association with nociceptive afferent fibers, is upregulated in some pathological conditions accompanied by elevated pain [80,81]. The local administration of BoNT/A [toxin serotype A] decreased TRPV1 expressed in the suburothelial nerve fibers in the human bladder [82]. BoNT/A reduces the total expression of TRPV1 by inhibiting the exocytosis of TRPV1-harboring vesicles, which leads to the proteosomal degradation of TRPV1 [83,84]. Therefore, the potential therapeutic utility of BoNT/A has extended to the modulation of TRPV1 surface expression in pain-associated pathological conditions."….

-Department of Life Science, School of Natural Science, Hanyang University, Seoul, Korea;
-BK21 PLUS Life Science for BioDefense Research (BDR) Team, Hanyang University, Seoul , Korea
-The Research Institute for Natural Science, Hanyang University, Seoul 133-791, Korea
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516922/

See also TRP Channels (Transient receptor potential channels)

Squamous Carcinoma Cell

"Squamous cell carcinoma (SCC) is the second most common form of skin cancer. It's usually found on areas of the body damaged by UV rays from the sun or tanning beds. Sun-exposed skin includes the head, neck, chest, upper back, ears, lips, arms, legs, and hands."

-WebMD
https://www.webmd.com/melanoma-skin-cancer/guide/squamous-cell-carcinoma

Metabolism of anandamide by COX-2 is necessary for endocannabinoid-induced cell death in tumorigenic keratinocytes.

"COX-2 also metabolizes endocannabinoids forming prostaglandin-ethanolamides (PG-EA); however, the role of these lipid molecules in tumor cell survival is unclear. The goal of this research is to determine if the metabolic products of COX-2 contribute to endocannabinoid-induced cell death. Anandamide [also known as arachidonyl ethanolamide (AEA)] induced cell death in the COX-2 overexpressing squamous carcinoma cell line JWF2."
…"These results suggest that AEA selectively induces cell death in tumorigenic keratinocytes due to COX-2 overexpression and the resulting metabolism of AEA to cytotoxic prostaglandins."

Department of Pharmacology and Toxicology, East Carolina University, Brody School of Medicine, Greenville, North Carolina
https://www.ncbi.nlm.nih.gov/pubmed/19148897

Anticancer effects of anandamide on head and neck squamous cell carcinoma cells via the production of receptor-independent reactive oxygen species

"Background: The endocannabinoids, anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), are considered promising potential anticancer agents. In this study, we examined the anticancer effects of AEA and 2-AG in head and neck squamous cell carcinoma (HNSCC) cell lines.

Methods and results: Our results showed that AEA effectively inhibited proliferation of HNSCC cells whereas 2-AG did not. The anticancer effect of AEA seemed to be mediated by a receptor-independent mechanism. Inhibitors of AEA intracellular transportation and transfection of HNSCC cells with fatty acid amide hydrolase, a key enzyme in AEA metabolism, reversed AEA-dependent inhibition of cell proliferation. We found that cyclooxygenase-2 (COX-2) did not mediate the anticancer effects of AEA; instead we observed an increase in reactive oxygen species (ROS) production after AEA treatment. Moreover, antioxidants partially reversed AEA-dependent inhibition of cell proliferation.

Conclusion: These findings suggest that AEA might have anticancer effects on HNSCC cells by mediating an increase in ROS levels through a receptor-independent mechanism."

-Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea.

-Department of Otorhinolaryngology, Seoul National University Hospital, Seoul, Korea.

-Clinical Research Institute, Seoul National University Hospital, Seoul, Korea.

-Sensory Organ Research Institute, Seoul National University Medical Research Center, Seoul National University Hospital, Seoul, Korea.

http://www.ncbi.nlm.nih.gov/pubmed/24797795

Metabolism of anandamide by COX-2 is necessary for endocannabinoid-induced cell death in tumorigenic keratinocytes

"Nonmelanoma skin cancer is the most prevalent cancer in the United States with approximately 1.25 million new cases diagnosed each year. Cyclooxygenase-2 (COX-2) expression is commonly elevated in these and other epithelial tumors. Cyclooxygenases metabolize arachidonic acid to prostaglandins, which promote growth and survival of tumor cells. COX-2 also metabolizes endocannabinoids forming prostaglandin-ethanolamides (PG-EA); however, the role of these lipid molecules in tumor cell survival is unclear. The goal of this research is to determine if the metabolic products of COX-2 contribute to endocannabinoid-induced cell death. Anandamide

[AEA] induced cell death in the COX-2 overexpressing squamous carcinoma cell line JWF2. In contrast, AEA did not initiate cell death in HaCaT keratinocytes, which express low basal levels of COX-2. Resistance to AEA-mediated cell death in HaCaT cells was reversed by overexpressing COX-2 in these cells. Next, ELISA assays were carried out to identify prostaglandins involved in AEA-mediated cell death. D-type prostaglandins were predominantly formed in AEA-exposed JWF2 cells although significant increases in E- and F-type prostaglandins were also seen. Cells were then treated with various prostaglandins or PG-EA to determine the contribution of each to AEA-induced cell death. PGD(2) and PGD(2)-EA were found to be cytotoxic to JWF2 keratinocytes and the PGD(2) dehydration products, PGJ(2) and 15-deoxy Delta(12,14) PGJ(2), were also potent inducers of cell death. These results suggest that AEA selectively induces cell death in tumorigenic keratinocytes due to COX-2 overexpression and the resulting metabolism of AEA to cytotoxic prostaglandins."

-Department of Pharmacology and Toxicology, East Carolina University, Brody School of Medicine, Greenville, North Carolina, USA.

https://pubmed.ncbi.nlm.nih.gov/19148897/

See also Cancer & Inflammation

Statins

Recent findings on the health effects of omega-3 fatty acids and statins, and their interactions: do statins inhibit omega-3?

..."Finally, statins favor the metabolism of omega-6 fatty acids (n-6), which in turn inhibits n-3 [omega-3] and, contrary to n-3, they increase insulin resistance and the risk of diabetes. Thus, n-3 and statins are counteractive at several levels and statins appear to inhibit n-3."

-Laboratoire Cœur et Nutrition, TIMC-IMAG CNRS 5525, Université Joseph Fourier, Faculté de Médecine de Grenoble, 38054 La Tronche, France

-Service de Cardiologie, Hôpital Universitaire Nord, 38054 La Tronche, France

-Clinique La Prairie, Chemin de la Prairie 2-10,1815 Clarens, Montreux,, Switzerland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3571733/

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"I observed that in rat liver cells, the statins stimulate the release of an essential fatty acid, arachidonic acid (AA) [omega-6s] and stimulate production of its metabolite, PGI2 [Prostacyclin (also called prostaglandin I2 or PGI2)]."

Department of Biochemistry, Brandeis University Waltham, MA 02454, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC153527/

Stearidonic Acid (SDA)

Stearidonic acid as a supplemental source of ω-3 polyunsaturated fatty acids to enhance status for improved human health

"There is substantial evidence to show that consumption and increased blood levels of the very long-chain (VLC) ω-3 polyunsaturated fatty acids (ω-3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are associated with health benefits. The consumption of oily fish is an effective way of increasing EPA and DHA intake and status, but intake in most Western countries remains below the levels recommended for optimal health. The reasons for this include not liking the taste, a concern about sustainability of fish supplies, or potential chemical and heavy metal contamination. Alternative dietary sources of ω-3 fatty acids to enhance EPA and DHA status in the body would therefore be beneficial. There are many non-fish food sources of the essential plant-derived ω-3 fatty acid α-linolenic acid, but conversion from this to longer-chain EPA and especially to DHA is poor. Stearidonic acid (SDA) is an intermediate fatty acid in the biosynthetic pathway from α-linolenic acid to VLC ω-3 PUFAs and the conversion from SDA is more efficient than from α-linolenic acid. However, there are few food sources rich in SDA. Oil crops naturally rich in SDA or enriched through genetic modification may offer an alternative supplemental oil to boost the population status of VLC ω-3 PUFAs. This review discusses the currently available evidence that increased SDA consumption can increase red blood cell EPA content, although this is less than the effect of supplementation directly with EPA. There is now a need for trials specifically designed to assess whether an increased SDA consumption would translate into improved human health outcomes."

-MRC Human Nutrition Research, Elsie Widdowson Laboratory, Cambridge, United Kingdom.
https://pubmed.ncbi.nlm.nih.gov/23102888/

Metabolism and functional effects of plant-derived omega-3 fatty acids in humans

"Alpha-linolenic acid (ALA) is an essential fatty acid and the substrate for the synthesis of longer-chain, more unsaturated ω-3 fatty acids, eicosapentaenoic acid (EPA), docosapentaenoic acid and docosahexaenoic acid (DHA). EPA and DHA are associated with human health benefits. The primary source of EPA and DHA is seafood. There is a need for sustainable sources of biologically

active ω-3 fatty acids. Certain plants contain high concentrations of ALA and stearidonic acid (SDA). Here we review the literature on the metabolism of ALA and SDA in humans, the impact of increased ALA and SDA consumption on concentrations of EPA and DHA in blood and cell lipid pools, and the extent to which ALA and SDA might have health benefits. Although it is generally considered that humans have limited capacity for conversion of ALA to EPA and DHA, sex differences in conversion to DHA have been identified. If conversion of ALA to EPA and DHA is limited, then ALA may have a smaller health benefit than EPA and DHA. SDA is more readily converted to EPA and appears to offer better potential for health improvement than ALA. However, conversion of both ALA and SDA to DHA is limited in most humans."

-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom.

-Hugh Sinclair Unit of Human Nutrition, Department of Food and Nutritional Sciences and Institute for Cardiovascular and Metabolic Research, University of Reading, Reading, United Kingdom.

-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

-NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom.

https://pubmed.ncbi.nlm.nih.gov/27496755/

Stem Cells

Cannabinoid Actions on Neural Stem Cells: Implications for Pathophysiology

…"With the ongoing discussion of cannabinoid usage for medical purposes and reports drawing attention to the effects of cannabinoids on NSC regulation, there is an enormous, and yet, uncovered potential for cannabinoids as treatment options for several neurological disorders, specifically when combined with stem cell therapy. In this manuscript, we review in detail how cannabinoids act as potent regulators of NSC biology and their potential to modulate several neurogenic features in the context of pathophysiology."…

-Institute of Pharmacology and Neurosciences, College of Medicine, University of Lisbon, Portugal.

-Institute of Molecular Medicine, College of Medicine, University of Lisbon, Portugal.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6480122/

See also Epilepsy

Sterile Inflammatory Response

"The acute inflammatory response is a double-edged sword. On the one hand it plays a key role in initial host defense particularly against many infections. On the other hand its aim is imprecise and as a consequence, when it is drawn into battle, it can cause collateral damage in tissues. In situations where the inciting stimulus is sterile, the cost-benefit ratio may be high; because of this, sterile inflammation underlies the pathogenesis of a number of diseases. While there have been major advances in our understanding of how microbes trigger inflammation, much less has been learned about this process in sterile situations. This review focuses on a subset of the many sterile stimuli that can induce inflammation – specifically dead cells and a variety of irritant particles, including crystals, minerals, and protein aggregates. Although this subset of stimuli is structurally very diverse and might appear to be unrelated, there is accumulating evidence that the innate immune system may recognize them in similar ways and stimulate the sterile inflammatory response via common pathways. Here we review established and emerging data about these responses."…

"We now know that most of the signs and symptoms of inflammation are caused by changes in the local vasculature of an affected tissue [5] [6, 7]. The smooth muscle of arterioles relaxes, leading to vasodilation and the signs of erythema and heat. This also increases hydrostatic pressure across the vascular bed, which in combination with changes in the permeability of the vascular endothelial barrier, leads to the leakage of protein rich fluid into the tissue, thereby causing edema. Endothelial cells in venules express adhesion molecules that allow neutrophils and subsequently monocytes to adhere and migrate between endothelial cells into the tissue. If the recruitment of neutrophils into the tissue is sufficiently robust it becomes visible to the naked eye as pus [7].

Once triggered, the inflammatory response can develop very rapidly. Vasodilation can occur within seconds and fluid leakage and leukocyte extravasation within minutes to hours [8]. The net result is rapid delivery of many of the body's innate defenses to the offending site. This includes soluble defenses, such as antibody, complement, and collectins, and cellular ones, such as granulocytes and monocytes. Once in the tissue these various components attempt to neutralize, sequester and/or otherwise contain the inciting stimulus. If this is successful, then the innate defenses help clear debris and stimulate tissue repair. Once the inciting stimulus is gone, then the inflammatory response resolves.

One of the major triggers of inflammation is infection, with the inciting stimulus being certain proinflammatory molecules of the invading microbe [9–11]. However, a potpourri of sterile stimuli including mechanical trauma, ischemia, toxins, minerals, crystals, chemicals and antigens also

triggers inflammation. Most of these sterile stimuli can be broadly categorized into ones that are injurious, irritant or antigenic."…

"While the inflammatory response is essential for host defense it is very much a double-edged sword. The effector mechanisms used by the innate immune system to kill microbes are extremely potent and can (and in fact do) also damage and kill mammalian cells. The recruited leukocytes kill microbes by producing highly reactive chemical species, such as reactive oxygen species, sodium hypochlorite (bleach), and other destructive molecules such as proteases. While these molecules are generally effective in destroying microbes, some of them leak from living and dying leukocytes and in so doing damage adjacent normal cells in the tissue. One of the major culprits in causing this collateral damage is the neutrophil, a cell type that is one of the focuses of this present review. In infections, tissue damage is a small price to pay to contain potentially life-threatening situations. Moreover, since infections are often rapidly cleared by immune mechanisms, the duration of the neutrophilic inflammatory response and (hence its attendant damage) are often limited.

However, the cost-benefit ratio may be very different in situations of sterile inflammation. Here the inciting stimulus may not be injurious to the host, and in any case, the innate immune mechanisms that are mobilized may do little or no good. As a result, the dominant effect of the inflammation in these situations may be collateral damage inflicted by the inflammatory response on otherwise healthy cells in the tissue. This process, if sufficiently robust, can cause acute disease and/or exacerbate damage from other etiologies. Moreover, if the sterile stimulus is not resolved this can lead to chronic inflammation and ongoing tissue damage that can also lead to and/or exacerbate disease. A number of these acute and chronic conditions will be described in the sections below."…

-Department of Pathology, University of Massachusetts Medical School, Worcester, MA
-Infectious Diseases and Immunology, University of Massachusetts Medical School, Worcester, MA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315152/

Steroids

Relationship between omega-3 fatty acids and plasma neuroactive steroids in alcoholism, depression and controls.

"Deficiency in the long-chain omega-3 fatty acid, docosahexaenoic acid (DHA) has been associated with increased corticotropin releasing hormone and may contribute to hypothalamic pituitary axis (HPA) hyperactivity."

…"In this pilot observational study, lower long-chain omega-3 essential fatty acid status was associated with higher neuroactive steroid concentrations, possibly indicating increased feedback inhibition of the HPA axis."

-National Institutes of Health, National Institutes on Alcoholism and Alcohol Abuse, Laboratory of Membrane Biophysics and Biochemistry, Bethesda, MD 20814, USA.

https://www.ncbi.nlm.nih.gov/pubmed/16959481

Mechanism of steroid action in inflammation: inhibition of prostaglandin synthesis and release.

…"We suggest that glucocorticosteroids reduce PGE release by limiting the availability of the substrate for prostaglandin biosynthesis, and this may well explain some of their anti-inflammatory properties."

-Prostaglandins. 1976 Sep;12(3):403-13.

-Floman Y, Zor U.

https://www.ncbi.nlm.nih.gov/pubmed/968054

Inhibition of arachidonic acid release from cells as the biochemical action of anti-inflammatory corticosteroids.

…"Hydrocrotisone inhibits this release but does not inhibit the production of prostaglandins from exogenously supplied arachidonic acid. This inhibition of arachidonic acid [omega-6] release from phospholipids may be the mechanism for the anti-inflammatory action of corticosteroids."

-Proceedings of the National Academy of Sciences of the USA

-S L Hong and L Levine

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC430374/

See also Prostaglandins

Steroid Responsive Meningitis (SRMA)

"Steroid responsive meningitis-arteritis (SRMA) is an immune-mediated inflammatory disease primarily affecting the leptomeninges and associated arteries."…

-Jennifer Michaels, DVM, DACVIM (Neurology)

https://www.mspca.org/angell_services/srma/

The endocannabinoid system in canine Steroid-Responsive Meningitis-Arteritis and Intraspinal Spirocercosis

"Endocannabinoids (ECs) are involved in immunomodulation, neuroprotection and control of inflammation in the central nervous system (CNS). Activation of cannabinoid type 2 receptors (CB2) is known to diminish the release of pro-inflammatory factors and enhance the secretion of anti-inflammatory cytokines. Furthermore, the endocannabinoid 2-arachidonoyl glycerol (2-AG) has been proved to induce the migration of eosinophils in a CB2 receptor-dependent manner in peripheral blood and activate neutrophils independent of CB activation in humans. The aim of the current study was to investigate the influence of the endocannabinoid system in two different CNS inflammatory diseases of the dog, i.e. Steroid-Responsive Meningitis-Arteritis (SRMA) and Intraspinal Spirocercosis (IS)."…

"The present study revealed an upregulated endocannabinoid system in dogs with inflammatory CNS diseases, highlighting the endocannabinoid system as a potential target for treatment of inflammatory CNS diseases."

-Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Hannover, Germany

- Center for Systems Neuroscience, Hannover, Germany

- Department of Pathology, University of Veterinary Medicine Hannover, Hannover, Germany

- Institute for Clinical Pharmacology, Hannover Medical School, Hannover, Germany

-Institute for Biometry, Epidemiology, and Information Processing, University of Veterinary Medicine Hannover, Hannover, Germany

-Koret School of Veterinary Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

-Department Clinical Research and Veterinary Public Health, Vetsuisse Faculty, University of Bern, Bern, Switzerland

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5800546

Steroid Withdrawal

"Symptoms of prednisone withdrawal can include body aches, mood swings, and extreme fatigue. Prednisone is a corticosteroid that doctors prescribe to treat swelling and inflammation. It relieves swelling, itching, and redness by suppressing the immune system."

-Medical News Today

https://www.medicalnewstoday.com/articles/322536

“Steroid therapy is frequently used for chronic pain, particularly inflammatory pain states. Steroid withdrawal syndrome can produce a broad array of signs and symptoms, some of which are not well recognized. High fever is among these. We describe several cases with this clinical scenario and review the syndrome in broader terms.”…

-University of Pittsburgh Medical Center (L.M., D.K.C.), Pittsburgh, Pennsylvania
-Albert Einstein College of Medicine (R.B.-S.), Bronx, New York
-PainCare Centers, Inc. (J.G.), Somersworth, New Hampshire, USA
https://www.jpsmjournal.com/article/S0885-3924(06)00718-4/pdf

Still's Disease

Also known as Systemic juvenile idiopathic arthritis (sJIA)
https://www.hindawi.com/journals/iji/2012/480373/

“Adult Still's disease is a rare type of inflammatory arthritis that features fevers, rash and joint pain. Some people have just one episode of adult Still's disease. In other people, the condition persists or recurs. This inflammation can destroy affected joints, particularly the wrists. Treatment involves medications, such as prednisone, that help control inflammation.”

-Mayo Clinic
https://www.mayoclinic.org/diseases-conditions/adult-stills-disease/symptoms-causes/syc-20351907

See also Rheumatoid Arthritis

Stress & Depression

Depression: a case of neuronal life and death?

"Preclinical and clinical studies have demonstrated that stress or depression can lead to atrophy and cell loss in limbic brain structures that are critically involved in depression, including the hippocampus. Studies in experimental animals demonstrate that decreased birth of new neurons in adult hippocampus could contribute to this atrophy. In contrast, antidepressant treatment increases neurogenesis in the hippocampus of adult animals and blocks the effects of stress. Moreover, blockade of hippocampal neurogenesis blocks the actions of antidepressants in behavioral models of depression, demonstrating a direct link between behavior and new cell birth. This perspective reviews the literature in support of the hypothesis that altered birth of

new neurons in the adult brain contributes to the etiology and treatment of depression and considers research strategies to test this hypothesis. "

-Yale University School of Medicine
https://www.ncbi.nlm.nih.gov/pubmed/15271581

Stress

Neurobiological Interactions Between Stress and the Endocannabinoid System

"Stress affects a constellation of physiological systems in the body and evokes a rapid shift in many neurobehavioral processes. A growing body of work indicates that the endocannabinoid (eCB) system is an integral regulator of the stress response. In the current review, we discuss the evidence to date that demonstrates stress-induced regulation of eCB signaling and the consequential role changes in eCB signaling have with respect to many of the effects of stress. Across a wide array of stress paradigms, studies have generally shown that stress evokes bidirectional changes in the two eCB molecules, anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), with stress exposure reducing AEA levels and increasing 2-AG levels. Additionally, in almost every brain region examined, exposure to chronic stress reliably causes a downregulation or loss of cannabinoid type 1 (CB1) receptors. With respect to the functional role of changes in eCB signaling during stress, studies have demonstrated that the decline in AEA appears to contribute to the manifestation of the stress response, including activation of the hypothalamic–pituitary–adrenal (HPA) axis and increases in anxiety behavior, while the increased 2-AG signaling contributes to termination and adaptation of the HPA axis, as well as potentially contributing to changes in pain perception, memory and synaptic plasticity. More so, translational studies have shown that eCB signaling in humans regulates many of the same domains and appears to be a critical component of stress regulation, and impairments in this system may be involved in the vulnerability to stress-related psychiatric conditions, such as depression and posttraumatic stress disorder. Collectively, these data create a compelling argument that eCB signaling is an important regulatory system in the brain that largely functions to buffer against many of the effects of stress and that dynamic changes in this system contribute to different aspects of the stress response."

-Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
-Mathison Centre for Mental Health Research and Education, University of Calgary, Calgary, AB, Canada
-Department of Molecular Physiology and Biophysics and Psychiatry, Vanderbilt Brain Institute, Vanderbilt-Kennedy Center for Research on Human Development, Vanderbilt University Medical Center, Nashville, TN, USA
-Department of Physiology and Pharmacology, University of Calgary, Calgary, AB, Canada

-Departments of Cell Biology and Anatomy and Psychiatry, University of Calgary, Calgary, AB, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4677118/

Linking stress to inflammation

"There is ample evidence for the influence of central nervous system modulation through inflammatory cellular reactions under psychosocial stress. These inflammatory reflexes might be of major influence not only for metabolic and vascular disease but also for many autoimmune diseases for which stress has been reported as a risk factor. In prospective trials on the influence of risk factors for the occurrence of cardiovascular events, both psychosocial stress and autonomic nervous control of the cardiovascular system were shown to have a major impact on event rates. The underlying cause of these findings seems to be explained in part by the direct influences of autonomic reflexes, potentially induced by psychosocial tasks, on the progression of atherosclerosis. Hence, future prospective studies that aim at deciphering the influence of chronic psychosocial stress and autonomic function on the pathogenesis of inflammatory and metabolic disease will need to include neurophysiologic, molecular, and clinical parameters. Because the neuroimmunologic axis can be seen as a system connecting mental states with inflammatory reactions, pro-inflammatory mediators and anti-inflammatory strategies should be studied as such in experimental settings."

-Department of Medicine I, INF 410, University of Heidelberg, Germany.
https://pubmed.ncbi.nlm.nih.gov/16927932/

Repeated Stress Impairs Endocannabinoid Signaling in the Paraventricular Nucleus of the Hypothalamus

"Endocannabinoids (eCBs) are ubiquitous retrograde signaling molecules in the nervous system that are recruited in response to robust neuronal activity or the activation of postsynaptic G-protein-coupled receptors. Physiologically, eCBs have been implicated as important mediators of the stress axis and they may contribute to the rapid feedback inhibition of the hypothalamic–pituitary–adrenal axis (HPA) by circulating corticosteroids (CORTs). Understanding the relationship between stress and eCBs, however, is complicated by observations that eCB signaling is itself sensitive to stress. The mechanisms that link stress to changes in synaptic eCB signaling and the impact of these changes on CORT-mediated negative feedback have not been resolved. Here, we show that repetitive immobilization stress, in juvenile male rats, causes a functional downregulation of CB1 receptors in the paraventricular nucleus of the hypothalamus (PVN). This loss of CB1 receptor signaling, which requires the activation of genomic

glucocorticoid receptors, impairs both activity and receptor-dependent eCB signaling at GABA and glutamate synapses on parvocellular neuroendocrine cells in PVN. Our results provide a plausible mechanism for how stress can lead to alterations in CORT-mediated negative feedback and may contribute to the development of plasticity of HPA responses."…

-Hotchkiss Brain Institute and Department of Physiology and Pharmacology, University of Calgary, Calgary, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6633493/

Remote CB1 receptor antagonist administration reveals multiple sites of tonic and phasic endocannabinoid neuroendocrine regulation

"Endogenous cannabinoids (endocannabinoids, eCB) are expressed throughout the body and contribute to regulation of the hypothalamo-pituitary-adrenal (HPA) axis and general stress reactivity. This study assessed the contributions of CB1 receptors (CB1R) in the modulation of basal and stress-induced neural and HPA axis activities. Catheterized adult male rats were placed in chambers to acclimate overnight, with their catheters connected and exteriorized from the chambers for relatively stress-free remote injections. The next morning, the CB1R antagonist AM251 (1 or 2 mg/kg) or vehicle was administered, and 30 min later, rats were exposed to loud noise stress (30 min) or no noise (basal condition). Blood, brains, pituitary and adrenal glands were collected immediately after the procedures for analysis of c-fos and CB1R mRNAs, corticosterone (CORT) and adrenocorticotropin hormone (ACTH) plasma levels. Basally, CB1R antagonism induced c-fos mRNA in the basolateral amygdala (BLA) and auditory cortex (AUD) and elevated plasma CORT, indicating disruption of eCB-mediated constitutive inhibition of activity. CB1R blockade also potentiated stress-induced hormone levels and c-fos mRNA in several regions such as the bed nucleus of the stria terminalis (BST), lateral septum (LS), and basolateral amygdala (BLA) and the paraventricular nucleus of the hypothalamus (PVN). CB1R mRNA was detected in all central tissues investigated, and the adrenal cortex, but at very low levels in the anterior pituitary gland. Interestingly, CB1R mRNA was rapidly and bidirectionally regulated in response to stress and/or antagonist treatment in some regions. eCBs therefore modulate the HPA axis by regulating both constitutive and activity-dependent inhibition at multiple levels."…

-Department of Psychology and Neuroscience, University of Colorado, Boulder, CO, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7566018/

Inflammation: The Common Pathway of Stress-Related Diseases

"While modernization has dramatically increased lifespan, it has also witnessed that the nature of stress has changed dramatically. Chronic stress result failures of homeostasis thus lead to various diseases such as atherosclerosis, non-alcoholic fatty liver disease (NAFLD) and depression. However, while 75%–90% of human diseases is related to the activation of stress system, the common pathways between stress exposure and pathophysiological processes underlying disease is still debatable. Chronic inflammation is an essential component of chronic diseases. Additionally, accumulating evidence suggested that excessive inflammation plays critical roles in the pathophysiology of the stress-related diseases, yet the basis for this connection is not fully understood. Here we discuss the role of inflammation in stress-induced diseases and suggest a common pathway for stress-related diseases that is based on chronic mild inflammation. This framework highlights the fundamental impact of inflammation mechanisms and provides a new perspective on the prevention and treatment of stress-related diseases."…

Stress is a state of threatened homeostasis provoked by a psychological, environmental, or physiological stressor. With rapid development of science and technology, as well as economy and strong social competition, the nature of stress has changed dramatically (Landsbergis, 2003). Stressful events engender multiple neurochemical, neurotransmitter and hormonal alterations by mainly activating the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. When stress stimuli are under control, the body responds to these in the physiological way. SNA and HPA axis are woken up to release chemical mediators to protect our body from stress. For instance, catecholamines are elevated to increase heart rate and blood pressure, which help us to fight or flight. This appropriate body reaction was called "allostasis" by Sterling and Eyer (1988). This state is beneficial to our survival and recovery. However, when stress stimuli are prolonged or over exaggerated, in another word, chronically increased allostasis lead to pathophysiology. In the last two decades, accumulating evidence indicated that severe or prolonged (chronic) stress resulted in increased risk for physical and psychiatric disorders, which is called stress-related disease. Stress is the common risk factor of 75%–90% diseases, including the diseases which cause the foremost morbidity and mortality. According to the former review, the most common stress-related diseases are cardiovascular diseases (CVD, i.e., hypertension and atherosclerosis), metabolic diseases (i.e., diabetes and non-alcoholic fatty liver disease, NAFLD), psychotic and neurodegenerative disorders (i.e., depression, Alzheimer's disease, AD and Parkinson's disease, PD), cancer (Cohen et al., 2007)."…

"Large bodies of evidence indicate that stress can activate inflammatory response in brain as well as peripherally (Rohleder, 2014; Calcia et al., 2016)."…

"Both pro-inflammatory and anti-inflammatory mechanisms depend on the type and intensity of

stressors. Acute stressors seem to enhance immune function, whereas chronic stressors are suppressive. Intense stressors over-activate the immune system, leading to the imbalance of inflammation and anti-inflammation. Reports from different labs have confirmed pro-inflammation induced by stress, including C-reactive protein (CRP), IL-6, TNFα, IL-1β and the transcription factor of "nuclear factor kappa B (NF-κB)" (Miller et al., 2009).

In addition to peripheral inflammation, central inflammation namely neuroinflammation, has also been found in stress condition (García-Bueno et al., 2008; Munhoz et al., 2008). Elevated pro-inflammatory cytokines, increased microglia activation and accumulation of peripherally-derived monocytes and macrophages were detected in the brain with psychological stress exposure (Johnson et al., 2005). As the brain-resident macrophages, microglia was considered to be the major pro-inflammatory cytokine source. Stress-elicited potentiate microglial activation is via both direct and indirect mechanisms. Microglia express both GC and mineralocorticoid receptors, thus microglia are likely to have direct response to corticosterone peak (Calcia et al., 2016). In addition, GC receptors also are highly present in the hippocampus and prefrontal cortex, so stress-induced corticosterone may have indirect effects on microglia."…

"Accumulating researches suggested that excessive inflammation plays critical roles in relationship between stress and stress-related diseases. Although stress and inflammation, or inflammation and diseases have been widely and nicely discussed, there are few literatures concerned of all these three factors (stress, inflammation and disease). In this part, we will discuss inflammation in different stress-related diseases and explore the inside mechanism (Table (Table11)."

-Laboratory of Stress Medicine, Faculty of Psychology and Mental Health, Second Military Medical University, Shanghai, China

-Edited by: Dieter J. Meyerhoff, University of California, San Francisco, United States

-Reviewed by: Masaaki Murakami, Hokkaido University, Japan; Leonardo Roever, Federal University of Uberlandia, Brazil; Hector A. Cabrera-Fuentes, Justus Liebig Universität

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5476783/

Note: Corticosterone has been shown to upregulate Anandamide (AEA) in animal studies.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951193

Stress Regulates Endocannabinoid-CB1 Receptor Signaling

"The CB1 cannabinoid receptor is a G protein coupled receptor that is widely expressed throughout the brain. The endogenous ligands for the CB1 receptor (endocannabinoids) are N-arachidonylethanolamine and 2-arachidonoylglycerol; together the endocannabinoids and CB1R subserve activity dependent, retrograde inhibition of neurotransmitter release in the brain.

Deficiency of CB1 receptor signaling is associated with anhedonia, anxiety, and persistence of negative memories. CB1 receptor-endocannabinoid signaling is activated by stress and functions to buffer or dampen the behavioral and endocrine effects of acute stress. Its role in regulation of neuronal responses is more complex. Chronic variable stress exposure reduces endocannabinoid-CB1 receptor signaling and it is hypothesized that the resultant deficiency in endocannabinoid signaling contributes to the negative consequences of chronic stress. On the other hand, repeated exposure to the same stress can sensitize CB1 receptor signaling, resulting in dampening of the stress response. Data are reviewed that support the hypothesis that CB1 receptor signaling is stress responsive and that maintaining robust endocannabinoid/CB1 receptor signaling provides resilience against the development of stress-related pathologies."

- *Cecilia J. Hillard Ph.D, Neuroscience Research Center and Department of Pharmacology and Toxicology, Medical College of Wisconsin*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4247817/

The endocannabinoid system in guarding against fear, anxiety and stress

"The endocannabinoid (eCB) system has emerged as a central integrator linking the perception of external and internal stimuli to distinct neurophysiological and behavioural outcomes (such as fear reaction, anxiety and stress-coping), thus allowing an organism to adapt to its changing environment. eCB signalling seems to determine the value of fear-evoking stimuli and to tune appropriate behavioural responses, which are essential for the organism's long-term viability, homeostasis and stress resilience; and dysregulation of eCB signalling can lead to psychiatric disorders. An understanding of the underlying neural cell populations and cellular processes enables the development of therapeutic strategies to mitigate behavioural maladaptation."

-Institute of Physiological Chemistry, University Medical Center Mainz, Duesbergweg 6, Mainz, Germany

-Institut national de la santé et de la recherche médicale (INSERM)

-U862 NeuroCentre Magendie, Group Endocannabinoids and Neuroadaptation, Bordeaux, France

-University of Bordeaux, 146 rue Léo Saignat, Bordeaux, France

-Laboratori de Neurofarmacologia, Facultat de Ciències de la Salut i de la Vida, Universitat Pompeu Fabra, Dr. Aiguader 88, Barcelona, Spain

-Department of Pharmacology and Toxicology, Neuroscience Research Center, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5871913/

Physiology, Cortisol

…"Cortisol, the stress hormone, is one of the many hormones responsible for this physiological

change. Cortisol is a glucocorticoid hormone produced by the adrenal glands and released for a variety of reasons. The hypothalamus-pituitary-adrenal axis regulates its release and when not controlled, overproduction and underproduction of cortisol cause Cushing's syndrome and Addison disease, respectively."

-Lauren Thau; Sandeep Sharma, Mery Fitzgerald Hospital
https://www.ncbi.nlm.nih.gov/books/NBK538239/

CB1 receptor mediates the effects of glucocorticoids on AMPK activity in the hypothalamus.

"AMP-activated protein kinase (AMPK), a regulator of cellular and systemic energy homeostasis, can be influenced by several hormones. Tissue-specific alteration of AMPK activity by glucocorticoids may explain the increase in appetite, the accumulation of lipids in adipose tissues, and the detrimental cardiac effects of Cushing's syndrome. Endocannabinoids are known to mediate the effects of various hormones and to influence AMPK activity. Cannabinoids have central orexigenic and direct peripheral metabolic effects via the cannabinoid receptor type 1 (CB1). In our preliminary experiments, WT mice received implants of a corticosterone-containing pellet to establish a mouse model of Cushing's syndrome. Subsequently, WT and Cb1 (Cnr1)-knockout (CB1-KO) littermates were treated with corticosterone and AMPK activity in the hypothalamus, various adipose tissues, liver and cardiac tissue was measured. Corticosterone-treated CB1-KO mice showed a lack of weight gain and of increase in hypothalamic and hepatic AMPK activity. In adipose tissues, baseline AMPK activity was higher in CB1-KO mice, but a glucocorticoid-induced drop was observed, similar to that observed in WT mice. Cardiac AMPK levels were reduced in CB1-KO mice, but while WT mice showed significantly reduced AMPK activity following glucocorticoid treatment, CB1-KO mice showed a paradoxical increase. Our findings indicate the importance of the CB1 receptor in the central orexigenic effect of glucocorticoid-induced activation of hypothalamic AMPK activity. In the periphery adipose tissues, changes may occur independently of the CB1 receptor, but the receptor appears to alter the responsiveness of the liver and myocardial tissues to glucocorticoids. In conclusion, our data suggest that an intact cannabinoid pathway is required for the full metabolic effects of chronic glucocorticoid excess."

-Centre for Endocrinology, William Harvey Research Institute, Barts

-London School of Medicine and Dentistry, Queen Mary University of London, London , UK

-Department of Endocrine Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Hungary

-Division of Endocrinology, Diabetes, Metabolism and Molecular Medicine, Department of Medicine, Tupper Research Institute, Tufts Medical Center, Boston, USA

-Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK.
https://www.ncbi.nlm.nih.gov/pubmed/23884964

Acute Stress Increases Circulating Anandamide and Other N-Acylethanolamines in Healthy Humans

"Stress plays an important role in psychiatric disorders, and preclinical evidence indicates that the central endocannabinoid system modulates endocrine and neuronal responses to stress. This study aimed to investigate the effect of acute stress on circulating concentrations of endocannabinoids (eCBs) in healthy humans. A total of 71 adults participated in two sessions in which they were exposed to either a standardized psychosocial stress procedure (Trier Social Stress Test) or a control task. Blood samples for eCB and cortisol assays and cardiovascular and subjective measures were obtained before and at regular intervals after the tasks. Serum concentrations of the eCBs, N-arachidonylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), as well as of the N-acylethanolamides (NAEs), N-palmitoylethanolamine (PEA) and N-oleoylethanolamine (OEA), and of the O-acylglycerol, 2-oleoylglycerol (2-OG), were determined. Compared with the control condition, stress increased serum concentrations of AEA and the other NAEs immediately after the stress period. Increases in PEA were positively correlated with increases in serum cortisol after stress. Furthermore, anxiety ratings at baseline were negatively correlated with baseline concentrations of AEA. The sex and menstrual cycle status of the subject affected the NAE responses to stress. Interestingly, subjects of Asian and African-American races exhibited different patterns of stress responses compared with the Caucasian subjects. These results indicate that stress increases circulating NAEs in healthy human volunteers. This finding supports a protective role for eCBs in anxiety. Further research is needed to elucidate the function of these lipid mediators, and to determine the mechanisms that regulate their appearance in the circulation."

…"Stress contributes to somatic and psychiatric disorders such as depression, anxiety, and substance abuse (Esler et al, 2008; Krishnan and Nestler, 2008; Parker et al, 2003; Sinha, 2008). Acute stress activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to release of glucocorticoids such as cortisol (Lopez et al, 1999; Chrousos et al, 2009), and the sympathetic-adrenomedullary system (SAM), leading to secretion of catecholamines (Lopez et al, 1999; Chrousos et al, 2009). Recent preclinical evidence indicates that stress also mobilizes the endocannabinoid (eCB) system in both the brain and the periphery, and that the eCB system can modulate behavioral and endocrine responses to both acute and chronic stress (Hill et al, 2010; Patel and Hillard, 2008)."

- Department of Psychiatry, University of Muenster
- Department of Psychiatry and Behavioral Neuroscience, University of Chicago
- Department of Pharmacology and Toxicology, Medical College of Wisconsin

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3442338/

Peripheral and central CB1 cannabinoid receptors control stress-induced impairment of memory consolidation.

…"Thus, CB1 [cannabinoid type 1] receptors on adrenergic and noradrenergic cells provide previously unrecognized cross-talk between central and peripheral mechanisms in the stress-dependent regulation of nonemotional memory consolidation, suggesting new potential avenues for the treatment of cognitive aspects on stress-related disorders."

-Laboratory of Neuropharmacology-NeuroPhar, Department of Experimental and Health Sciences, University Pompeu Fabra, Barcelona, Spain; Endocannabinoids and Neuroadaptation Group, NeuroCentre Magendie, INSERM, Bordeaux, France;

-Laboratory of Neuropharmacology-NeuroPhar, Department of Experimental and Health Sciences, University Pompeu Fabra, Barcelona, Spain;

-Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany.

-Endocannabinoids and Neuroadaptation Group, NeuroCentre Magendie, INSERM, Bordeaux, France;

-Laboratory of Neuropharmacology-NeuroPhar, Department of Experimental and Health Sciences, University Pompeu Fabra, Barcelona, Spain;

https://www.ncbi.nlm.nih.gov/pubmed/27528659

The Role of the Endocannabinoid System and Genetic Variation in Adolescent Brain

"During adolescence, both rodent and human studies have revealed dynamic changes in the developmental trajectories of corticolimbic structures, which are known to contribute to the regulation of fear and anxiety-related behaviors. The endocannabinoid (eCB) system critically regulates stress responsivity and anxiety throughout the life span. Emerging evidence suggests that during adolescence, changes in eCB signaling contribute to the maturation of local and corticolimbic circuit populations of neurons, such as mediating the balance between excitatory and inhibitory neurotransmission within the prefrontal cortex. This function of the eCB system facilitates efficient communication within and between brain regions and serves a central role in establishing complex and adaptive cognitive and behavioral processing. Although these peri-adolescent changes in eCB signaling promote brain development and plasticity, they also render this period a particularly sensitive one for environmental perturbations to these normative fluctuations in eCB signaling, such as stress, potentially leading to altered developmental trajectories of neural circuits governing emotional behaviors. In this review, we focus on the role of eCB signaling on the regulation of stress and anxiety-related behaviors both during and after adolescence. Moreover, we discuss the functional implications of human genetic variation in the

eCB system for the risk for anxiety and consequences of stress across development and into adulthood."

-Department of Psychiatry, Weill Cornell Medical College
-Sackler Institute for Developmental Psychobiology, Weill Cornell Medical College
-Department of Psychology, Yale University, New Haven
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5719094/

Amygdala FAAH and anandamide: mediating protection and recovery from stress

"A long-standing literature linking endocannabinoids (ECBs) to stress, fear, and anxiety has led to growing interest in developing novel anxiolytics targeting the ECB system. Following rapid on-demand biosynthesis and degradation upon neuronal activation, the ECB N-arachidonoylethanolamide (anandamide, AEA) is actively degraded by the serine hydrolase enzyme, fatty acid amide hydrolase (FAAH). Exposure to stress rapidly mobilizes FAAH to deplete the signaling pool of AEA and increase neuronal excitability in a key anxiety-mediating region--the basolateral amygdala (BLA). Gene deletion or pharmacological inhibition of FAAH prevents stress-induced reductions in AEA and associated increases in BLA dendritic hypertrophy and anxiety-like behavior. Additionally, inhibition of FAAH facilitates long-term fear extinction and rescues deficient fear extinction in rodent models by enhancing AEA-CB1 (cannabinoid type 1) receptor signaling and synaptic plasticity in the BLA. These preclinical findings propose restoring deficient BLA AEA levels by pharmacologically inhibiting FAAH as a mechanism to therapeutically mitigate the effects of traumatic stress."

-Laboratory of Behavioral and Genomic Neuroscience, National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health, Bethesda, MD, USA.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4169112

■■■

"The endocannabinoid signaling system is a widespread, neuromodulatory system in brain and is also widely utilized in the periphery to modulate metabolic functions and the immune system. Preclinical data demonstrate that endocannabinoid signaling is an important stress buffer and modulates emotional and cognitive functions. These data suggest the hypothesis that endocannabinoid signaling could be dysfunctional in a number of mental disorders. Genetic polymorphisms in the human genes for two important proteins of the endocannabinoid signaling system, the CB1 cannabinoid receptor (CB1R) and fatty acid amide hydrolase (FAAH), have been

explored in the context of normal and pathological conditions. In the case the gene for FAAH, the mechanistic relationships among the common genetic polymorphism, the expression of the FAAH protein and its likely impact on endocannabinoid signaling are understood. However, multiple polymorphisms in the gene for the CB1R occur and are associated with human phenotypic differences without an understanding of the functional relationships among the gene, mRNA, protein and protein function. The endocannabinoid ligands are found in the circulation and several studies have identified changes in their concentrations under various conditions. These data are reviewed for the purpose of generating hypotheses and to encourage further studies in this very interesting and important area."….

-Department of Pharmacology and Neuroscience Research Center, Medical College of Wisconsin
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288440

Endocannabinoid Signaling in the Etiology and Treatment of Major Depressive Illness

…"The eCBs [Endocannabinoids] can be measured in both plasma and serum (see [86] for a recent review). Macrophages [87–89] and platelets [87] synthesize eCBs and several inflammatory conditions are accompanied by significantly elevated circulating eCBs [90–92]. Both CB1R [93] and CB2R [6] are expressed by circulating immune cells and activation of the CB2R exerts anti-inflammatory effects [6]. **Thus, circulating eCBs could contribute to the regulation of inflammation through effects on immune cells in the blood.**

Physiological stress increases eCB concentrations in the circulation. For example, circulating 2-AG [2-Arachidonoylglycerol] concentrations are increased significantly in patients undergoing cardiopulmonary bypass [92]. Parabolic flight maneuvers that produce a significant physiological stress increase both AEA [Anandamide] and 2-AG concentrations in the circulation with different time courses [89]. Intense exercise produces a significant increase in plasma AEA [94]. The role of the eCBs in the context of physiological stress could be to dampen stress-induced inflammation. In addition, circulating cortisol concentrations were inversely related to AEA concentrations in the flight study [89] and positively correlated with orthostatic tolerance in a head-up tilt study [95], suggesting that eCBs might buffer endocrine and neuronal responses to stress as well."…

-Research Center, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4002665/

Stroke

- "Stroke is a leading cause of serious long-term disability, with an estimated 5.4 million stroke survivors currently alive today. The American Heart Association estimates that in 2003, stroke cost about $51.2 billion in both direct and indirect costs in the U.S. alone.
- The most recent prevalence statistics from the American Heart Association estimate that 5,400,000 people have experienced stroke."

- American Association of Neurological Surgeons
https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Cerebrovascular-Disease

■■■

"The health benefits of ω-3 fatty acids are mediated, in part, through metabolic conversion to bioactive epoxides. Here we detail the discovery and initial characterization of naturally occurring ω-3–derived endocannabinoid epoxides that are formed via enzymatic oxidation of ω-3 endocannabinoids by cytochrome P450s. These dual functional ω-3 endocannabinoid epoxides are anti-inflammatory and vasodilatory and reciprocally modulate platelet aggregation. By virtue of their physiological properties, they are expected to play important roles in neuroinflammation and in cerebrovascular diseases such as stroke."…

-Department of Comparative Biosciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Medical Scholars Program, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Biochemistry, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Materials Science and Engineering, University of Illinois at Urbana–Champaign, Champaign, IL,
-Department of Pharmacology, University of Michigan, Ann Arbor, MI;
-Division of Nutritional Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-College of Veterinary Medicine, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Animal Sciences, University of Illinois at Urbana–Champaign, Champaign, IL;
-Department of Bioengineering, University of Illinois at Urbana–Champaign, Champaign IL;
-Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI;
-Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana–Champaign, Champaign, IL,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5544256

See Cerebrovascular Events

Substance Abuse

…"Preclinical research has demonstrated dysregulation in glutamatergic signaling within a corticostriatal circuit (prefrontal cortex-nucleus accumbens) following periods of self-administration and withdrawal across multiple substances of abuse [20–24]. These data indicate that glutamate plays a key role in drug-seeking and reinstatement models, suggesting that glutamate is a promising neurochemical target for medication development to treat substance use disorders (SUDs) [25, 26]. Further, evidence suggests that cannabinoid administration disrupts normal glutamate functioning [27–33] and indirectly disinhibits dopamine transmission [34, 35]. Among potential glutamate-targeted pharmacotherapies for SUDs, N-acetylcysteine (NAC) has emerged as a particularly strong candidate [21, 25, 26]. NAC is an N-acetyl pro-drug of the naturally occurring amino acid cysteine, and stimulates cystine-glutamate exchange, thus increasing non-synaptic glial release of glutamate [36]. NAC has also been shown to reduce the reinstatement of drug-seeking in animal models across multiple substances [36–43]."…

-Medical University of South Carolina School of Medicine, 67 President St., Charleston, SC, 29425, United States

-Addiction Sciences Division, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 3131 Harvey Avenue, Cincinnati, OH 45229, United States

-Yale University School of Medicine, 950 Campbell Ave, West Haven, CT 06516, United States

-Center for the Clinical Trials Network, National Institute on Drug Abuse, 6001 Executive Boulevard, MSC 9557, Bethesda, MD 20892, United States

-The EMMES Corporation, 401 N. Washington St., Rockville, MD 20850, United States

-Johns Hopkins University, School of Medicine, 5510 Nathan Shock Dr., Baltimore, MD 21224, United States

-Columbia University/New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, United States

-Division of Alcohol and Drug Abuse, McLean Hospital, 115 Mill St., Belmont, MA, 02478, United States; Department of Psychiatry, Harvard Medical School, 25 Shattuck St., Boston, MA, 02115, United States

-University of California, Los Angeles, David Geffen School of Medicine, 1640 S. Sepulveda Blvd., Suite 120, Los Angeles, CA 90025, United States

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252394

N-acetylcysteine reduces extinction responding and induces enduring reductions in cue- and heroin-induced drug-seeking

Background: Previous studies show that the acute administration of N-acetylcysteine (NAC) inhibits the desire for cocaine in addicts and cocaine-seeking in animals."…

"**Conclusions**: These data show that daily NAC inhibits heroin-induced reinstatement and produces an enduring reduction in cue- and heroin-induced drug seeking for over 1 month after the last injection of NAC. Both the inhibitory effect of NAC on the reinstatement of heroin-seeking and the ability of NAC to reduce extinction-responding support clinical evaluation of

repeated NAC administration to decrease in drug-seeking in heroin addicts."

-Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina, USA.
https://pubmed.ncbi.nlm.nih.gov/17719565

See also N-Acetylcysteine (NAC)

Sudden Cardiac Death (SCD)

Reduction of heart rate by omega-3 fatty acids and the potential underlying mechanisms

"An elevated resting heart rate is one of the strongest predictors of cardiovascular mortality and is independently associated with sudden cardiac death (SCD). Agents capable of reducing heart rate without significant side effects are therefore of particular interest for the prevention of SCD. Recent human and animal studies have shown that omega-3 fatty acids can reduce heart rate. Our work has shown that omega-3 fatty acids significantly reduce membrane electrical excitability of the cardiac myocyte by lowering its resting membrane potential and the duration of the refractory period through inhibition of ion channels. We propose that these actions may be the underlying mechanisms for the omega-3 fatty acid-induced reduction of heart rate observed in both humans and animals. The heart rate-lowering capability of omega-3 fatty acids may contribute to their preventive effect against SCD."

-Laboratory for Lipid Medicine and Technology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3483717

Suicide

Neurobiology of suicidal behaviour

…."Disorders of opioid and endocannabinoid systems can also be found in suicide victims. Pathogenesis of suicidal behaviour also contains abnormalities of cell signalising and pathology of glial cells."..

-Adult Psychiatry Clinic of the University Hospital in Krakow.
(Klinika Psychiatrii Dorosłych Szpitala Uniwersyteckiego w Krakowie.)
http://www.ncbi.nlm.nih.gov/pubmed/22232983

Role of the endocannabinoid system in depression and suicide

“Depression is one of the most prevalent forms of neuropsychiatric disorder and is a major cause of suicide worldwide. The prefrontal cortex is a crucial brain region that is thought to be involved in the regulation of mood, aggression and/or impulsivity and decision making, which are altered in suicidality. Evidence of the role of the endocannabinoid (EC) system in the neurobiology of neuropsychiatric disorders is beginning to emerge. The behavioral effects of ECs are believed to be mediated through the central cannabinoid CB1 receptor. Alterations in the levels of ECs, and in the density and coupling efficacy of CB1 receptors, have been reported in the prefrontal cortex of depressed and alcoholic suicide victims. These findings support our hypothesis that altered EC function contributes to the pathophysiological aspects of suicidal behavior. Here, we provide a brief overview of the role of the EC system in alcoholism, depression and suicide, and discuss possible therapeutic interventions and directions for future research.

-Division of Analytical Psychopharmacology, New York State Psychiatric Institute, NY, USA
https://pubmed.ncbi.nlm.nih.gov/16919786/

Suicide Deaths of Active Duty U.S. Military and Omega-3 Fatty Acid Status: A Case Control Comparison

“The recent escalation of US Military suicide deaths to record numbers has been an sentinel for impaired force efficacy and has accelerated the search for reversible risk factors.”…

“Suicides rates among active duty US Military have increased to record numbers, doubling since the inception of Operation Enduring Freedom (OEF, Afghanistan) and Operation Iraqi Freedom (OIF, Iraq). Army Vice Chief of Staff General Chiarelli described the record suicide rate “horrible” and voiced frustration that “the Army has not yet been able to identify any causal links among the suicide cases” 1.

Deficiencies of nutrients critical for brain function may be a significant contributing risk factor for psychiatric pathology, especially suicide and stress related psychiatric symptoms [2]. Highly unsaturated omega-3 polyunsaturated fatty acids (n-3 HUFAs), in particular, docosahexaenoic acid (DHA), are selectively concentrated in neural tissues and required for optimal neural function 3. These fatty acids cannot be made de novo but are available only from dietary sources, with seafood being the richest source. Nutritional deficiencies in n-3 HUFAs may increase vulnerability to combat deployment stress manifesting as psychiatric symptoms including adjustment disorders, major depression, impulsive violence and suicide [4]. In civilian populations, observational studies indicate low fish consumption is associated with increased risk of

completed suicides [5, 6] and greater suicidal ideation [7]. Low DHA status was associated with increased risk of past suicide attempts 8 and future suicide attempts [9]. In comparison to placebo, 2 gm/d of n-3 HUFA reduced suicidal thinking, depressive symptoms and reduced the perception of stress, among subjects (n=49) with deliberate self harm [10].

These suggest that low DHA levels may be a contributing factor for adverse psychiatric symptoms. Here, we posited that low DHA status would be associated with increased risk of suicide death among military personnel. Prospectively collected serum and supporting data was available from Armed Forces Health Surveillance Center (AFHSC) for a large number of active duty suicide deaths (n=800) and matched controls (n=800). To our knowledge, this is the largest study of biological factors among suicide deaths."…

"Here we found that low DHA status is a significant risk factor for suicide death among active duty US military. Nearly all US military personnel had low n-3 HUFA status in comparison to North American [13], Australasian [14], Mediterranean [15] and Asian [8] populations. The low amounts and narrow range of DHA in this US Military population in comparison to world and US diversity, made detection of an association difficult and impaired the evaluation of risk relationships among people with higher n-3 HUFA status. For example, the lowest DHA status in a population of suicide attempters in China appeared to be higher than nearly all the US military personnel reported here [8]. Chinese subjects in the lowest quartile of DHA status in erythrocytes (mean 2.72% range 0.56–3.72) had a higher odds of a suicide attempt (OR =4.76, 95%CI, 1.67–14.28, $p<0.0003$) compared to the highest quartile (mean 6.9%, range 6.15–8.94) 8. When compared across these two populations, the lowest DHA status may be associated with a 5–6 fold increased risk of suicidal behaviors compared to the highest status. The maximal benefit may not have been assessed in this sample of US military personnel.

Increased risk for suicide is likely due to multiple social, psychiatric and environmental risk factors underscoring the complexity of psychological health issues among service members. The relative impact of low DHA status on increased suicide risk (62%) can be put into perspective in comparison to the relative impact of severe combat stress or prior mental health problems on increased suicide risk. Personnel with a positive response to "Did you see wounded, killed or dead coalition during deployment?" had an increased risk of suicide death by 54%. The strength of the relationship between more numerous prior mental health visits and increased risk of suicide death was also similar to that of low DHA status."

-Uniformed Services University, Bethesda MD
-National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda MD
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3259251/

Suicide and Microglia: Recent Findings and Future Perspectives Based on Human Studies

“Suicide is one of the most disastrous outcomes for psychiatric disorders. Recent advances in biological psychiatry have suggested a positive relationship between some specific brain abnormalities and specific symptoms in psychiatric disorders whose organic bases were previously completely unknown. Microglia, immune cells in the brain, are regarded to play crucial roles in brain inflammation by releasing inflammatory mediators and are suggested to contribute to various psychiatric disorders such as depression and schizophrenia. Recently, activated microglia have been suggested to be one of the possible contributing cells to suicide and suicidal behaviors via various mechanisms especially including the tryptophan-kynurenine pathway. Animal model research focusing on psychiatric disorders has a long history, however, there are only limited animal models that can properly express psychiatric symptoms. In particular, to our knowledge, animal models of human suicidal behaviors have not been established. Suicide is believed to be limited to humans, therefore human subjects should be the targets of research despite various ethical and technical limitations. From this perspective, we introduce human biological studies focusing on suicide and microglia. We first present neuropathological studies using the human postmortem brain of suicide victims. Second, we show recent findings based on positron emission tomography (PET) imaging and peripheral blood biomarker analysis on living subjects with suicidal ideation and/or suicide-related behaviors especially focusing on the tryptophan-kynurenine pathway. Finally, we propose future perspectives and tasks to clarify the role of microglia in suicide using multi-dimensional analytical methods focusing on human subjects with suicidal ideation, suicide-related behaviors and suicide victims.”

…"Neuroinflammation is suggested to be linked to suicide. Microglia, immune cells in the brain, are regarded to play crucial roles in neuroinflammation via releasing inflammatory mediators and are suggested to contribute to various psychiatric disorders."…

-National Hospital Organization Shimofusa Psychiatric Medical Center, Chiba, Japan

-Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

-Neuropathology Department, Sainte-Anne Hospital, Paris, France

-Human Histopathology and Animal Models Laboratory, Institute Pasteur, Paris, France

-Department of Pathology and Forensic Medicine, Raymond Poincaré University Hospital, Garches, France

-Department of Clinical Chemistry and Laboratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

-Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

-Edited by: Jose Luis Venero, Universidad de Sevilla, Spain

-Reviewed by: Andrew Dwork, Columbia University, United States; Naguib Mechawar, McGill University, Canada; Ana María Espinosa Oliva, Universidad de Sevilla, Spain

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6381042/

Medical Marijuana Laws and Suicides by Gender and Age

…"Suicides among men aged 20 through 39 years fell after medical marijuana legalization compared with those in states that did not legalize. The negative relationship between legalization and suicides among young men is consistent with the hypothesis that marijuana can be used to cope with stressful life events. However, this relationship may be explained by alcohol consumption. The mechanism through which legalizing medical marijuana reduces suicides among young men remains a topic for future study."

-D. Mark Anderson is with the Department of Agricultural Economics and Department of Economics, Montana State University, Bozeman.

-Daniel I. Rees is with the Department of Economics, University of Colorado Denver.

-Joseph J. Sabia is with the Department of Economics, San Diego State University, San Diego, CA.

https://ajph.aphapublications.org/doi/abs/10.2105/AJPH.2013.301612

See also Glial Cells, Psychiatric Disorders

Sulfonyl Fluoride

"Sulfonyl fluorides are known to inhibit esterases. Early work from our laboratory has identified hexadecyl sulfonylfluoride (AM374) as a potent in vitro and in vivo inhibitor of fatty acid amide hydrolase (FAAH). We now report on later generation sulfonyl fluoride analogs that exhibit potent and selective inhibition of FAAH. Using recombinant rat and human FAAH we show that 5-(4-hydroxyphenyl)pentanesulfonyl fluoride (AM3506) has similar inhibitory activity for both the rat and the human enzyme, while rapid dilution assays and mass spectrometry analysis suggest that the compound is a covalent modifier for FAAH and inhibits its action in an irreversible manner. Our SAR results are highlighted by molecular docking of key analogs."

-Center for Drug Discovery and Departments of Chemistry and Chemical Biology and Pharmaceutical Sciences, Northeastern University, Boston, MA, USA

-Department of Chemistry and Chemical Biology and Barnett Institute of Chemical and Biological Analysis, Northeastern University, Boston, MA, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678964/

See Fatty Acid Amide Hydrolase (FAAH)

Sunburn

“Sunburn is a commonly occurring acute inflammatory process, with dermal vasodilatation and leukocyte infiltration as central features. Ultraviolet (UV) B-induced hydrolysis of membrane phospholipids releases polyunsaturated fatty acids, and their subsequent metabolism by cyclooxygenases (COXs) and lipoxygenases (LOXs) may produce potent eicosanoid mediators modulating different stages of the inflammation. “…

”We show that vasodilatory prostaglandins (PGs) PGE2, PGF2α, and PGE3 accompany the erythema in the first 24–48 h, associated with increased COX-2 expression at 24 h. Novel, potent leukocyte chemoattractants 11-, 12-, and 8-monohydroxy-eicosatetraenoic acid (HETE) are elevated from 4 to 72 h, in association with peak dermal neutrophil influx at 24 h, and increased dermal CD3+ lymphocytes and 12- and 15-LOX expression from 24 to 72 h. Anti-inflammatory metabolite 15-HETE shows later expression, peaking at 72 h. Sunburn is characterized by overlapping sequential profiles of increases in COX products followed by LOX products that may regulate subsequent events and ultimately its resolution.”…

“Acute ultraviolet (uv) b exposure of the skin produces sunburn, an inflammatory response evident visually as erythema and characterized histologically by a mixed dermal neutrophilic and lymphocytic infiltrate. Peak vasodilatation is reached at 24 h (1) and neutrophil infiltration at 24–48 h [2,3,4], while dermal infiltration by T lymphocytes may exhibit a later time course [5]. Whereas prostaglandin (PG) E2 and nitric oxide have roles in the vasodilatation [1, 6, 7], and cytokines, including interleukin-8, contribute to the leukocyte infiltration [3], the mediation of induction and resolution of the sunburn response is incompletely understood and is anticipated to involve a wider range of eicosanoids.

Skin displays highly active metabolism of polyunsaturated fatty acids (PUFAs), resulting in the production of eicosanoids that modulate physiological processes at low concentrations and elicit inflammatory reactions at higher levels [8]. Activation of membrane phospholipase A2 by UVB effects release of fatty acids, notably the ω (n)-6 PUFA arachidonic acid (AA; 20:4n-6), and potentially the n-3 PUFA eicosapentaenoic acid (EPA; 20:5n-3), which has also been detected in human skin (9) (Scheme 1). Subsequently, these PUFAs may be metabolized by cyclooxygenases (COXs) and lipoxygenases (LOXs) to a wide range of eicosanoids and other lipid mediators. High COX-2, 12-LOX, and 15-LOX activity is reported in epidermal cells, and infiltrating neutrophils may possess 5-LOX activity [8, 10]. Considerable species differences are reported for LOX expression [11], and additional fatty acid metabolism by cytochrome P-450 and nonenzymatic oxidation may contribute to production of a wide diversity of metabolites [12].”

-Photobiology Unit, Dermatological Sciences, School of Translational Medicine, University of

Manchester, Salford Royal National Health Service Foundation Hospital, Manchester Academic Health Sciences Centre, Manchester, UK

-Centre for Skin Sciences, School of Life Sciences
-School of Pharmacy, University of Bradford, Bradford, UK
-School of Clinical and Laboratory Sciences, University of Newcastle upon Tyne, Newcastle upon Tyne, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2791058/

…"Finally, to add a further layer to the complexity of the system, it is noteworthy that another cannabinoid-responsive receptor (namely TRPV4) was also found to play a role in detecting UVB. Indeed, UVB-induced sunburn and pain was found to be mediated via direct (i.e., UVB-induced) activation of TRPV4 ion channels in epidermal keratinocytes, and the subsequent release of endothelin-1 [86]."…

-Department of Physiology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-Department of Immunology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary
-HCEMM Nonprofit Ltd., Szeged, Hungary
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429381/

Supplements

"Docosahexaenoic acid (DHA) [omega-3] is uniquely concentrated in the brain, and is essential for its function, but must be mostly acquired from diet. Most of the current supplements of DHA, including fish oil and krill oil, do not significantly increase brain DHA, because they are hydrolyzed to free DHA and are absorbed as triacylglycerol, whereas the transporter at blood brain barrier is specific for phospholipid form of DHA."…

-Department of Medicine, University of Illinois at Chicago, Chicago, IL USA
-Department of Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, IL USA
-Jesse Brown VA Medical Center, Chicago, IL USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5596017

"Triacylglycerols are formed by linking fatty acids with an ester linkage to three alcohol groups in glycerol. Triacylglycerols are the form in which fat energy is stored in adipose tissue. Triacylglycerols are sometimes referred to as triglycerides."

-Omega Fatty Acids in Brain and Neurological Health (Second Edition), 2019
https://www.sciencedirect.com/topics/neuroscience/triacylglycerol

…"However, just as in the review of effects on cardiovascular disease, the authors point out that there was substantial variability from study to study in the dosages, proportions of specific omega-3 fatty acids administered (i.e., formulations), duration of supplementation, sample sizes and specific outcomes assessed. This again suggests that further studies are needed to better understand the specific formulations, dosages and markers of effectiveness for omega-3 fatty acid supplementation."…

-Angela M. Zivkovic, Associate Director of Scientific Development and Translation, Foods for Health Institute, Department of Food Science and Technology, UC Davis;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030645/

Surgery

"Objective: Polyunsaturated fatty acid supplementation may produce beneficial effects after surgery. We investigated the influence of preoperative administration of a supplement rich in arginine, omega-3 fatty acids, and RNA, Impact (Japan), on inflammatory and immune responses in patients undergoing major surgery for cancer."…

"Results: After taking the supplement, significant increases in omega-3 fatty acids and rapid turnover proteins were found the day after ending supplementation (POD-0), whereas thromboxane B(2) levels and the ratio of omega-6 fatty acids to omega-3 fatty acids were significantly lower than before supplementation ($P < 0.001$). On POD-0 only, inflammatory markers and cytokine receptors in the supplement group showed low levels in comparison with the control group ($P < 0.05$). On POD-1 and POD-3, remarkable decreases in polymorphonuclear leukocyte-elastase and interleukin-8 in the supplement group were observed.

Conclusion: Our findings suggest that oral administration of a supplement rich in omega-3 fatty acids for 5 d before surgery may improve not only preoperative nutritional status but also preoperative and postoperative inflammatory and immune responses in patients who have cancer."

-Department of Clinical Pharmacy and Pharmacology, Graduate School of Medical and Dental Sciences, Kagoshima University, Japan
https://pubmed.ncbi.nlm.nih.gov/15925286/

See also Supplements

Synaptic Plasticity

Endocannabinoid signaling and synaptic function

"Endocannabinoids are key modulators of synaptic function. By activating cannabinoid receptors expressed in the central nervous system, these lipid messengers can regulate several neural functions and behaviors. As experimental tools advance, the repertoire of known endocannabinoid-mediated effects at the synapse, and their underlying mechanism, continues to expand. Retrograde signaling is the principal mode by which endocannabinoids mediate short- and long-term forms of plasticity at both excitatory and inhibitory synapses. However, growing evidence suggests that endocannabinoids can also signal in a non-retrograde manner. In addition to mediating synaptic plasticity, the endocannabinoid system is itself subject to plastic changes. Multiple points of interaction with other neuromodulatory and signaling systems have now been identified. Synaptic endocannabinoid signaling is thus mechanistically more complex and diverse than originally thought. In this review, we focus on new advances in endocannabinoid signaling and highlight their role as potent regulators of synaptic function in the mammalian brain."

-Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY 10461
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3517813

Supply and demand for endocannabinoids

"The endocannabinoid system consists of G-protein coupled cannabinoid receptors that can be activated by cannabis-derived drugs and small lipids called endocannabinoids, plus associated biochemical machinery (precursors, synthetic and degradative enzymes, transporters). The endocannabinoid system in the brain primarily influences neuronal synaptic communication, and affects biological – functions including eating, anxiety, learning and memory, growth and development – via an array of actions throughout the nervous system. While many aspects of synaptic regulation by endocannabinoids are becoming clear, details of the subcellular organization and regulation of the endocannabinoid system are less well understood. This review focuses on recent investigations that illuminate fundamental issues of endocannabinoid storage, release, and functional roles."….

Endocannabinoids as retrograde messengers for synaptic plasticity

"In the central nervous system, the active agent in cannabis preparations (marijuana, hashish, etc), Δ9-tetrahydrocannabinol (THC) [1], mainly activates the type 1 cannabinoid receptor (CB1R),

a G-protein-coupled receptor (GPCR) often found in high density on certain presynaptic nerve terminals. Two fatty acid derivatives, N-arachidonoyl-ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), are the major endogenous ligands for CB1R. Endocannabinoids have numerous functions, and it is useful to distinguish between intercellular "signaling", "growth-related or metabolic", and "housekeeping" [2] roles. At synapses, endocannabinoids generally decrease neurotransmitter release via transient retrograde actions (Box 1) that are mainly detected electrophysiologically. Growth-related or metabolic actions take place over longer time periods and are detected with morphological or behavioral methods. In housekeeping roles, endocannabinoids are precursors or products of chemical processes not directly related to CB1R activation. Growth-regulation and housekeeping are considered "non-signaling" functions."

- *Department of Physiology, University of Maryland School of Medicine, 655 W. Baltimore St., Baltimore, MD, USA*
- *Program in Neuroscience, University of Maryland School of Medicine, 655 W. Baltimore St., Baltimore, MD, USA*
- *Institute of Molecular Medicine and Genetics, Medical College of Georgia, Georgia Health Sciences University, GA*
- *Graduate Program in Neuroscience, Medical College of Georgia, Georgia Health Sciences University, Augusta, GA*
- *Department of Neurology, Medical College of Georgia, Georgia Health Sciences University, Augusta, GA*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3106144

Endocannabinoids and synaptic function in the CNS

"Marijuana affects neural functions through the binding of its active component (Delta(9)-THC) to cannabinoid receptors in the CNS. Recent studies have elucidated that endogenous ligands for cannabinoid receptors, endocannabinoids, serve as retrograde messengers at central synapses. Endocannabinoids are produced on demand in activity-dependent manners and released from postsynaptic neurons. The released endocannabinoids travel backward across the synapse, activate presynaptic CB1 cannabinoid receptors, and modulate presynaptic functions. Retrograde endocannabinoid signaling is crucial for certain forms of short-term and long-term synaptic plasticity at excitatory or inhibitory synapses in many brain regions, and thereby contributes to various aspects of brain function including learning and memory. Molecular identities of the CB1 receptor and enzymes involved in production and degradation of endocannabinoids have been elucidated. Anatomical studies have demonstrated unique distributions of these molecules around synapses, which provide morphological bases for the roles of endocannabinoids as retrograde messengers. CB1-knockout mice exhibit various behavioral abnormalities and multiple defects in synaptic plasticity, supporting the notion that endocannabinoid signaling is involved in various aspects of neural function. In this review article, the authors describe molecular mechanisms of the endocannabinoid-mediated synaptic modulation and its possible physiological significance."

-Department of Neurophysiology, Graduate School of Medicine, Osaka University, Suita, Japan.
https://pubmed.ncbi.nlm.nih.gov/17404373

Synovial Membrane

"A synovial membrane surrounds moveable joints. Inside the membrane synovial fluid lubricates and nourishes joint tissue, such as cartilage."

-Nucleus Medical Media
https://www.youtube.com/watch?v=Yc-9dfem3lM

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…"Many members of the endocannabinoid system are reported to inhibit synovial inflammation, hyperplasia, and cartilage destruction in RA. In particular, specific activation of CB2 may relieve RA by inhibiting not only the production of autoantibodies, proinflammatory cytokines, and MMPs, but also bone erosion, immune response mediated by T cells, and the proliferation of FLSs. In this review, we will discuss the possible functions of the endocannabinoid system in the modulation of RA, which may be a potential target for treatment."

-Department of Pharmacy, Children's Hospital of Soochow University, Suzhou, China; Department of Rheumatology & Immunology, Changhai Hospital, Second Military Medical University, Shanghai, China.

-Department of Rheumatology & Immunology, Changhai Hospital, Second Military Medical University, Shanghai, China.

-Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, USA; Division of Pain Medicine, Mayo Clinic, Rochester, MN, USA.

-Department of Pharmacy, Children's Hospital of Soochow University, Suzhou, China.

-Department of Rheumatology & Immunology, Changhai Hospital, Second Military Medical University, Shanghai, China.

https://www.ncbi.nlm.nih.gov/pubmed/25791728

Synovial fluid and plasma n3 [omega-3] long chain polyunsaturated fatty acids in patients with inflammatory arthritis.

…"Relationships between n-3 [omega-3] long chain polyunsaturated fatty acids (LC-PUFA) in plasma and synovial fluid (SF) were examined in 36 patients with knee effusion within the context of a variety of rheumatic diagnoses and various stated fish oil (FO) intakes (from 0 to 30mL of standard FO daily) of variable duration. In a sub-group of patients, correlations between PUFA in SF mononuclear cells (MNC) and cell-free supernatants of SF and between SF MNC and

peripheral blood (PB) MNC were examined."

…"In conclusion, plasma n-3 LC-PUFA is a strong indicator of SF n-3 LC-PUFA status across a broad range of rheumatic diagnoses and FO intakes. Higher n-3 LC-PUFA in plasma and SF were associated with lesser pain experience."

-Arthritis Research Laboratory, Hanson Institute, SA Pathology, Adelaide, South Australia 5000, Australia
-Discipline of Medicine, University of Adelaide, Adelaide, South Australia 5000, Australia;
-Rheumatology Unit, Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia. Electronic
https://www.ncbi.nlm.nih.gov/pubmed/25817850

Synthetic Cannabinoids & Derivatives

Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities.

"Human tissues express cannabinoid CB(1) and CB(2) receptors that can be activated by endogenously released 'endocannabinoids' or exogenously administered compounds in a manner that reduces the symptoms or opposes the underlying causes of several disorders in need of effective therapy. Three medicines that activate cannabinoid CB(1)/CB(2) receptors are now in the clinic: Cesamet (nabilone), Marinol (dronabinol; Δ(9)-tetrahydrocannabinol (Δ(9)-THC)) and Sativex (Δ(9)-THC with cannabidiol). These can be prescribed for the amelioration of chemotherapy-induced nausea and vomiting (Cesamet and Marinol), stimulation of appetite (Marinol) and symptomatic relief of cancer pain and/or management of neuropathic pain and spasticity in adults with multiple sclerosis (Sativex). This review mentions several possible additional therapeutic targets for cannabinoid receptor agonists. These include other kinds of pain, epilepsy, anxiety, depression, Parkinson's and Huntington's diseases, amyotrophic lateral sclerosis, stroke, cancer, drug dependence, glaucoma, autoimmune uveitis, osteoporosis, sepsis, and hepatic, renal, intestinal and cardiovascular disorders. It also describes potential strategies for improving the efficacy and/or benefit-to-risk ratio of these agonists in the clinic. These are strategies that involve (i) targeting cannabinoid receptors located outside the blood-brain barrier, (ii) targeting cannabinoid receptors expressed by a particular tissue, (iii) targeting upregulated cannabinoid receptors, (iv) selectively targeting cannabinoid CB(2) receptors, and/or (v) adjunctive 'multi-targeting'."

School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK.
https://www.ncbi.nlm.nih.gov/pubmed/23108552

Plant, synthetic, and endogenous cannabinoids in medicine

"Although used for more than 4000 years for recreational and medicinal purposes, Cannabis and its best-known pharmacologically active constituents, the cannabinoids, became a protagonist in medical research only recently. This revival of interest is explained by the finding in the 1990s of the mechanism of action of the main psychotropic cannabinoid, Delta9-tetrahydrocannabinol (THC), which acts through specific membrane receptors, the cannabinoid receptors. The molecular characterization of these receptors allowed the development of synthetic molecules with cannabinoid and noncannabinoid structure and with higher selectivity, metabolic stability, and efficacy than THC, as well as the development of antagonists that have already found pharmaceutical application. The finding of endogenous agonists at these receptors, the endocannabinoids, opened new therapeutic possibilities through the modulation of the activity of cannabinoid receptors by targeting the biochemical mechanisms controlling endocannabinoid tissue levels."

-Endocannabinoid Research Group, Institutes of Biomolecular Chemistry, National Research Council, Via Campi Flegrei

https://pubmed.ncbi.nlm.nih.gov/16409166/

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…"Pharmacological manipulation of the ECS, however, has its problems and caveats. The CB1 antagonist rimonabant (Acomplia [Sanofi-Aventis, United Kingdom]) had already been introduced as an anti-obesity drug, but was withdrawn from the market due to its serious psychoactive side effects including sedation, drowsiness, depression and paranoia. This exemplifies the primary obstacle to the pharmacological exploitation of CB1 ligands: unwanted central effects that are only overcome if CB1 ligands are prevented from crossing the blood-brain barrier, or if they are chemically modified such that their psychoactive effects are mitigated. It is not certain whether ligands remain fully effective if their actions are restricted only to peripheral CB receptors. The generation of CB1 ligands that predominantly act at peripheral sites will be an important step toward the clinical use of these drugs. Because expression of CB2 in the central nervous system is low, targeting of CB2 receptors will be less of a problem. The absence of unwanted psychoactivity suggests that CB2 agonists may be useful drugs for GI inflammation. The discovery of novel CB receptors and proteins that regulate endoCB metabolism will expand the definition of the ECS and will offer new therapeutic targets to reduce the problem of unwanted psychoactive effects associated with CB treatment."

-Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Austria;
-Division of Gastroenterology, Department of Medicine, University of Calgary, Calgary, Alberta;
-Department of Medicine, Ludwig Maximilians University, Munich, Germany

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3174079/

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…"Recent reports of serious adverse effects from synthetic cannabinoids highlight the need for additional investigation of cannabinoids to establish their efficacy and safety."…

"For cannabis in particular, additional investigation regarding appropriate dosing and timing, given known adverse effects of its chronic use, and careful monitoring of potential bleeding complications with synthetic cannabinoids are imperative."

-Department of Medicine, Division of Gastroenterology and Hepatology, University of Maryland School of Medicine, Baltimore, MD, USA.

https://pubmed.ncbi.nlm.nih.gov/30635796/

Endocannabinoid System: A Multi-Facet Therapeutic Target

"Cannabis sativa is also popularly known as marijuana. It has been cultivated and used by man for recreational and medicinal purposes since many centuries. Study of cannabinoids was at bay for very long time and its therapeutic value could not be adequately harnessed due to its legal status as proscribed drug in most of the countries. The research of drugs acting on endocannabinoid system has seen many ups and downs in the recent past. Presently, it is known that endocannabinoids has role in pathology of many disorders and they also serve "protective role" in many medical conditions. Several diseases like emesis, pain, inflammation, multiple sclerosis, anorexia, epilepsy, glaucoma, schizophrenia, cardiovascular disorders, cancer, obesity, metabolic syndrome related diseases, Parkinson's disease, Huntington's disease, Alzheimer's disease and Tourette's syndrome could possibly be treated by drugs modulating endocannabinoid system. Presently, cannabinoid receptor agonists like nabilone and dronabinol are used for reducing the chemotherapy induced vomiting. Sativex (cannabidiol and THC combination) is approved in the UK, Spain and New Zealand to treat spasticity due to multiple sclerosis. In US it is under investigation for cancer pain, another drug Epidiolex (cannabidiol) is also under investigation in US for childhood seizures. Rimonabant, CB1 receptor antagonist appeared as a promising anti-obesity drug during clinical trials but it also exhibited remarkable psychiatric side effect profile. Due to which the US Food and Drug Administration did not approve Rimonabant in US. It sale was also suspended across the EU in 2008. Recent discontinuation of clinical trial related to FAAH inhibitor due to occurrence of serious adverse events in the participating subjects could be discouraging for the research fraternity. Despite some mishaps in clinical trials related to drugs acting on endocannabinoid system, still lot of research is being carried out to explore and establish the therapeutic targets for both

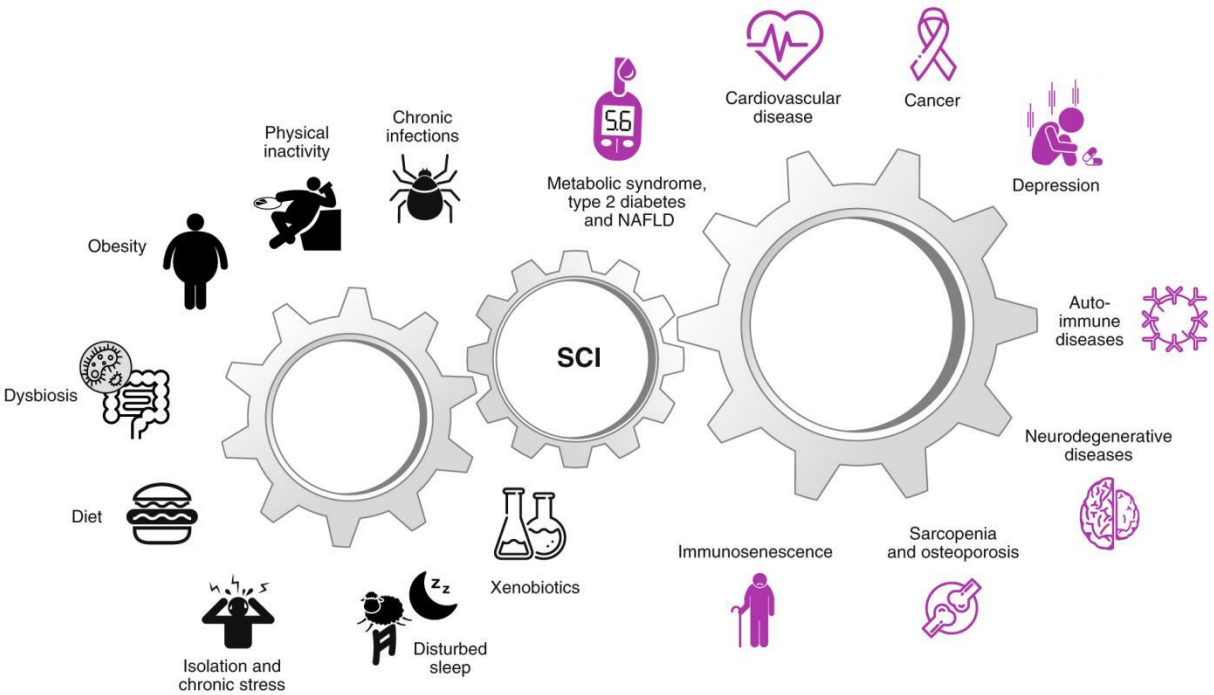
cannabinoid receptor agonists and antagonists. One challenge is to develop drugs that target only cannabinoid receptors in a particular tissue and another is to invent drugs that act selectively on cannabinoid receptors located outside the blood brain barrier. Besides this, development of the suitable dosage forms with maximum efficacy and minimum adverse effects is also warranted. Another angle to be introspected for therapeutic abilities of this group of drugs is non-CB1 and non-CB2 receptor targets for cannabinoids. In order to successfully exploit the therapeutic potential of endocannabinoid system, it is imperative to further characterize the endocannabinoid system in terms of identification of the exact cellular location of cannabinoid receptors and their role as "protective" and "disease inducing substance", time-dependent changes in the expression of cannabinoid receptors."

-Department of Pharmacology, AIIMS, Jodhpur, Rajasthan, India.
https://pubmed.ncbi.nlm.nih.gov/27086601/

See also Acetaminophen, AM404

Systemic Chronic Inflammation / Systemic Inflammatory Disease

Causes and consequences of low-grade systemic chronic inflammation.



…"Several causes of low-grade systemic chronic inflammation (SCI) and their consequences have been identified. As shown on the left, the most common triggers of SCI (in counter-clockwise direction) include chronic infections, physical inactivity, (visceral) obesity, intestinal dysbiosis, diet, social isolation, psychological stress, disturbed sleep and disrupted circadian rhythm, and exposure to xenobiotics such as air pollutants, hazardous waste products, industrial chemicals and tobacco smoking. As shown on the right, the consequences of SCI (in clockwise direction) include metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, cancer, depression, autoimmune diseases, neurodegenerative diseases, sarcopenia, osteoporosis and immunosenescence."…

-Buck Institute for Research on Aging, Novato, CA, USA.

-Stanford 1000 Immunomes Project, Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, CA, USA.

-Institute for Research in Translational Medicine, Universidad Austral, CONICET, Pilar, Buenos Aires, Argentina.

-Iuve Inc., San Mateo, CA, USA.

-Lawrence Berkeley National Laboratory, Berkeley, CA, USA.

-Center for Primary Health Care Research, Lund University/Region Skåne, Skåne University Hospital, Malmö, Sweden.

-Medical Scientist Training Program, University of California, San Francisco, San Francisco, CA, USA.

-IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy.

-Department of Applied Mathematics and Laboratory of Systems Biology of Aging, Lobachevsky University, Nizhny Novgorod, Russia.

-Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA.

-Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, University College London, London, UK.

-MassGeneral Hospital for Children, Harvard Medical School, Boston, MA, USA.

-Department of Environmental Health Sciences, School of Public Health, Columbia University Medical Center, New York, NY, USA.

-Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA.

-Humanitas Clinical and Research Center, Rozzano, Milan, Italy.

-Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy.

-William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University, London, UK.

-Division of Immunology and Rheumatology, Department of Medicine, Stanford University, Stanford, CA, USA.

-Departments of Medicine and Genetics, Albert Einstein College of Medicine, New York, NY, USA.

-Paul F. Glenn Center for the Biology of Aging, Stanford University School of Medicine, Stanford, CA, USA.

-Center for Tissue Regeneration, Repair and Restoration, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA.

-Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA.

-Department of Pathology, University of California, Los Angeles, Los Angeles, CA, USA.

-Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain.

-Research Institute of the Hospital 12 de Octubre (i+12), Madrid, Spain.

-Biostatistics and Computational Biology Branch, Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA.

-NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental

Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA.

-Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147972/

Why and How Meet n-3 PUFA Dietary Recommendations?

"Obesity and the metabolic syndrome are systemic inflammatory diseases reaching epidemic proportions. Contemporary changes in human nutrition occurred characterized by increased consumption of fat and of vegetable oils rich in n-6 polyunsaturated fatty acids (PUFAs) together with decrease in n-3 PUFA-rich foods, resulting in an n-6/n-3 ratio of 10–20/1 in Western diet for a ratio around 1/1 in the diet of our ancestors. The literature provides compelling evidence for the health benefit of n-3 PUFA consumption on inflammation and metabolic syndrome prevention and treatment. Such evidence led to the establishment of comprehensive recommendations. However, we show here that, both in collective catering proposed to children and in hospital diet, it is not straightforward to meet such recommendations. Willingness of governments to institute changes, with accountable decisions on catering, nutritional education, and food processing, is required to face our neglected responsibility in promoting balanced diet and consumption of foods rich in essential nutrients in the general population."

-Laboratory of Hepato-Gastroenterology, Institute for Experimental and Clinical Research, Catholic University of Louvain (UCL), GAEN 53/79 Avenue Mounier, 53, 1200 Brussels, Belgium

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3004387/

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…"High-dose Ω-3 appeared to be beneficial in multiple studies, in addition to the results produced by REDUCE-IT. OMEGA-REMODEL found that 4 g/day Ω-3 (EPA + DHA) for 6 months after acute MI demonstrated a reduction in adverse left ventricular remodeling, non-infarct myocardial fibrosis and serum biomarkers of systemic inflammation beyond the current guideline-based standard of care [25]."…

-Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA, USA

-Tulane Medical Center, New Orleans, LA, USA;

-Director Medical and Scientific Communications, Pharmavite LLC., West Hills, CA, USA;

-Saint Luke's of Kansas City, Mid America Heart Institute, University of Missouri, Kansas City, MO, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7827286/

Systemic Lupus

"When people use the term "lupus," they usually refer to systemic lupus erythematosus, or "SLE." Throughout this website, the term "lupus" is used to signal systemic lupus, since SLE constitutes the most common form of the disease. Systemic lupus is so-named because it affects many different organ systems in the body."

-John's Hopkins Lupus Center
https://www.hopkinslupus.org/lupus-info/types-lupus/

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Takayasu Disease

"Takayasu arteritis (pulseless disease) is a systemic inflammatory condition characterized by damage to the large and medium arteries and their branches. It presents at first with nonspecific constitutional symptoms such as fever, malaise, weight loss, and anorexia. Other presentations such as hypertension, neurologic manifestations, and upper limb claudication occur secondary to arterial insufficiency. This activity illustrates the evaluation and management of Takayasu arteritis and explains the role of the interprofessional team in improving care for patients with this condition."…

- University of Arizona Medical Center
- University of Massachusetts Memorial Medical Center
- Michigan State University
https://www.ncbi.nlm.nih.gov/books/NBK459127/

Tart Cherry

Tart cherry anthocyanins suppress inflammation-induced pain behavior in rat

…"These data suggest that tart cherry anthocyanins may have a beneficial role in the treatment of inflammatory pain. The antihyperalgesic effects may be related to the anti-inflammatory and antioxidant properties of anthocyanins. A better understanding of the modulatory role of dietary constituents and phytonutrients on pain will offer further therapeutic options for treating

patients with persistent and chronic pain conditions."

-Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital

https://pubmed.ncbi.nlm.nih.gov/15219719/

An examination of anthocyanins' and anthocyanidins' affinity for cannabinoid receptors

"A growing body of evidence suggests that anthocyanins and anthocyanidins may possess analgesic properties in addition to neuroprotective and anti-inflammatory activities. These functionalities suggest a role for the cannabinoid receptor (CB) in mediating biological effects."…

-Department of Psychiatry, University of Regensburg, Regensburg, Germany.

https://pubmed.ncbi.nlm.nih.gov/20041802/

T-Cell & B-Cells

Formation of B and T cell subsets require the cannabinoid receptor CB2.

"A recent and surprising body of research has linked changes in immune function to biologic and therapeutic targeting of cannabinoid receptors, which prototypically respond to delta-9 tetrahydrocannabinol. The peripheral cannabinoid receptor CB2 is highly expressed in immune cell types (macrophages, dendritic cells, and B cells), and pharmacologically alters their cytokine production and responsiveness. Accordingly, cannabinoid agonists can powerfully alter susceptibility to certain microbial infections, atherosclerosis, and cancer immunotherapy. What is unknown is the physiologic role of natural levels of endocannabinoids and their receptors in normal immune homeostasis. Galphai2-/- mice are deficient in the formation of certain B and T cell subsets and are susceptible to immune dysregulation, notably developing inflammatory bowel disease. A key issue is the identity of the Gi-coupled receptors relevant to this Galphai2-signaling pathway. We find that mice deficient in CB2, the Gi-coupled peripheral endocannabinoid receptor, have profound deficiencies in splenic marginal zone, peritoneal B1a cells, splenic memory CD4+ T cells, and intestinal natural killer cells and natural killer T cells. These findings partially phenocopy and extend the lymphocyte developmental disorder associated with the Galphai2-/- genotype, and suggest that the endocannabinoid system is required for the formation of T and B cell subsets involved in immune homeostasis. This noncompensatable requirement for physiologic function of the endocannabinoid system is novel. Because levels of endocannabinoids are highly restricted microanatomically, local regulation of their production and receptor expression offers a new principle for regional immune

homeostasis and disease susceptibility, and extends and refines the rationale for CB2-targeted immunotherapy in immune and inflammatory diseases."

-Department of Pediatrics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA.

https://www.ncbi.nlm.nih.gov/pubmed/16924491

Cannabinoids and the immune system

"The effect of cannabimimetic agents on the function of immune cells such as T and B lymphocytes, natural killer cells and macrophages has been extensively studied over the past several decades using human and animal paradigms involving whole animal models as well as tissue culture systems. From this work, it can be concluded that these drugs have subtle yet complex effects on immune cell function and that some of the drug activity is mediated by cannabinoid receptors expressed on the various immune cell subtypes. However, the overall role of the cannabinoid system of receptors and ligands in human health and disease is still unclear and requires extensive elucidation. Further studies will define the precise structure and function of the putative immunocannabinoid system, the potential therapeutic usefulness of these drugs in chronic diseases such as acquired immune deficiency syndrome and multiple sclerosis, the effects of these agents on tumour growth and induction of apoptosis, and the potential anti-inflammatory and proinflammatory properties of cannabimimetic compounds. It is likely that the cannabinoid system, along with other neuroimmune systems, has a subtle but significant role in the regulation of immunity and that this role can eventually be exploited in the management of human disease."

-University of South Florida, College of Medicine, Tampa, Florida, USA

https://www.ncbi.nlm.nih.gov/pubmed/11854771

Cannabinoids and the immune system: an overview.

Cannabinoids can influence the immune network. Data on the impact of exogenous cannabinoid ligands on immune function serve not only to understand how the endocannabinoid system modulates immune phenomena associated with infection or inflammation, but also to identify therapeutic targets for immune diseases. Cannabinoids can modulate immune reactions in the periphery but also in the brain, influence T cell subset balance and cytokine expression and play a role in the balance between neuroinflammation and neurodegeneration. Immune cells can synthesize endocannabinoids and also be influenced by cannabinoid analogues. Cannabinoid

receptors show different expression on immune cells depending on activation status and stimuli. The complexity of relation between cannabinoid ligands of various classes and cannabinoid receptors brought the need to refine the simple conceptual frame of agonist-antagonists and offered potential implications for understanding interactions in pathological conditions. The immune influence of cannabinoid ligands is not fully elucidated. However, aspects of their immunomodulatory effects provide the basis for a context-dependent targeted therapeutic approach, thus leading to the possibility for the use of cannabinoids in the treatment of inflammatory disease.

-Department of Neurology, Colentina Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

https://www.ncbi.nlm.nih.gov/pubmed/20153077

Terpenes

…"Exogenous plant-based cannabinoids (phytocannabinoids) and chemically related compounds, like the terpenes, commonly found in many foods, have been found to exert significant analgesic effects in various chronic pain conditions. "…

-Professor of Anesthesiology, Pain Research and Management Centers, Department of Anesthesiology, School of Medicine, University of Utah, Salt Lake City, Utah, USA

-Chief Executive Officer, ISA Scientific, Draper, Utah, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3820295/

The Anti-Inflammatory Properties of Terpenoids from Cannabis

…"The different Cannabis chemotypes showed distinct compositions of terpenoids. The terpenoid-rich essential oils exert anti-inflammatory and antinociceptive activities in vitro and in vivo, which vary according to their composition. Their effects seem to act independent of TNFα. None of the essential oils was as effective as purified CBD. In contrast to CBD that exerts prolonged immunosuppression and might be used in chronic inflammation, the terpenoids showed only a transient immunosuppression and might thus be used to relieve acute inflammation."

-The Lautenberg Center for General and Tumor Immunology, The Hadassah Medical School, The Hebrew University of Jerusalem, Jerusalem, Israel.

-Department of Medicinal and Natural Products, Institute for Drug Research, The Hadassah Medical School, The Hebrew University of Jerusalem, Jerusalem, Israel.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6308289/

See also Beta-caryophyllene (β-caryophyllene)

Testicular Cancer

…"Prostate cancer is about 25 times more common than testicular cancer, and we know much more about its risk factors. But testicular cancer is on the rise, and scientists are starting to ask if diet may have a role in the disease, which tends to strike white males between the ages of 20 and 35. One study evaluated the impact of diet on testicular cancer. Only dairy products were linked to an increased risk; cheese was a particular culprit.

More study is needed, but for now, it appears that like older men at risk for prostate cancer, young men at risk for testicular cancer who don't say "cheese" when planning their menus may have the last smile."

-Harvard Health Publishing, Harvard Medical School
https://www.health.harvard.edu/cancer/on-call-diet-testicular-cancer-and-prostate-cancer

Cyclooxygenase-1 and -2 in human testicular tumours

"In this study, we investigated the expression of cyclooxygenase (COX)-1 and -2 in human testicular cancer (TC) and normal testis (NT) tissues, as well as the effects of COX ligands on viability and proliferation. Tumour specimens were obtained from 72 patients with TC and 20 patients with NT. RT-PCR and immunohistochemical methods were used to determine COX expression. While COX expression was not noted in any of the NT tissues, a marked expression was observed in the TC samples. The extent and intensity of immunoreactive COX-1 and -2 polypeptides in the TC tissues was statistically greater than the expression in the NT tissues. The synthetic COX inhibitors inhibited the growth of the TC cells. Both COX-1 and COX-2 are induced in testicular cancer, and these results indicate that both COX-1 and COX-2 are essential for the growth of TC cells."

-Department of Urology, Osaka City University Medical School, 1-4-3 Asahi-machi, Abenoku, Osaka, Japan

https://pubmed.ncbi.nlm.nih.gov/12957459/

Thallium (Metal)

"The mechanisms by which the heavy metal thallium (Tl+) produces toxicity in the brain remain unclear."…"Our results suggest that energy depletion, oxidative damage, and Na+/K+-ATPase activity inhibition account for the toxic pattern elicited by Tl+ in nerve terminals. In addition, the efficacy of the drugs employed against Tl+ toxicity supports an active role of excitatory/cannabinoid and oxidative components in the toxic pattern elicited by the metal."

-Exciting Amino Acid Laboratory, National Institute of Neurology and Neurosurgery, Mexico City, Mexico.

-University Center for Exact Sciences and Engineering, University of Guadalajara, Jalisco, Mexico.

-Escuela Superior de Medicina, Instituto Politécnico Nacional, Mexico City, Mexico.

-Department of Neurochemistry, National Institute of Neurology and Neurosurgery, Mexico City, Mexico.

-Department of Biochemistry and Molecular Biology, Faculty of Medicine and Nursing, Maimonides Institute for Biomedical Research of Córdoba (IMIBIC), University of Córdoba, Córdoba, Spain.

-Exciting Amino Acid Laboratory, National Institute of Neurology and Neurosurgery, Insurgentes Sur 3877, 14269, Mexico City, Mexico

https://www.ncbi.nlm.nih.gov/pubmed/29313218

THC (Delta^{9}-tetrahydrocannabinol)

"Humans produce endogenous cannabinoids (endocannabinoids), a group of molecules that activate the same receptors as tetrahydrocannabinol."…

-Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, NC, USA

-Departamento de Ginecologia e Obstetrícia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4527420/

…"Although the underlying mechanism is not clear, high doses of intravenous THC appear to influence endogenous cannabinoid concentrations and presumably EC -signalling."

-Department of Anaesthesiology, Ludwig - Maximilians University of Munich, Germany.

https://www.ncbi.nlm.nih.gov/pubmed/24424856

See also Anandamide (AEA)

Thrombosis

…"In the cardiovascular system 2-AG is generated by both activated endothelial cells and platelets, and participates in the regulation of inflammation and thrombosis."…

-Department of Clinical and Experimental Medicine, University of Eastern Piedmont, Novara, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/18647220

Varying the ratio of dietary n-6/n-3 polyunsaturated fatty acid alters the tendency to thrombosis and progress of atherosclerosis in apoE-/- LDLR-/- double knockout mouse

"We have investigated the influence of dietary n-6/n-3 (ù-6/ù-3) polyunsaturated fatty acid-balance on the tendency to arterial thrombosis and the progress of atherosclerosis in apoE-/- LDLR-/- double knockout mouse. "…

"The degree of atherosclerosis was measured using the entire aorta method employing image analysis software. The n-6/n-3 ratio had a dose-dependent antithrombotic effect (thrombus volume decreased 23%, Group 1 vs. Group 4), In addition, the extent of atherosclerosis was less in the animals fed a low n-6/n-3 ratio compared with the high n-6/n-3 ratio group (atherosclerotic area decreased 40%, Group 1 vs. Group 4). The lowest n-6/n-3 ratio tested (0.29) was the most effective in suppressing the thrombotic and atherosclerotic parameters in these DKO mice."

-Laboratory of Physiology, Faculty of Nutrition, and High Technology Research Center, Kobe Gakuin University, Kobe, Japan.
https://pubmed.ncbi.nlm.nih.gov/16122552

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"**Background:** The endocannabinoid system has previously been implicated in the regulation of neurons and inflammatory cells. Additionally, it has been reported that endocannabinoid receptors are present on circulating platelets, but there has been conflicting evidence on their contribution to platelet function.
Objectives: Our aim was to examine the role of endocannabinoids in platelet function in vitro and in vivo.

Methods and results: We studied the effects of the well-characterized endogenous endocannabinoid anandamide on platelet aggregation in suspension, α-granule release, calcium mobilization, Syk phosphorylation, as well as platelet spreading and aggregate formation under flow. Anandamide inhibits platelet aggregation and α-granule release by collagen, collagen-derived peptide CRP-XL, ADP, arachidonic acid and thromboxane A2 analogue U46619. However, activation via thrombin receptor PAR-1 stays largely unaffected. Calcium mobilization is significantly impaired when platelets are stimulated with collagen or CRP-XL, but remains normal in the presence of the other agonists. In line with this finding, we found that anandamide prevents collagen-induced Syk phosphorylation. Furthermore, anandamide-treated platelets exhibit reduced spreading on immobilized fibrinogen, have a decreased capacity for binding fibrinogen in solution and show perturbed platelet aggregate formation under flow over collagen. Finally, we investigated the influence of Cannabis sativa consumption by human volunteers on platelet activation. Similar to our in vitro findings with anandamide, ex vivo collagen-induced platelet aggregation and aggregate formation on immobilized collagen under flow were impaired in whole blood of donors that had consumed Cannabis sativa.

Conclusions: Endocannabinoid receptor agonists reduce platelet activation and aggregate formation both in vitro and ex vivo after Cannabis sativa consumption. Further elucidation of this novel regulatory mechanism for platelet function may prove beneficial in the search for new antithrombotic therapies."

-Department of Clinical Chemistry and Haematology, Utrecht University Medical Center, Utrecht, The Netherlands.
https://pubmed.ncbi.nlm.nih.gov/25264625

Mechanism of platelet activation induced by endocannabinoids in blood and plasma

"Platelets play a central role in atherosclerosis and atherothrombosis, and circulating endocannabinoids might modulate platelet function. Previous studies concerning effects of anandamide (N-arachidonylethanolamide) and 2-arachidonoylglycerol (2-AG) on platelets, mainly performed on isolated cells, provided conflicting results. We therefore investigated the action of three main endocannabinoids [anandamide, 2-AG and virodhamine (arachidonoylethanolamine)] on human platelets in blood and platelet-rich plasma (PRP). 2-AG and virodhamine induced platelet aggregation in blood, and shape change, aggregation and adenosine triphosphate (ATP) secretion in PRP. The EC50 of 2-AG and virodhamine for platelet aggregation in blood was 97 and 160 μM, respectively. Lower concentrations of 2-AG (20 μM)

and virodhamine (50 µM) synergistically induced aggregation with other platelet stimuli. Platelet activation induced by 2-AG and virodhamine resembled arachidonic acid (AA)-induced aggregation: shape change, the first platelet response, ATP secretion and aggregation induced by 2-AG and virodhamine were all blocked by acetylsalicylic acid (ASA) or the specific thromboxane A2 (TXA2) antagonist daltroban. In addition, platelet activation induced by 2-AG and virodhamine in blood and PRP were inhibited by JZL184, a selective inhibitor of monoacylglycerol lipase (MAGL). In contrast to 2-AG and virodhamine, anandamide, a substrate of fatty acid amidohydrolase, was inactive. Synthetic cannabinoid receptor subtype 1 (CB1) and 2 (CB2) agonists lacked stimulatory as well as inhibitory platelet activity. We conclude that 2-AG and virodhamine stimulate platelets in blood and PRP by a MAGL-triggered mechanism leading to free AA and its metabolism by platelet cyclooxygenase-1/thromboxane synthase to TXA2. CB1, CB2 or non-CB1/CB2 receptors are not involved. Our results imply that ASA and MAGL inhibitors will protect platelets from activation by high endocannabinoid levels, and that pharmacological CB1- and CB2-receptor ligands will not affect platelets and platelet-dependent progression and complications of cardiovascular diseases."

-Institute for Prevention of Cardiovascular Diseases, Ludwig Maximilians University of Munich , Munich , Germany.
https://pubmed.ncbi.nlm.nih.gov/23789792

Regulation of platelet function and thrombosis by omega-3 and omega-6 polyunsaturated fatty acids

"Thrombosis is the most common underlying pathology responsible for morbidity and mortality in cardiovascular disease (CVD). Platelet adhesion, activation, and aggregation play central roles in hemostasis; however, the same process may also cause thrombosis and vessel occlusion at the site of ruptured atherosclerotic lesions leading to heart attack and stroke. ω-3 and ω-6 polyunsaturated fatty acids (PUFAs) are an essential component of the platelet phospholipid membrane and play a major role in many aspects of platelet function. Dietary supplementation of ω-3 and ω-6 PUFAs has long been used to slow the progression of CVD and to prevent acute cardiovascular events. Despite this, the role of ω-3 and ω-6 PUFAs and their oxylipin metabolites in platelet function remains controversial due to the lack in our understanding of the mechanistic regulation controlling platelet reactivity in vitro and substantial evidence for PUFA regulation of thrombotic events in vivo. In this review, we will outline the role of platelet physiology in hemostasis and the effect of ω-3 and ω-6 PUFAs on platelet function, with special emphasis on in vivo effects on hemostasis and thrombosis due to the role of PUFAs and their bioactive lipids in circulation. Further, recent mechanistic insights and evidence for cardio-protective effects of PUFAs and their bioactive lipids will be discussed."

-Department of Pharmacology, University of Michigan, Ann Arbor, MI
-Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6242736

See also 2-AG , Atherosclerosis

Thyroid Disease

"The oxidative processes (oxygen consumption, superoxoid anion generation, arachidonic acid cascade) of human polymorphonuclear granulocytes (PMNs) obtained from patients suffering from thyroid disorders of autoimmune origin (Graves' disease and Hashimoto's thyroiditis), and non autoimmune origin (toxic adenoma) were investigated. All Graves' and toxic adenoma patients were hyperthyroid. Hashimoto's thyroiditis patients were euthyroid. Healthy age and sex matched volunteers served as controls. The results are as follows: 1) In PMNs from both hyperthyroid groups (Graves' disease and toxic adenoma), independently from the autoimmune origin of the disease, a significantly increased Antimycin A sensitive mitochondrial oxygen consumption and a slightly increased superoxide anion generation were detected. 2) In both autoimmune thyroid disease groups (Graves' disease and Hashimoto's thyroiditis)--depending on the functional state of the thyroid gland--a significantly altered intracellular killing activity was measured. 3) An increased arachidonic acid cascade--triggered by opsonized zymozan (OZ)--was detected in both autoimmune thyroid diseases. The increased arachidonic acid cascade was sensitive to phospholipase A2 inhibiting Mepacrin treatment. 4) The PMNs from both autoimmune thyroid diseases produced large amount of leukotriens (LTs)--LTC4 and LTB4--after stimulation through their Fc receptors but the synthesis of prostagalandins (PGs) has not changed. There are no data indicating local, specific effects of circulating leukotriens in the thyroid gland itself, but based on authors' data, their general, regulating role on both the endocrine-- as well as on the immune system--seems to be plausible."

-First Department of Medicine, University Medical School, Debrecen, Hungary.
https://pubmed.ncbi.nlm.nih.gov/8740942/

Tinnitus

TINNITUS: A MAJOR SCIENTIFIC BREAKTHROUGH

…"Given that most cases of tinnitus originate in the periphery of the inner ear, the cochlea, a crucial hearing organ, is of interest as a "tinnitus generator." From this conclusion, two animal research protocols were developed. The first involved the injection of high doses of salicylate, a component of aspirin. The second involved overexposure to noise. Salicylate-induced tinnitus proved to be easily controllable. Once the salicylate was stopped, the tinnitus disappeared.

On the other hand, exposure to high noise levels creates long-term and generally irreversible tinnitus. Not all subjects, human or animal, developed tinnitus after exposure to loud noises. However, both research models helped us understand the mechanisms behind the first phase of tinnitus. The electrical transmission of nerve impulses between the cilia and the cochlea and the primary auditory neurons themselves have become areas of interest when it comes to initiating tinnitus. When observing the effects of salicylate on rats, an abnormal nervous signal was discovered. **Salicylate inhibits an enzyme called cyclooxygenase, which increases arachidonic acid in the membranes of cochlear cilia. Certain glutamate receptors (NMDA) are particularly sensitive to the presence of this acid in the lipid composition of these cells' membranes.**"…

-Translated transcription of a speech given by Matthieu J. Guitton, researcher and professor at Laval University's Faculty of Medicine, before the Association des malentendants du Québec (AMQ) on March 21, 2012.
https://www.lobe.ca/en/blog/protect-my-hearing/tinnitus-scientific-breakthrough

Tissue Remodeling

"Human aortic aneurysms have been associated with inflammation and vascular remodeling. Since the endocannabinoid system modulates inflammation and tissue remodeling, we investigated its components in human aortic aneurysms."…

"Several experimental and clinical studies showed association between endocannabinoids and tissue remodeling [15, 17], and we therefore compared collagen and related remodeling markers between the aneurysms and controls."…

-Department of Cardiac Surgery, University Clinical Centre Bonn, Sigmund-Freud Street 25, Bonn, Germany
-Institute of Molecular Psychiatry, Life & Brain Center, Sigmund-Freud Street 25, Bonn, Germany
-Institute of Physiological Chemistry, University Medical Centre of the Johannes Gutenberg University Mainz, Duesbergweg 6, Mainz, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619808/

Titanium Dioxide

Long-term exposure to titanium dioxide nanoparticles promotes diet-induced obesity through exacerbating intestinal mucus layer damage and microbiota dysbiosis

"Titanium dioxide nanoparticles (TiO2-NPs) are commonly used as food additives, including some high-fat foods that are risk factors for obesity. However, little is known about the effects of chronic TiO2-NPs digestion in the population on high fat diet (HFD). Herein, we reported that TiO2-NPs exacerbated HFD-induced obesity by disruption of mucus layer and alterations of gut microbiota. Oral intake of TiO2-NPs significantly increased body weight, liver weight, and amount of adipose tissues, especially in HFD-fed mice. Mechanistic studies revealed TiO2-NPs induced colonic mucus layer disruption and obesity-related microbiota dysbiosis. The damage on mucus was demonstrated through down-regulation of Muc2 gene and the absorption of mucin protein by TiO2-NPs. Consequently, mucus layer damage combined microbiota dysbiosis escalated the low-grade systemic inflammation, which exacerbated HFD-induced obesity. In contrast, gut microbiota depletion eliminated these effects, indicating gut microbiota were necessary for TiO2-NPs-induced inflammation and obesity. All the results stated the alarming role of TiO2-NPs in the HFD-driven obesity and emphasized the reevaluating the health impacts of nanoparticles commonly used in daily life, particularly, in susceptible population."….

-National Engineering Research Center for Nanomedicine, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan, 430074, China

-Department of Biotechnology, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan, 430074, China

-CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology of China, Beijing, 100190, China

https://link.springer.com/article/10.1007/s12274-020-3210-1

Critical review of the safety assessment of titanium dioxide additives in food

"Nanomaterial engineering provides an important technological advance that offers substantial benefits for applications not only in the production and processing, but also in the packaging and storage of food. An expanding commercialization of nanomaterials as part of the modern diet will substantially increase their oral intake worldwide. While the risk of particle inhalation received much attention, gaps of knowledge exist regarding possible adverse health effects due to gastrointestinal exposure. This problem is highlighted by pigment-grade titanium dioxide (TiO2), which confers a white color and increased opacity with an optimal particle diameter of

200–300 nm. However, size distribution analyses showed that batches of food-grade TiO2 always comprise a nano-sized fraction as inevitable byproduct of the manufacturing processes. Submicron-sized TiO2 particles, in Europe listed as E 171, are widely used as a food additive although the relevant risk assessment has never been satisfactorily completed. For example, it is not possible to derive a safe daily intake of TiO2 from the available long-term feeding studies in rodents. Also, the use of TiO2 particles in the food sector leads to highest exposures in children, but only few studies address the vulnerability of this particular age group. Extrapolation of animal studies to humans is also problematic due to knowledge gaps as to local gastrointestinal effects of TiO2 particles, primarily on the mucosa and the gut-associated lymphoid system. Tissue distributions after oral administration of TiO2 differ from other exposure routes, thus limiting the relevance of data obtained from inhalation or parenteral injections. Such difficulties and uncertainties emerging in the retrospective assessment of TiO2 particles exemplify the need for a fit-to-purpose data requirement for the future evaluation of novel nano-sized or submicron-sized particles added deliberately to food."….

"Based on these findings, the authors concluded that food-grade TiO2 particles induce a low-grade local inflammation in the mucosa that has the potential to initiate preneoplastic lesions in the colonic mucosa. An important caveat in this interpretation of the reported findings is that the relevance of abnormal crypt foci as an early precursor of colorectal cancer is controversially discussed."…

"In conclusion, the existing toxicity studies cannot completely exclude human health risks from the long-term ingestion of TiO2 particles. The above hypothetical upper safe levels for dietary intake (between 0.4 and 5 mg/kg body weight per day) calculated from rodent studies are in no way conclusive and are only meant to illustrate in quantitative terms the wide range of uncertainty in the current risk assessment of this ubiquitous food additive. Especially the estimated consumption by children suggests that, in any case, the dietary exposure to TiO2 particles should be reduced to remain, even in a worst-case exposure scenario, below this proposed lowest safety threshold of 0.4 mg/kg daily. Further studies are needed to reduce existing uncertainties."

-Institute of Food, Nutrition and Health, Department of Health Sciences and Technology, ETH Zurich, Switzerland
-Institute of Pharmacology and Toxicology, University of Zurich-Vetsuisse, Winterthurerstrasse, Zurich, Switzerland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5984422/

Effect of Long-Term Intake of Dietary Titanium Dioxide Nanoparticles on Intestine Inflammation in Mice

"Early stage exposure of foodborne substances, such as brightening agent titanium dioxide nanoparticles (TiO2 NPs), can cause long-term effects in adulthood. We aimed to explore the potential adverse effect of long-term dietary intake of TiO2 NPs. After feeding for 2–3 months from weaning, TiO2 NPs-exposed mice showed lower body weight and induced intestinal inflammation. However, this phenomenon was not observed in gut microbiota-removed mice. TiO2 NPs exposure rarely affected the diversity of microbial communities, but significantly decreased the abundance of several probiotic taxa including Bifidobacterium and Lactobacillus. Additionally, TiO2 NPs aggravated DSS-induced chronic colitis and immune response in vivo, and reduced the population of CD4+T cells, regulatory T cells, and macrophages in mesenteric lymph nodes. Therefore, dietary TiO2 NPs could interfere with the balance of immune system and dynamic of gut microbiome, which may result in low-grade intestinal inflammation and aggravated immunological response to external stimulus, thus introducing potential health risk."…

-School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, P. R. China

-Henan Business Research Institute Company, Limited, Zhengzhou 450000, P. R. China

-CAS Key Laboratory of Nutrition, Metabolism and Food safety, Shanghai Institute of Nutrition and Health, Shanghai Institutes for Biological Sciences, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200031, P. R. China

-School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, P. R. China

-Key Laboratory of Food Safety Risk Assessment, Ministry of Health, Beijing 100021, P. R. China

https://pubs.acs.org/doi/10.1021/acs.jafc.9b02391

Titanium dioxide in our everyday life; is it safe?

…"The mechanistic toxicological studies showed that TiO2 NPs induced adverse effects are predominantly mediated by oxidative stress, which may lead to cell damage, genotoxic effects, inflammatory responses and changes in cell signalling. The studies also showed that these effects strongly depend on numerous chemical and physical characteristics of the TiO2 particles: size, crystal structure, specific surface area, particle shape, purity, surface charge, solubility, agglomeration rate, photo-activation, etc. TiO2 particles are without doubt associated with the hazardous properties, and the risk for human health and environment depends on the route and extent of exposure.

Based on the widespread use of creams with SPF based on nano-sized TiO2, human exposure to TiO2 NPs by dermal applications is apparently enormous. In vitro studies with skin models showed that TiO2 NPs are taken up by keratinocytes, fibroblasts, and melanocytes, in which they

cause toxic effects that are not different from the effects observed in other cell types. Current experimental evidence indicates that TiO2 NPs do not penetrate through healthy skin and thus do not reach viable skin cells and distribute to other organs and tissues. However, the data on TiO2 NPs skin penetration during long-term or repeated exposure and in the presence of UV, which is actually characteristic for real life exposure, are insufficient. Therefore, there is no simple answer to the question regarding safety of the use of TiO2 NPs in sunscreens. The safety of the use of TiO2 in cosmetics is often argumented by the claim, that it has been used for decades without observing any adverse effects on human health. This, however, is not completely true, as no monitoring and post market health surveillance has been conducted, neither for submicron-sized nor for nano-sized TiO2 in sunscreens. Such surveillance is currently impossible, since current legislation does not require labelling whether the products contain nano-sized TiO2, which is also incorrect to customers who have no possibility to make a choice whether to use or not the sunscreen containing nano-sized TiO2. In our opinion dermal applications of TiO2 NPs as sunscreen should be limited until appropriate long-term experimental studies confirm their harmlessness."…

-Jožef Stefan Institute, Department for Nanostructured Materials, Ljubljana, Slovenia
-National Institute of Biology, Department for Genetic Toxicology and Cancer Biology, Ljubljana, Slovenia
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3423755/

Transglutaminase

Also known as "Meat Glue"

Science for food

"Professional chefs at high-end restaurants are respecting not only the chemistry, but also the biology when they add the naturally occurring enzyme transglutaminase—known on the street as "meat glue"—to bond different meats together to create new dishes and dining experiences. Meanwhile, mass-market food chains and providers of food to institutions such as hospitals, universities, schools, or prisons use transglutaminase to stretch their provisions and control costs by bonding together scraps of meat into larger portions."

-Freelance writer in Chicago, IL, USA
-Public radio reporter in Columbia, MO, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364866/

Tissue Transglutaminase and Its Product Isopeptide Are Increased in Alzheimer's Disease and APPswe/PS1dE9 Double Transgenic Mice Brains

"It has been ever hypothesized that multi-factors such as trauma [30, 31], inflammation [32, 33], or ischemic damage [34, 35] in sporadic AD [Alzheimer's Disease] or overproduction of Aβ [amyloid-β] in familial AD might lead to cross-linking of AD-related proteins. The overproduction of tTG-catalyzed protein cross-linking in turn aggravates the pathogenesis of AD progress [15]. tTG can covalently cross-link AD-related proteins including Aβ and Tau into stable and insoluble polymers by forming γ-glutamyl-ε-lysine isopeptide. Highly resistant to proteolysis, this bond can induce protein aggregation and deposition. Thus, tTG may play an important role in AD.

Previous studies have found higher levels of tTG protein or enzyme activity levels in AD compared to controls [15, 36, 14]."

…"Increasing evidence suggests that tTG plays an important role in the pathogenesis of AD."

…"These observations indicated not only that tTG may play a role in pathogenesis of AD by cross-linking proteins that form intracellular and extracellular aggregates but also opens up a new disease target and novel therapies for AD."

-Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai, China

-Department of Nutrition and Food Health, School of Public Health, Wuhan University, Wuhan, China

-Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA

-Department of Pathology and Laboratory Medicine, School of Medicine and Public Health, University of Wisconsin, 1300 University Avenue, Madison, WI, USA

-Department of Pathology (Neuropathology) and Neuroscience, Mayo Clinic College of Medicine, Jacksonville, FL USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4799778/

■■■

"Many reports have shown an increase of TGase [transglutaminase] activity in diseases associated with inflammation. These diseases include celiac disease (17), Crohn disease (18), and sporadic inclusion-body myositis (19). An increase of TGase 2 activity in these diseases might be associated with important physiological regulation such as activation of PLA_2 [phospholipase A2]."

…"Therefore, a TGase 2 **inhibitor** might have dual anti-inflammatory properties."

-Department of Ophthalmology, Asan Medical Center, Seoul, Republic of Korea

-Department of Neuroscience, Weill Medical College of Cornell University and Burke Medical Research Institute, White Plains, New York, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC151832/

"PLA2 [phospholipase A2] is essential to inflammation and the immune response.[107] Arachidonic acid is released from phospholipids by PLA2 and is further oxidized to prostaglandins or thromboxanes by the actions of COX or 5-LOX, respectively.[107] The inhibition of PLA2 by polyphenolic flavonoids has been reported in a number of in vitro and in vivo studies. Quercetin was found to be an effective inhibitor of PLA2 in human leukocytes.[9,108] Bioflavonoids such as amentoflavone, bilobetin, morelloflavone and ginkgetin derived from certain medicinal plants have been shown to inhibit PLA2 as well.[107,109] Curcumin affects arachidonic acid metabolism by blocking the phosphorylation of cytosolic PLA2, resulting in decreased COX-2 expression.[9,110] Since PLA2 is coupled with COXs and LOXs depending on the cells, PLA2 becomes the molecular target of polyphenols to cause the inhibition of COX or LOX activity and inflammation."

-Polyphenols in Human Health and Disease, 2014
https://www.sciencedirect.com/topics/neuroscience/phospholipase-a2

Traumatic Axonal Injury

Docosahexaenoic acid [omega-3 DHA] reduces traumatic axonal injury in a rodent head injury model

"Traumatic brain injury (TBI) remains the most common cause of death in persons under age 45 in the Western world. Recent evidence from animal studies suggests that supplementation with omega-3 fatty acids (O3FA) improves functional outcomes following focal neural injury. The purpose of this study is to determine the benefits of DHA supplementation following diffuse axonal injury in rats. Four groups of 10 adult male Sprague-Dawley rats were subjected to an impact acceleration injury and then received 30 days of supplementation with either 10 mg/kg/d or 40 mg/kg/d of docosahexaenoic acid (DHA). Serum fatty acid levels were determined from the isolated plasma phospholipids prior to injury and at the end of the 30 days of DHA supplementation. Following sacrifice, brainstem white matter tracts underwent fluorescent immunohistochemical processing for labeling of β-amyloid precursor protein (APP), a marker of axonal injury. Dietary supplementation with either 10 mg/kg/d or 40 mg/kg/d of DHA for 30 days results in significantly ($p < 0.05$) increased DHA serum levels of 123% and 175% over baseline, respectively. Immunohistochemical analysis reveals significantly ($p < 0.05$) decreased numbers of APP-positive axons in animals receiving dietary supplementation with DHA, 26.1 (SD 5.3) for 10 mg/kg/d, and 19.6 (SD 4.7) for 40 mg/kg/d axons per mm(2), versus 147.7 (SD 7.1) axons in

unsupplemented animals. Sham-injured animals had 6.4 (SD 13.9) APP positive axons per mm(2). Dietary supplementation with DHA increases serum levels in a dose-dependent manner. DHA supplementation significantly reduces the number of APP-positive axons at 30 days post-injury, to levels similar to seen those in uninjured animals. DHA is safe, affordable, and readily available worldwide to potentially reduce the burden of TBI."

-Department of Neurosurgery, West Virginia University School of Medicine, Morgantown, West Virginia, USA
https://pubmed.ncbi.nlm.nih.gov/20597639/

Traumatic Brain Injury

Endocannabinoids and traumatic brain injury

"Traumatic brain injury (TBI) represents the leading cause of death in young individuals. It triggers the accumulation of harmful mediators, leading to secondary damage, yet protective mechanisms are also set in motion. The endocannabinoid (eCB) system consists of ligands, such as anandamide and 2-arachidonoyl-glycerol (2-AG), receptors (e.g. CB1, CB2), transporters and enzymes, which are responsible for the 'on-demand' synthesis and degradation of these lipid mediators. There is a large body of evidence showing that eCB are markedly increased in response to pathogenic events. This fact, as well as numerous studies on experimental models of brain toxicity, neuroinflammation and trauma supports the notion that the eCB are part of the brain's compensatory or repair mechanisms. These are mediated via CB receptors signalling pathways that are linked to neuronal survival and repair. The levels of 2-AG, the most highly abundant eCB, are significantly elevated after TBI and when administered to TBI mice, 2-AG decreases brain oedema, inflammation and infarct volume and improves clinical recovery. The role of CB1 in mediating these effects was demonstrated using selective antagonists or CB1 knockout mice. CB2 were shown in other models of brain insults to reduce white blood cell rolling and adhesion, to reduce infarct size and to improve motor function. This review is focused on the role the eCB system plays as a self-neuroprotective mechanism and its potential as a basis for the development of novel therapeutic modality for the treatment of CNS pathologies with special emphasis on TBI."

-The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Israel
-Institute of Drug Research, Medical Faculty, Hebrew University of Jerusalem,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165950/

Endocannabinoids: A Promising Impact for Traumatic Brain Injury

"The endogenous cannabinoid (endocannabinoid) system regulates a diverse array of physiological processes and unsurprisingly possesses considerable potential targets for the potential treatment of numerous disease states, including two receptors (i.e., CB1 and CB2 receptors) and enzymes regulating their endogenous ligands N-arachidonoylethanolamine (anandamide) and 2-arachidonyl glycerol (2-AG). Increases in brain levels of endocannabinoids to pathogenic events suggest this system plays a role in compensatory repair mechanisms. Traumatic brain injury (TBI) pathology remains mostly refractory to currently available drugs, perhaps due to its heterogeneous nature in etiology, clinical presentation, and severity. Here, we review pre-clinical studies assessing the therapeutic potential of cannabinoids and manipulations of the endocannabinoid system to ameliorate TBI pathology. Specifically, manipulations of endocannabinoid degradative enzymes (e.g., fatty acid amide hydrolase, monoacylglycerol lipase, and α/β-hydrolase domain-6), CB1 and CB2 receptors, and their endogenous ligands have shown promise in modulating cellular and molecular hallmarks of TBI pathology such as; cell death, excitotoxicity, neuroinflammation, cerebrovascular breakdown, and cell structure and remodeling. TBI-induced behavioral deficits, such as learning and memory, neurological motor impairments, post-traumatic convulsions or seizures, and anxiety also respond to manipulations of the endocannabinoid system. As such, the endocannabinoid system possesses potential drugable receptor and enzyme targets for the treatment of diverse TBI pathology. Yet, full characterization of TBI-induced changes in endocannabinoid ligands, enzymes, and receptor populations will be important to understand that role this system plays in TBI pathology. Promising classes of compounds, such as the plant-derived phytocannabinoids, synthetic cannabinoids, and endocannabinoids, as well as their non-cannabinoid receptor targets, such as TRPV1 receptors, represent important areas of basic research and potential therapeutic interest to treat TBI."…

-Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA
-Edited by: Rukiyah Van Dross-Anderson, The Brody School of Medicine at East Carolina University, USA
-Reviewed by: Gaurav Bedse, Vanderbilt University, USA; Emilio Russo, Magna Græcia University, Italy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5314139

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"Traumatic brain injury (TBI) is one of the most disabling clinical conditions that could lead to neurocognitive disorders in survivors. Our group and others previously reported that prophylactic enrichment of dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs) markedly ameliorate cognitive deficits after TBI."
…"

Among all mice receiving post-TBI n-3 PUFA treatments, the combined treatment of fish oil dietary supplement and n-3 PUFA injections demonstrated a reproducible beneficial effect in attenuating cognitive deficits although without reducing gross tissue loss. Mechanistically, the combined treatment promoted post-TBI restorative processes in the brain, including generation of immature neurons, microvessels, and oligodendrocytes, each of which was significantly correlated with the improved cognitive recovery. These results indicated that repetitive and prolonged n-3 PUFA treatments after TBI are capable of enhancing brain remodeling and could be developed as a potential therapy to treat TBI victims in the clinic."

…"The extent of TBI-induced neuronal death strongly correlates with the development of cognitive deficits[37,38]. TBI leads to rapid neuronal cell death resulting from direct contusion, followed by progressive secondary cell death in surrounding tissues8. n-3 PUFAs have been shown to exert potent protection against oxidative stress, glutamate-induced excitotoxicity, apoptotic cell death, and inflammation[16,39,40]. In mice receiving 2 months of prophylactic n-3 PUFA dietary supplementation, TBI caused a less extensive loss of CA3 neurons compared to mice on a regular diet[15]."

-Department of Neurosurgery, General Hospital of PLA, Beijing, P.R. China

-Pittsburgh Institute of Brain Disorders and Recovery and Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA

-State Key Laboratory of Medical Neurobiology and Institute of Brain Sciences, Fudan University, Shanghai, P.R. China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5531869

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"Phospholipid (PL) abnormalities are observed in the cerebrospinal fluid of patients with traumatic brain injury (TBI), suggesting their role in TBI pathology. Therefore, PL levels were examined in a TBI mouse model that received 1.8 mm deep controlled cortical impact injury or craniectomy only (control). The rotarod and Barnes maze acquisition and probe tests were performed within 2 wk after injury, with another probe test performed 3 mo postinjury. Liquid chromatography/mass spectrometry analyses were performed on lipid extracts from several brain regions and plasma from injured and control mice collected at 3 mo postinjury. Compared to controls, injured mice with sensorimotor and learning deficits had decreased levels of cortical and cerebellar phosphatidylcholine (PC) and phosphatidylethanolamine (PE) levels, while hippocampal PC, sphingomyelin and PE levels were elevated. Ether PE levels were lower in the cortices and plasma of injured animals. Polyunsaturated fatty acid-containing PC and PE species, particularly ratios of docosahexaenoic acid (DHA) [omega-3s] to arachidonic acid [omega-6s], were lower in the hippocampi and cortices and plasma of injured mice. Given the importance of DHA in maintaining neuronal function and resolving inflammation and of peroxisomes in

synthesis of ether PLs, normalizing these PLs may be a useful strategy for treating the chronic pathology of TBI."

-Roskamp Institute, Sarasota, Florida, USA;
-James A. Haley Veterans Affairs Hospital, Tampa, Florida, USA
http://www.ncbi.nlm.nih.gov/pubmed/25208845

"The phospholipid bilayer plays a central role in the lifecycle of the endogenous cannabinoid N-arachidonoylethanolamine (**anandamide**, 1)."…

-Department of Chemistry and Biochemistry, Kennesaw State University, Kennesaw, Georgia, USA.
https://www.ncbi.nlm.nih.gov/pubmed/16033262

TRP Channels (Transient receptor potential channels)

…"Endocannabinoids have also been shown to activate the transient receptor potential (TRP) superfamilly of cation-non selective channels, which are involved in the transduction of remarkable diverse stimuli, including temperature, pH, mechanical and osmotic stimuli, taste, the effects of xenobiotic substances, and endogenous lipids (Venkatachalam and Montel, 2007). Among these channels, TRPV1, also known as vanilloid receptor 1 (VR1) is the first TRP channel cloned. This channel was first identified as a receptor for capsaicin, a pungent ingredient of hot chili pepper (Caterina et al., 1997). Subsequent work from different research groups has established that eCBs such as anandamide and N-arachidonyl dopamine, but not 2-AG, bind with high affinity to TRPV1 and activate these channels (Zygmunt et al., 1999, for review, see Tóth et al., 2009). More recently, results from several electrophysiological studies have provided strong evidence that the activation of TRPV1 by eCBs modulates synaptic transmission and plasticity in various brain areas (Grueter et al., 2010; Chávez et al., 2010). Together results from these studies suggest that TRPV1 channel may represent an "ionotropic" cannabinoid receptor."…

-Research Institute on Addictions, University at Buffalo, State University of New York, Buffalo, New York
-Corresponding author: Samir Haj-Dahmane, Ph.D, Research Institute on Addictions, University at Buffalo, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110547/

TRPA1 : A Sensory Channel of Many Talents

“In mammals, TRPA1 is the sole member of the TRPA gene subfamily. Recent reports identified TRPA1 as a target for the noxious and inflammatory irritant mustard oil in peripheral sensory neurons, implicating a functional role in pain and neurogenic inflammation. Other studies suggest that TRPA1 participates in additional sensory processes, such as cold sensation and hearing. In this chapter, we summarize and discuss these recent findings and speculate about the potential physiological role of TRPA1 in chemosensation and pain transduction.”

-Marilia Z. P. Guimaraes and Sven-Eric Jordt.
-Universidade Federal do Rio de Janeiro
-Yale University School of Medicine
https://www.ncbi.nlm.nih.gov/books/NBK5237/

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...“The first-discovered of these 'endocannabinoids' was arachidonoylethanolamide [anandamide] and there is convincing evidence that this ligand and some of its metabolites can activate vanilloid VRI (TRPV1) receptors. “...

-School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK
https://pubmed.ncbi.nlm.nih.gov/16570099

■■■

...”AEA [anandamide] has been shown to contribute to endocannabinoid-mediated synaptic transmission in several ways. AEA is a full agonist of TRPV1, which is purported to participate in endocannabinoid signaling [32]”...

-Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, Canada;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5877694/

Cannabinoid Ligands Targeting TRP Channels

“Transient receptor potential (TRP) channels are a group of membrane proteins involved in the transduction of a plethora of chemical and physical stimuli. These channels modulate ion entry, mediating a variety of neural signaling processes implicated in the sensation of temperature, pressure, and pH, as well as smell, taste, vision, and pain perception. Many diseases involve TRP channel dysfunction, including neuropathic pain, inflammation, and respiratory disorders. In the pursuit of new treatments for these disorders, it was discovered that cannabinoids can modulate a certain subset of TRP channels. The TRP vanilloid (TRPV), TRP ankyrin (TRPA), and TRP

melastatin (TRPM) subfamilies were all found to contain channels that can be modulated by several endogenous, phytogenic, and synthetic cannabinoids. To date, six TRP channels from the three subfamilies mentioned above have been reported to mediate cannabinoid activity: TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, and TRPM8. The increasing data regarding cannabinoid interactions with these receptors has prompted some researchers to consider these TRP channels to be "ionotropic cannabinoid receptors." Although CB1 and CB2 are considered to be the canonical cannabinoid receptors, there is significant overlap between cannabinoids and ligands of TRP receptors. The first endogenous agonist of TRPV1 to be discovered was the endocannabinoid, anandamide (AEA). Similarly, N-arachidonyl dopamine (NADA) and AEA were the first endogenous TRPM8 antagonists discovered. Additionally, Δ9-tetrahydrocannabinol (Δ9-THC), the most abundant psychotropic compound in cannabis, acts most potently at TRPV2, moderately modulates TRPV3, TRPV4, TRPA1, and TRPM8, though Δ9-THC is not reported to modulate TRPV1. Moreover, TRP receptors may modulate effects of synthetic cannabinoids used in research. One common research tool is WIN55,212-2, a CB1 agonist that also exerts analgesic effects by desensitizing TRPA1 and TRPV1. In this review article, we aim to provide an overview and classification of the cannabinoid ligands that have been reported to modulate TRP channels and their therapeutic potential."…

"It has been widely demonstrated that cannabinoid ligands exert numerous physiopathological functions by modulating TRP channels. These cannabinoid-related TRP channels include members from the vanilloid, ankyrin, and melastatin subfamilies. The six channels discussed in this review are also considered thermo-TRP channels, due to their location in sensory neurons and their ability to be activated by a wide range of temperatures. The modulation of these six channels by temperature and cannabinoids is complex, and the relationship between the channels and their activation in response to cannabinoids can be further explored for various therapeutic uses, including chronic pain and inflammation. Current knowledge on how and which cannabinoids target TRP channels is still scarce, but has largely increased in the last decade. By classifying the cannabinoid structures able to modulate these receptors, we aim to provide an analysis that helps identifying key features involved in their activity at each particular channel."

This research paper has a number of images which shows the structure of selected endocannabinoids, phytocannabinoids and synthetic cannabinoids which target TRP Channels.

-*Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, NC, USA*

-*Edited by: Eric Murillo-Rodriguez, Anahuac Mayab University, Mexico*
-*Reviewed by: Chiayu Chiu, Universidad de Valparaíso, Chile; Jeong Hee Hong, Gachon University, South Korea*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340993/

…"TRPM8 agonists include compounds that induce a cooling sensation when applied intraorally or topically, including menthol, linalool (from lavender oil and rosewood), geraniol (from bergamont and coriander) and the synthetic agonist icilin (Behrendt et al., 2004)."…

-Dept of Neurobiology, Physiology and Behavior, University of California, Davis, CA 95616, USA
-Dept of Neurosurgery, Johns Hopkins University, Baltimore, MD 21287, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4572737/

TRPM8 Activation by Menthol, Icilin, and Cold Is Differentially Modulated by Intracellular pH

…"TRPM8 is a nonselective cation channel activated by cold and the cooling compounds menthol and icilin (Peier et al., 2002). "…

-Novartis Institute for Medical Sciences, London WC1E 6BN, United Kingdom
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6729305/

Herbal Compounds and Toxins Modulating TRP Channels

"Finding healing powers in plants is an ancient idea. People in all continents have long used hundreds, if not thousands, of indigenous plants for treatment of various ailments dating back to prehistory. Over the years, natural products have contributed enormously to the development of important therapeutic drugs used currently in modern medicine. Besides the clinical use of natural products or their compounds to treat diseases, these substances have also been important tools for the discovery of new targets such as receptors or ion channels. Exemplary in this regard is the transient receptor potential (TRP) family of ion channels."

At the moment more than 50 members of the TRP family have been characterized in yeast, worms, insects, fish and mammals [84, 127]. "

…"Nematodes use TRP channels at the tips of neuronal dendrites in their 'noses' to detect and avoid noxious chemicals. Humans use distinct TRP channels to appreciate sweet, bitter and umami tastes, and warmth, heat and cold [25]. TRP channels can serve as versatile sensors that allow individual cells and entire organisms to detect changes in their environment [124]. In fact, members of the TRP family are at the vanguard of our sensory systems, responding to

temperature, touch, pain, osmolarity, pheromones, taste and other stimuli.

In this review we show that many TRP channels are chemesthetic receptors. Since several naturally occurring substances are able to modulate/ interact with these sensing channels, they provide a range of new potential targets for the development of therapeutic drugs."

-Laboratory of Ion Channel Research, Department of Mol. Cell Biology, Division of Physiology, Campus Gasthuisberg, KU Leuven, Herestraat 49, B-3000 LEUVEN, Belgium

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2645550/

See also Ginger

Tumors

"Emerging evidence has demonstrated promising effects of cannabinoids on inhibition of tumor cell growth by modulating different cell signaling pathways in diverse cancer cells, such as lymphoma, hepatocellular carcinoma cells, breast cancer, pancreatic cancer, and skin cancer cells [1–7]. Natural and synthetic cannabinoids act by interacting with two distinctive G protein-coupled cannabinoid receptors, subtype 1 (CB1) and 2 (CB2) [8,9]. CB1 is expressed abundantly in central nervous system and certain peripheral nerve terminal sites, whereas CB2 is expressed dominantly in the immune system, especially on plasma cells [10,11]. "

-Department of Pharmaceutical Sciences and Drug Discovery Institute, University of Pittsburgh, Pittsburgh, PA

-Department of Computational Biology, Joint Pitt/CMU Computational Biology Program, University of Pittsburgh, Pittsburgh, PA

-Division of Hematology/Oncology, Columbia University, NY

-Hematology/Oncology, Department of Medicine, Indiana University, Indianapolis, IN

-Hisun Institute, Zhejiang Hisun Pharmaceutical Co. Ltd., Taizhou, Zhejiang, China

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504841/

Glyphosate Primes Mammary Cells for Tumorigenesis by Reprogramming the Epigenome in a TET3-Dependent Manner

…"The impact of glyphosate on human health has been analyzed and discussed for several years now (Gillezeau et al., 2019). Recently, glyphosate exposure was correlated with shortened gestational lengths (Parvez et al., 2018), and the level of glyphosate excretion was associated with steatohepatitis and advanced liver fibrosis in patients with fatty liver disease (Mills et al., 2019). However, the multiple research studies that investigated the tumorigenic effect of glyphosate as the sole risk factor had not led to convincing evidence of its implication.

It is assumed that only 5–10% of cancers are directly caused by inherited genetic abnormalities. The remaining 90% of cancers are linked to environmental factors that directly or indirectly affect DNA, possibly triggering genetic defects or aberrations in the reading and/or expression of DNA (Perera, 1997; Anand et al., 2008). Environmental and lifestyle factors are pleiotropic and include diet, tobacco, infections, obesity, alcohol, radiation, stress, physical activity, exposure to heavy metals and other pollutants, such as glyphosate. We are reporting that glyphosate exposure is not oncogenic by itself, but it acts as an oncogenic hit factor that, combined with another oncogenic hit, promotes the development of mammary tumors. At the molecular level, our findings demonstrate that glyphosate exposure can predispose breast cells to tumorigenesis via epigenetic reprogramming occurring via TET3-mediated global and local DNA hypomethylation (Figure 6)." ...

-CRCINA, INSERM, Université de Nantes, Nantes, France
-Equipe Apoptose et Progression tumorale, LaBCT, Institut de Cancérologie de l'Ouest, Saint Herblain, France
-Cancéropole Grand-Ouest, réseau Epigénétique (RepiCGO), Nantes, France
-LabEX IGO, Université de Nantes, Nantes, France
-Service de toxicologie, Faculté de pharmacie de Nantes, Nantes, France
-Department of Basic Medical Sciences, Purdue University, West Lafayette, IN, United States
-Purdue University Center for Cancer Research, West Lafayette, IN, United States
https://www.frontiersin.org/articles/10.3389/fgene.2019.00885/full

Glyphosate - an herbicide used in the production of GMO foods and house hold gardening products such as round-up.

The stress-regulated protein p8 mediates cannabinoid-induced apoptosis of tumor cells

"One of the most exciting areas of current research in the cannabinoid field is the study of the potential application of these compounds as antitumoral drugs. Here, we describe the signaling pathway that mediates cannabinoid-induced apoptosis of tumor cells. By using a wide array of experimental approaches, we identify the stress-regulated protein p8 (also designated as candidate of metastasis 1) as an essential mediator of cannabinoid antitumoral action and show that p8 upregulation is dependent on de novo-synthesized ceramide. We also observe that p8 mediates its apoptotic effect via upregulation of the endoplasmic reticulum stress-related genes ATF-4, CHOP, and TRB3. Activation of this pathway may constitute a potential therapeutic strategy for inhibiting tumor growth."

-Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/16616335/

Involvement of cannabinoids in cellular proliferation

"The endogenous canabinoid system (ECS) is involved in the regulation of an important number of central and peripheral physiological effects. Among all these functions, the control of the cellular proliferation has become a focus of major attention as opening new therapeutic possibilities for the use of cannabinoids as potential antitumor agents. The capacity of endogenous and synthetic cannabinoids to induce apoptosis of different tumoral cells in culture and in vivo, the mechanism underlying and the potential therapeutic applications are discussed in this review."

-Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, Madrid, Spain.
https://pubmed.ncbi.nlm.nih.gov/15638794

Cannabinoid receptor systems: therapeutic targets for tumour intervention

"The past decade has witnessed a rapid expansion of our understanding of the biological roles of cannabinoids and their cognate receptors. It is now certain that Delta9-tetrahydrocannabinol, the principle psychoactive component of the Cannabis sativa plant, binds and activates membrane receptors of the 7-transmembrane domain, G-protein-coupled superfamily. Several putative endocannabinoids have since been identified, including anandamide, 2-arachidonyl glycerol and noladin ether. Synthesis of numerous cannabinomimetics has also greatly expanded the repertoire of cannabinoid receptor ligands with the pharmacodynamic properties of agonists, antagonists and inverse agonists. Collectively, these ligands have proven to be powerful tools both for the molecular characterisation of cannabinoid receptors and the delineation of their intrinsic signalling pathways. Much of our understanding of the signalling mechanisms activated by cannabinoids is derived from studies of receptors expressed by tumour cells; hence, this review provides a succinct summary of the molecular pharmacology of cannabinoid receptors and their roles in tumour cell biology. Moreover, there is now a genuine expectation that the manipulation of cannabinoid receptor systems may have therapeutic potential for a diverse range of human diseases. Thus, this review also summarises the demonstrated antitumour actions of cannabinoids and indicates possible avenues for the future development of cannabinoids as antitumour agents."

-Molecular Pharmacology Group, Biomedical Sciences Division, School of Applied Sciences, University of Wolverhampton, Wulfruna Street, UK.
https://pubmed.ncbi.nlm.nih.gov/14640910

Changes in the Endocannabinoid System May Give Insight into new and Effective Treatments for Cancer

…."In conclusion, the endocannabinoid system exerts a myriad of effects on tumor cell growth, progression, angiogenesis, and migration. With a notable few exceptions, targeting the endocannabinoid system with agents that activate cannabinoid receptors or increase the endogenous levels of AEA [anandamide] may prove to have therapeutic benefit in the treatment of various cancers. Further studies into the downstream consequences of AEA treatment are required and may illuminate other potential therapeutic targets."

-Department of Medicine, Texas A&M Health Science Center, College of Medicine, Temple, Texas, USA

-Division of Research and Education, Scott & White Hospital, Temple, Texas, USA

-Systems Biology and Translational Medicine, Texas A&M Health Science Center, College of Medicine, Temple, Texas, USA

-Division of Research, Central Texas Veterans Health Care System, Temple, Texas, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2791688

Tumor Necrosis Factor-alpha (TNF-a)

…"Tumour necrosis factor α (TNFα) is a potent paracrine and endocrine mediator of inflammatory and immune functions. It is also known to regulate growth and differentiation of a wide variety of cells types. TNFα is selectively cytotoxic for many transformed cells, especially in combination with IFNα. In vivo, it leads to necrosis of methylcholanthrene-induced murine sarcomas. Many of the actions of TNFα occur in combination with other cytokines as part of the cytokine network 1–3. TNFα is expressed as a type II membrane protein attached by a signal anchor transmembrane domain in the propeptide, and is processed by a matrix metallo-proteinase, termed TNFα-converting enzyme (TACE)4."…

-The Cytokine FactsBook and Webfacts (Second Edition), 2001

https://www.sciencedirect.com/topics/neuroscience/tumor-necrosis-factor-alpha

■■■

"Tumor necrosis factor-α (TNFα) was cloned over 2 decades ago and its identification in part led to the discovery of a super family of tumor necrosis factors (TNFs) and their receptors. TNFα signals through two transmembrane receptors, TNFR1 and TNFR2, and regulates a number of

critical cell functions including cell proliferation, survival, differentiation, and apoptosis. Macrophages are the major producers of TNFα and interestingly are also highly responsive to TNFα. Aberrant TNFα production and TNF receptor signaling have been associated with the pathogenesis of several diseases, including rheumatoid arthritis, Crohn's disease, atherosclerosis, psoriasis, sepsis, diabetes, and obesity. TNFα has been shown to play a pivotal role in orchestrating the cytokine cascade in many inflammatory diseases and because of this role as a "master-regulator" of inflammatory cytokine production, it has been proposed as a therapeutic target for a number of diseases. Indeed anti-TNFα drugs are now licensed for treating certain inflammatory diseases including rheumatoid arthritis and inflammatory bowel disease. In this review we discuss the discovery of TNFα and its actions especially in regulating macrophage biology. Given its importance in several human diseases, we also briefly discuss the role of anti-TNFα therapeutics in the treatment of inflammatory diseases."…

-Department of Physiology and Division of Pathology, Michigan State University, East Lansing, Michigan, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3066460

U

Ultraviolet Radiation

..."Degradation of lipids caused by UV [ultraviolet radiation] induces inflammation, release of arachidonic acid, which is next converted to prostaglandins [7]."…

-Department of Cosmetic Raw Materials Chemistry, Medical University of Lodz, Lodz, Poland
-Department of Cosmetology and Aesthetic Dermatology, Medical University of Lodz, Lodz, Poland
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4440198/

Uveitis & Uveoretinitis

"Uveitis or uveoretinitis is a general term referring to inflammation of the retina and uvea (the pigmented vascular coat of the eyeball, consisting of the choroid, ciliary body, and iris)."

-Rachel R. Caspi Ph.D, Laboratory of Immunology, National Eye Institute, NIH, Bethesda, Maryland, USA.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929721/

■■■

"Omega (ω)–3 long-chain polyunsaturated fatty acids (LCPUFAs) inhibit the production of inflammatory mediators and thereby contribute to the regulation of inflammation. Experimental autoimmune uveitis (EAU) is a well-established animal model of autoimmune retinal inflammation. To investigate the potential effects of dietary intake of ω-3 LCPUFAs on uveitis, we examined the anti-inflammatory properties of these molecules in comparison with ω-6 LCPUFAs in a mouse EAU model."

…"Our results thus show that a diet enriched in ω-3 LCPUFAs suppressed uveitis in mice in association with inhibition of Th1 and Th17 cell function."

…"Lipid autacoids have well-established roles in physiology and pathophysiology. Omega (ω)–3 and ω-6 long-chain polyunsaturated fatty acids (LCPUFAs) are two classes of dietary lipid [1] that are highly enriched in the retina [2] and which have opposing physiological effects. Mammals depend on dietary intake of LCPUFAs because they lack the enzymes capable of synthesizing these molecules de novo, with ω-6 LCPUFAs being the primary polyunsaturated fatty acids present in Western diets and ω-3 LCPUFAs serving as substrates for the generation of potent and protective autacoids such as resolvins and neuroprotectin D1 [3]. The balance of eicosanoids derived from ω-3 and ω-6 LCPUFAs is an important determinant of cardiovascular [4–6] and renal [7] function, vascular tone [8], and inflammatory and immune processes [9]. ω-3 LCPUFAs have been shown to suppress ocular inflammation in a mouse endotoxin-induced uveitis (EIU) model [10] as well as ocular neovascularization in animal models of age-related macular degeneration [11, 12] or of oxygen-induced retinopathy [3]. The mechanism of such suppression of ocular inflammation by ω-3 LCPUFAs has remained unclear, however."

- Department of Ophthalmology, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan,

- Angiogenesis Laboratory, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Cambridge, Massachusetts, USA,

- Department of Immunology, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan,

- Department of Ophthalmology, Osaka Medical Collage, Osaka, Japan,

-Max Delbrueck Center for Molecular Medicine, GERMANY,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4578775/

Turning Down the Thermostat: Modulating the Endocannabinoid System in Ocular Inflammation and Pain

"The endocannabinoid system (ECS) has emerged as an important regulator of both physiological and pathological processes. Notably, this endogenous system plays a key role in the modulation

of pain and inflammation in a number of tissues. The components of the ECS, including endocannabinoids, their cognate enzymes and cannabinoid receptors, are localized in the eye, and evidence indicates that ECS modulation plays a role in ocular disease states. Of these diseases, ocular inflammation presents a significant medical problem, given that current clinical treatments can be ineffective or are associated with intolerable side-effects. Furthermore, a prominent comorbidity of ocular inflammation is pain, including neuropathic pain, for which therapeutic options remain limited. Recent evidence supports the use of drugs targeting the ECS for the treatment of ocular inflammation and pain in animal models; however, the potential for therapeutic use of cannabinoid drugs in the eye has not been thoroughly investigated at this time. This review will highlight evidence from experimental studies identifying components of the ocular ECS and discuss the functional role of the ECS during different ocular inflammatory disease states, including uveitis and corneal keratitis. Candidate ECS targeted therapies will be discussed, drawing on experimental results obtained from both ocular and non-ocular tissue(s), together with their potential application for the treatment of ocular inflammation and pain."

…"Recent evidence suggests that the ECS could be a therapeutic target in the treatment of ocular inflammation. The effects of cannabinoids have been shown to be beneficial in several animal models of intraocular inflammation (Xu et al., 2007; Altinsoy et al., 2011; Toguri et al., 2014, 2015). These studies have included models of EIU in rabbit (Altinsoy et al., 2011), rat (Toguri et al., 2014, 2015), and EAU in mouse (Xu et al., 2007). Uveitis is an overarching term which typically describes inflammation of any part of the uvea (iris, ciliary body, and choroid). Inflammation can be strictly localized to uveal tissue or be more extensive and involve ocular structures including: sclera, retina, vitreous, and optic nerve (Jabs et al., 2005; Read, 2006; Larson et al., 2011). Anterior uveitis, is additionally associated with pain and photophobia (Smith et al., 1998; Dunn, 2015)."…

-Department of Pharmacology, Dalhousie University, Halifax, NS, Canada
-Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada
-Anesthesia, Pain Management & Perioperative Medicine, Dalhousie University, Halifax, NS, Canada
-Edited by: Allyn C. Howlett, Wake Forest School of Medicine, USA
-Reviewed by: Kyriaki Thermos, University of Crete, Greece; Jean-Francois Bouchard, Université de Montréal, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5024674/

■■■

"To date, the involvement of CB2 receptors in immune responses in the eye has not been extensively examined. However, activation of CB2 receptors had anti-inflammatory effects in the retina in a chronic experimental model of autoimmune uveoretinitis, and was associated with inhibition of leukocyte trafficking in vivo and reduction of inflammatory mediators in vitro (Xu et al., 2007). "

Anti-inflammatory effects of cannabinoid CB2 receptor activation in endotoxin-induced uveitis

"**Conclusion and Implications:** Activation of CB2 [cannabinoid 2] receptors was anti-inflammatory in a model of acute EIU [experimental endotoxin-induced uveitis] and involved a reduction in NF-κB [prototypical proinflammatory signaling pathway], AP-1 and inflammatory mediators. CB2 receptors may be promising drug targets for the development of novel ocular anti-inflammatory agents."

-Department of Pharmacology, Dalhousie University, Halifax, NS, Canada
-Department of Microbiology and Immunology, Dalhousie University, Halifax, NS, Canada
-Department of Anesthesia, Dalhousie University, Halifax, NS, Canada
-Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3954484/

Partial List of Acetaminophen Containing Brands

Acephen Rectal Suppository®	Genebs®	Q-Pap®
Aceta®	Gericet®	Redutemp®
Actamin®	Goody's®	Ridenol®
Actifed®	Halenol®	Robitussin®
Adprin B®	Infantaire®	S-T Febrol®
Alka-Seltzer Plus LiquidGels®	Liquiprin®	Saint Joseph®
Anacin®	Lopap®	Silapap®
Anacin®	Mapap Extra Strength®	Sinutab®
Apacet®	Mapap Rectal Suppository®	Sudafed®
Apara®	Mapap®	T-Panol®
Apra®	Masophen®	Tactinal Extra Strength®
Aspirin-Free Singlet®	Meda Cap®	Tactinal®
Benadryl®	Midol®	Tactinal®
Cepacol®	Neopap Supprettes Rectal Suppository®	Tempra®
Conacetol®	Nyquil®	Theraflu®
Contac®	Ofirmev®	Triaminic®
Coricidin®	Pain Relief Extra Strength®	Tycolene®
Dayquil®	Pain-Eze®	Tylenol®
		TYLENOL® Brand Products

Dimetapp®	Panadol®	Tylophen®
Dolono®	Panex®	Uni-Ace®
Dristan®	Paracetamol®	Uniserts Rectal Suppository®
Excedrin®	Paramol®	Vanquish®
Feverall Rectal Suppository®	Pediapap®	Vicks®
FeverAll®	Pharbetol®	Vitapap®
Formula 44®	Powders Liquiprin®	Zicam®
Genapap®		

This is for reference only, always consult a medical professional to find out more information about every medication.

"Acetaminophen is the most common drug ingredient in America. It is found in more than 600 different over-the-counter and prescription medicines, including generic and store brand pain relievers, fever reducers, and sleep aids as well as cough, cold, and allergy medicines."

- American Liver Foundation

https://liverfoundation.org/wp-content/uploads/2017/10/Common-Medicines-with-Acetaminophen-Know-Your-Dose.pdf

bit.do/acetaminophen

Vasodilator

Cardiovascular Pharmacology of Cannabinoids

"….anandamide produce major vasodilation in the coronary and cerebral circulation,"…

- Wagner et al.

- Referenced by Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda MD, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2228270/

■■■

…"Our results indicate that anandamide induces vasodilation by activating vanilloid receptors on perivascular sensory nerves and causing release of CGRP [calcitonin-gene-related peptide]. The vanilloid receptor may thus be another molecular target for endogenous anandamide, besides cannabinoid receptors, in the nervous and cardiovascular systems."

-Department of Clinical Pharmacology, Institute of Laboratory Medicine, University of Lund, Sweden.

https://www.ncbi.nlm.nih.gov/pubmed/10440374

■■■

…"In several isolated organ models, cannabinoids act as strong vasodilators that relax arterial tone via activated CB1 receptors [12], specific anandamide receptors [38, 18], VR1 vanilloid receptors [45], or arachidonic acid products [14]. In anesthetized rats, cannabinoids are potent coronary, cerebral, and renal vasodilator agents in vivo [39]."…

-Department of Internal Medicine I/Center of Cardiovascular Medicine, University of Wu¨rzburg, Germany
https://journals.physiology.org/doi/pdf/10.1152/ajpheart.00718.2005

Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide.

"The endogenous cannabinoid receptor agonist anandamide is a powerful vasodilator of isolated vascular preparations, but its mechanism of action is unclear. Here we show that the vasodilator response to anandamide in isolated arteries is capsaicin-sensitive and accompanied by release of calcitonin-gene-related peptide (CGRP). The selective CGRP-receptor antagonist 8-37 CGRP, but not the cannabinoid CB1 receptor blocker SR141716A, inhibited the vasodilator effect of anandamide. Other endogenous (2-arachidonylglycerol [2-AG], palmitylethanolamide [PEA]) and synthetic (HU 210, WIN 55,212-2, CP 55,940) CB1 and CB2 receptor agonists could not mimic the action of anandamide. The selective 'vanilloid receptor' antagonist capsazepine inhibited anandamide-induced vasodilation and release of CGRP. In patch-clamp experiments on cells expressing the cloned vanilloid receptor (VR1), anandamide induced a capsazepine-sensitive current in whole cells and isolated membrane patches. Our results indicate that anandamide induces vasodilation by activating vanilloid receptors on perivascular sensory nerves and causing release of CGRP. The vanilloid receptor may thus be another molecular target for endogenous anandamide, besides cannabinoid receptors, in the nervous and cardiovascular systems."

Department of Clinical Pharmacology, Institute of Laboratory Medicine, University of Lund, Sweden.
https://www.ncbi.nlm.nih.gov/pubmed/10440374
Capsaicin - Chili Pepper Extract

■■■

"We have previously shown that the endocannabinoid anandamide and its metabolically stable analog (R)-methanandamide produce vasorelaxation in rabbit aortic ring preparations in an endothelium-dependent manner that could not be mimicked by other CB(1) cannabinoid receptor agonists (Am J Physiol 282: H2046-H2054, 2002). "…

-Neuroscience of Drug Abuse Research Program, J. L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, NC, USA.
https://pubmed.ncbi.nlm.nih.gov/17379772

See also Hypertension

Viral Infections

Effects of cannabinoids and their receptors on viral infections

"Cannabinoids, the active ingredient in marijuana, and their derivatives have received remarkable attention in the last two decades because they can affect tumor growth and metastasis. There is a large body of evidence from in vivo and in vitro models showing that cannabinoids and their receptors influence the immune system, viral pathogenesis, and viral replication. The present study reviews current insights into the role of cannabinoids and their receptors on viral infections. The results reported here indicate that cannabinoids and their receptors have different sequels for viral infection. Although activation or inhibition of cannabinoid receptors in the majority of viral infections are proper targets for development of safe and effective treatments, caution is required before using pharmaceutical cannabinoids [synthetic cannabinoids] as a treatment agent for patients with viral infections."

-Departmentof Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
-Department of Biochemistry, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
-Department of Immunology, Medical University of Warsaw, Center of Biostructure Research, Warsaw, Poland.
https://pubmed.ncbi.nlm.nih.gov/26059175

Vitamin B6

Marginal Vitamin B-6 Deficiency Decreases Plasma (n-3) and (n-6) PUFA Concentrations in Healthy Men and Women

…"These data indicate that short-term vitamin B-6 restriction decreases plasma (n-3) and (n-6) PUFA concentrations and tends to increase the plasma (n-6):(n-3) PUFA ratio. Such changes in blood lipids may be associated with the elevated risk of cardiovascular disease in vitamin B-6 insufficiency."…

-Food Science and Human Nutrition Department, Institute of Food and Agricultural Sciences
-Division of Endocrinology and Metabolism, Department of Medicine, College of Medicine
-Department of Biostatistics
-Department of Health Outcomes and Policy
-Clinical Research Center, and
-Department of Biochemistry and Molecular Biology, College of Medicine, University of Florida, Gainesville, FL; and

-Nutrition and Metabolism Center, Duke University Medical Center, Durham, NC
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3442793/

Vitamin E

"Vitamin E (α-tocopherol) is recognised as a key essential lipophilic antioxidant in humans protecting lipoproteins, PUFA, cellular and intra-cellular membranes from damage. The aim of this review was to evaluate the relevant published data about vitamin E requirements in relation to dietary PUFA intake. Evidence in animals and humans indicates a minimal basal requirement of 4–5 mg/d of RRR-α-tocopherol when the diet is very low in PUFA. The vitamin E requirement will increase with an increase in PUFA consumption and with the degree of unsaturation of the PUFA in the diet. The vitamin E requirement related to dietary linoleic acid, which is globally the major dietary PUFA in humans, was calculated to be 0·4–0·6 mg of RRR-α-tocopherol/g of linoleic acid. Animal studies show that for fatty acids with a higher degree of unsaturation, the vitamin E requirement increases almost linearly with the degree of unsaturation of the PUFA in the relative ratios of 0·3, 2, 3, 4, 5 and 6 for mono-, di-, tri-, tetra-, penta- and hexaenoic fatty acids, respectively. Assuming a typical intake of dietary PUFA, a vitamin E requirement ranging from 12 to 20 mg of RRR-α-tocopherol/d can be calculated. A number of guidelines recommend to increase PUFA intake as they have well-established health benefits. It will be prudent to assure an adequate vitamin E intake to match the increased PUFA intake, especially as vitamin E intake is already below recommendations in many populations worldwide."…

"PUFA, categorised into n-3 and n-6 fatty acids, are important cell membrane components and key elements in child development, brain and visual functioning and physical health and well-being throughout the life course. Dietary sources that are rich in PUFA include many vegetable oils, nuts, seeds and certain types of fish. As PUFA contain double bonds, they are highly sensitive to oxidative stress; consequently, the oxidation of PUFA and the resulting lipid peroxides can have detrimental effects on development, brain function and human health. Normal metabolic, cell-signalling and host defence activities result in the release of oxidants and free radicals. If there are low concentrations of antioxidants present to counter-balance excessive concentrations of oxidants and free radicals – a situation often termed 'oxidative stress' – detrimental effects on cell components can occur[1]. The antioxidant defence system keeps the levels of oxidants and antioxidants balanced, and thus protects the body from the effects of oxidative stress[1]. In the human body, a complex network of antioxidant defence systems (mainly endogenous enzymatic antioxidant systems) is supported by, and interacts with, small antioxidant molecules derived from the diet to protect the tissues from oxidative stress. Vitamin E, or more specifically its α-tocopherol isoform, is one of the essential antioxidants that

humans derive from the diet. Similar to PUFA, vegetable oils, nuts and seeds are particularly rich sources of vitamin E. Many nutrient databases and nutrition labels do not distinguish between the different isoforms of vitamin E, and often include the contribution of all eight naturally occurring vitamin E isoforms, presented as α-tocopherol equivalent."…

-DSM Nutritional Products, Switzerland
-Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, UK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4594047/

Extreme caution should be taken into account when consuming vegetable oils or other cooking oils, due to the high omega-6:omega-3 ratio and other compounds as a result of the high heat manufacturing process. See Cooking Oils for more research on this topic.

See also Alzheimer's Disease , Astaxanthin , Dyslexia , Fibrocystic Breast Disease , Lipopolysaccharide (LPS) , Lupus , Olive Leaf & Oleuropein Extracts

Vitamin D

(a prehormone)

…"Despite the original misnaming of vitamin D (since it is actually a prehormone) this term has continued to be used."

Vitamin D Toxicity

"During the period between the 1930s and 1950s considerable experience was gained with vitamin D toxicity when overdoses of vitamin D were often provided to patients being treated for hypocalcaemic disorders such as hypoparathyroidism. Incidences of vitamin D over-dosing also occurred with the general public when batches of vitamin D-supplemented foods were poorly mixed. Clinical biochemistry studies of patients receiving large doses of vitamin D demonstrated that the first adverse side effect of vitamin D to develop was hypercalcaemia. Following the development of an assay for serum 25OHD to quantitatively assess vitamin D status, it was demonstrated that hypercalcaemia did not develop until 25OHD levels were over at least 500 nmol/L and most commonly above 750 nmol/L5 (Figure 1). These levels have been confirmed with more recent studies.[6,7] This experience has left a strong clinical concern regarding vitamin D supplementation and the risk of vitamin D toxicity. Consequently the medical profession takes a

very conservative approach today. However in current clinical practice it is very rare to observe levels of 25OHD approaching one fifth of the levels required for toxicity to occur."…

-Professor Howard Morris PhD, FAACB, FFSc (RCPA).

-Hanson Institute

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1240026/

Altered gut microbiota and endocannabinoid system tone in vitamin D deficiency-mediated chronic pain

"Recent evidence points to the gut microbiota as a regulator of brain and behavior, although it remains to be determined if gut bacteria play a role in chronic pain. The endocannabinoid system is implicated in inflammation and chronic pain processing at both the gut and central nervous system (CNS) levels. In the present study, we used low Vitamin D dietary intake in mice and evaluated possible changes in gut microbiota, pain processing and endocannabinoid system signaling. Vitamin D deficiency induced a lower microbial diversity characterized by an increase in Firmicutes and a decrease in Verrucomicrobia and Bacteroidetes. Concurrently, vitamin D deficient mice showed tactile allodynia associated with neuronal hyperexcitability and alterations of endocannabinoid system members (endogenous mediators and their receptors) at the spinal cord level. Changes in endocannabinoid (anandamide and 2-arachidonoylglycerol) levels were also observed in the duodenum and colon. Remarkably, the anti-inflammatory anandamide congener, palmitoylethanolamide, counteracted both the pain behaviour and spinal biochemical changes in vitamin D deficient mice, whilst increasing the levels of Akkermansia, Eubacterium and Enterobacteriaceae, as compared with vehicle-treated mice. Finally, induction of spared nerve injury in normal or vitamin D deficient mice was not accompanied by changes in gut microbiota composition. Our data suggest the existence of a link between Vitamin D deficiency - with related changes in gut bacterial composition - and altered nociception, possibly via molecular mechanisms involving the endocannabinoid and related mediator signaling systems."

-Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy.

-Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Pozzuoli, Italy.

-Department of Agricultural Sciences, University of Naples Federico II, Portici, Italy; Task Force on Microbiome Studies, University of Naples Federico II, Naples, Italy.

-Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Pozzuoli, Italy; Canada Excellence Research Chair on the Microbiome-Endocannabinoidome Axis in Metabolic Health, Quèbec Heart and Lung Institute and Institute for Nutrition and Functional Foods, Université Laval, 2325 Rue de l'Université, Québec, QC G1V 0A6, Canada.

-Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy.

https://pubmed.ncbi.nlm.nih.gov/30953765/

Inflammation and vitamin D: the infection connection

"Inflammation is believed to be a contributing factor to many chronic diseases. The influence of vitamin D deficiency on inflammation is being explored but studies have not demonstrated a causative effect."….

"Inflammation is involved in many chronic diseases and concern has been raised about the influence of vitamin D deficiency on inflammatory processes. When studies found an association between inflammatory diseases and low serum 25-hydroxyvitamin D (25(OH)D), further research found evidence of low vitamin D in a large segment of the general population. This led some authorities to declare a world-wide epidemic of vitamin D deficiency and to recommend vitamin D supplementation. Experts are debating the definition of vitamin D deficiency and the appropriate vitamin D doses, while further research is being done to determine if vitamin D supplementation has the intended effect."…

"An infectious pathogenesis posits that intracellular bacteria disrupt the vitamin D regulated immune system, resulting in persistent infection and chronic inflammation. In the clinical setting, a novel immunotherapy is demonstrating the ability to resolve vitamin D metabolism dysfunction, restore immune function, and thus, eliminate infection and reduce inflammation. This review ponders the question, "Is low 25(OH)D a cause of, or a consequence of inflammation?" The answer is found in the evidence that adds persistent intracellular infection to the equation."…

"Consequently, more vitamin D experts are beginning to reconsider vitamin D supplementation among the general population [60]. Recommending higher vitamin D intake to large populations carries the potential risk of overdosing certain individuals [61]. It is difficult to ingest too much vitamin D from food, and natural mechanisms regulate the amount of vitamin D3 photosynthesized from sunlight [62]. However, elevated 25(OH)D and hypervitaminosis-D can occur due to vitamin D supplementation [63]. A study by Noordam et al. [65] cast doubt on the causal nature of previously reported associations between low levels of vitamin D and age-related diseases and mortality. A comprehensive review by Autier et al. [65] concluded that low concentrations of 25(OH)D are most likely an effect of health disorders and not a cause of illness. Commenting on the findings in a press statement, Autier et al. [64] advised against vitamin D supplementation and explained the observed discrepancy between observational and randomized trials:"

> *"Decreases in vitamin D levels are a marker of deteriorating health. Ageing and inflammatory processes involved in disease occurrence and clinical course reduce vitamin D concentrations, which would explain why vitamin D deficiency is reported in a wide*

range of disorders. We postulate that inflammation is the common factor between most non-skeletal health disorders and low 25(OH)D concentrations. Inflammatory processes involved in disease occurrence and clinical course would reduce 25(OH)D, which would explain why low vitamin D status is reported in a wide range of disorders. However, increases in 25(OH)D have no effect on inflammatory processes or on disorders at the origin of these processes."

- Chronic Illness Recovery, Fort Worth, Texas, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4160567

Vitamin D deficiency influences fatty acid metabolism

"Reports indicate that maternal vitamin D deficiency may be associated with increased inflammation. Long chain polyunsaturated fatty acids (LCPUFAs); omega-3 and omega-6 fatty acids are known to have anti-inflammatory and pro-inflammatory properties respectively. The present study examines the effect of vitamin D deficiency on fatty acid composition and metabolism in a rat model."…

"Animals from the VDD [vitamin D deficient] group demonstrated lower Δ9-desaturase activity index ($p < 0.01$ for all) in the liver, plasma and placenta. The plasma Δ5-desaturase activity index ($p < 0.05$) was higher although no change was observed in the Δ6-desaturase activity index. However, the mRNA levels of liver Δ6-desaturase was lower ($p < 0.05$) in the VDD group. Our findings indicate that maternal vitamin D deficiency influences fatty acid desaturase activity and expression and therefore alters maternal fatty acid metabolism."

-Mother and Child Health, Interactive Research School for Health Affairs (IRSHA), Bharati Vidyapeeth (Deemed to be University), India.
https://pubmed.ncbi.nlm.nih.gov/30553405/

Vomiting (emesis) & Nausea

"Nausea and vomiting (emesis) are important elements in defensive or protective responses that animals use to avoid ingestion or digestion of potentially harmful substances. However, these neurally-mediated responses are at times manifested as symptoms of disease and they are frequently observed as side-effects of a variety of medications, notably those used to treat cancer. Cannabis has long been known to limit or prevent nausea and vomiting from a variety of causes. This has led to extensive investigations that have revealed an important role for cannabinoids and their receptors in the regulation of nausea and emesis. With the discovery of

the endocannabinoid system, novel ways to regulate both nausea and vomiting have been discovered that involve the production of endogenous cannabinoids acting centrally. Here we review recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system, and we discuss the potential to utilize the endocannabinoid system in the treatment of these frequently debilitating conditions."…

"Cannabis is a well-known anti-emetic whose actions have been extensively reviewed (Cotter, 2009; Darmani and Chebolu, 2013; Izzo and Sharkey, 2010; Parker et al., 2011; Tramèr et al., 2001). Following the isolation of Δ9-THC, the mechanism and site of action of cannabinoids were established. In humans and animal models, plant-derived cannabinoids, synthetic cannabinoids and endocannabinoids inhibit emesis evoked peripherally or centrally with drugs or natural stimuli. Cannabinoids block both acute and delayed emesis. Where it has been examined, these effects are mediated by CB1 receptors in the DVC (Darmani, 2001a, 2001b; Darmani et al., 2003b; Ray et al., 2009; Van Sickle et al., 2003). Interestingly, there is dissociation between the antiemetic doses of Δ9-THC and effects of Δ9-THC on impairing motor function (Darmani, 2001b; Darmani and Crim, 2005)."…

"In cancer patients, administration of oral Δ9-THC has been shown to significantly suppress the experience of nausea and vomiting, in comparison to placebo controls (Chang et al., 1979; Frytak et al., 1979; Orr et al., 1980; Sallan et al., 1975; Sweet et al., 1981) and when compared to the D2 receptor antagonists available at the time, Δ9-THC was at least as effective (Carey et al., 1983; Crawford and Buckman, 1986; Cunningham et al., 1988; Frytak et al., 1979; Tramèr et al., 2001; Ungerleider et al., 1984) if not more effective (Ekert et al., 1979; Orr and McKernan, 1981) at reducing nausea and vomiting. Clinical evidence suggests that Δ8-THC suppresses anticipatory nausea in child patients (Abrahamov et al., 1995)."

-Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, Alberta, Canada
-Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, California, USA
-Department of Psychology, University of Guelph, Ontario, Canada
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883513/

W

Wheat

The dietary intake of wheat and other cereal grains and their role in inflammation

"Wheat is one of the most consumed cereal grains worldwide and makes up a substantial part of

the human diet. Although government-supported dietary guidelines in Europe and the U.S.A advise individuals to eat adequate amounts of (whole) grain products per day, cereal grains contain "anti-nutrients," such as wheat gluten and wheat lectin, that in humans can elicit dysfunction and disease. In this review we discuss evidence from in vitro, in vivo and human intervention studies that describe how the consumption of wheat, but also other cereal grains, can contribute to the manifestation of chronic inflammation and autoimmune diseases by increasing intestinal permeability and initiating a pro-inflammatory immune response."…

"Inflammation is the response of the innate immune system triggered by noxious stimuli, microbial pathogens and injury. When a trigger remains, or when immune cells are continuously activated, an inflammatory response may become self-sustainable and chronic. Chronic inflammation has been associated with many medical and psychiatric disorders, including cardiovascular disease, metabolic syndrome, cancer, autoimmune diseases, schizophrenia and depression [1,2,3]. Furthermore, it is usually associated with elevated levels of pro-inflammatory cytokines and acute phase proteins, such as interferons (IFNs), interleukin (Il)-1, Il-6, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). While clear peripheral sources for this chronic inflammation are apparent in some conditions (i.e., fat production of cytokines in the metabolic syndrome), in other disorders, such as major depression, the inflammatory source is not completely understood. Genetic vulnerability, psychological stress and poor dietary patterns have all been repeatedly implicated as being of significant importance in the development of an inflammatory phenotype [3,4,5]. Dietary factors associated with inflammation include a shift towards a higher n-6:n-3 fatty acid ratio [5] and a high intake of simple sugars [6]. Other substances in our daily food, like those found in wheat and other cereal grains, are also capable of activating pro-inflammatory pathways."

-University of Girona, Plaça Sant Domènec, 3 Edifici Les Àligues, Girona, Spain;
-Uni for Life, University of Graz, Beethovenstraße 9, Austria
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3705319/

X

Xanthan Gum

Late onset necrotizing enterocolitis in infants following use of a xanthan gum-containing thickening agent.

"Adverse event reports submitted to the US Food and Drug Administration suggested a possible

association between necrotizing enterocolitis and ingestion of a commercial feed thickener by premature infants. Review in 2011 of 22 cases with exposure revealed a distinct illness pattern."

-Center for Food Safety and Applied Nutrition, US Food and Drug Administration, Riverdale, MD, USA.
https://www.ncbi.nlm.nih.gov/pubmed/22575248

A diet including xanthan gum triggers a pro-inflammatory response in Wistar rats inoculated with Walker 256 cells.

"The aim of this study was to evaluate the effect of adding xanthan gum to the diet of rats on the production of cytokines and pro-inflammatory factors and on tumor development in rats inoculated with Walker 256 tumor cells."

…"The continuous use of xanthan gum triggered a pro-inflammatory response, promoting an increase in pro-inflammatory cytokines in the adipose tissue, but it did not have an effect on the tumor development in the animals inoculated with Walker 256 tumor cells."

-Universidade Federal de São Paulo, Escola Paulista de Medicina, Departamento de Fisiologia, São Paulo, Brasil.
-Department of Cell and Developmental Biology, Institute of Biomedical Sciences, University of São Paulo, São Paulo (SP), Brasil.
https://www.ncbi.nlm.nih.gov/pubmed/31211796

Z

Zinc

…"Zinc deficiency induced inflammatory response in part by eliciting aberrant immune cell activation and altered promoter methylation. Our results suggested potential interactions between zinc status, epigenetics, and immune function, and how their dysregulation could contribute to chronic inflammation."…

-School of Biological & Population Health Sciences, Oregon State University, USA
-Linus Pauling Institute, Oregon State University, Corvallis, USA
-Moore Family Center for Whole Grain Foods, Nutrition and Preventive Health, Oregon State University, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425307/

Zinc: A promising agent in dietary chemoprevention of cancer

"Proper intake of dietary nutrients is considered crucial for preventing the initiation of events leading to the development of carcinoma. Many dietary compounds have been considered to

contribute in cancer prevention including zinc, which plays a pivotal role in host defense against the initiation and promotion of several malignancies. Zinc is an essential element that is integral to many proteins and transcription factors which regulate key cellular functions such as the response to oxidative stress, DNA replication, DNA damage repair, cell cycle progression, and apoptosis. Zinc has been ascribed roles in the metabolism and interaction of malignant cells, particularly in apoptosis. Zinc is involved in structural stabilization and activation of the p53 that appears to be an important component of the apoptotic process and also in activation of certain members of the caspase family of proteases. Zinc exerts a positive beneficial effect against chemically induced preneoplastic progression in rats and provides an effective dietary chemopreventive approach to disease in vulnerable section of population with family history of carcinoma. The present review provides an insight into the research conducted on animals as well as on human subjects for providing the concept that zinc deficiency is an important factor in the development and progression of malignancy and that zinc could be efficacious in the prevention and treatment of several cancers viz., colon, pancreas, oesophageal and head and neck. However, it needs further exploration with regard to other definitive bioassays including protein expression and documentation of specific molecular markers to establish the exact mechanism for zinc-mediated cancer chemoprevention. Preclinical trials need to investigate the genetic and epigenetic pathways of chemoprevention by zinc."

-Department of Biophysics, Panjab University, Chandigarh, India
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3102454

Zinc in Infection and Inflammation

"Micronutrient homeostasis is a key factor in maintaining a healthy immune system. Zinc is an essential micronutrient that is involved in the regulation of the innate and adaptive immune responses. The main cause of zinc deficiency is malnutrition. Zinc deficiency leads to cell-mediated immune dysfunctions among other manifestations. Consequently, such dysfunctions lead to a worse outcome in the response towards bacterial infection and sepsis. For instance, zinc is an essential component of the pathogen-eliminating signal transduction pathways leading to neutrophil extracellular traps (NET) formation, as well as inducing cell-mediated immunity over humoral immunity by regulating specific factors of differentiation. Additionally, zinc deficiency plays a role in inflammation, mainly elevating inflammatory response as well as damage to host tissue. Zinc is involved in the modulation of the proinflammatory response by targeting Nuclear Factor Kappa B (NF-κB), a transcription factor that is the master regulator of proinflammatory responses. It is also involved in controlling oxidative stress and regulating inflammatory cytokines. Zinc plays an intricate function during an immune response and its

homeostasis is critical for sustaining proper immune function. This review will summarize the latest findings concerning the role of this micronutrient during the course of infections and inflammatory response and how the immune system modulates zinc depending on different stimuli."

-Institute of Immunology, Faculty of Medicine, RWTH Aachen University, University Hospital, Aachen, Germany
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5490603/

Inflammatory response under zinc deficiency is exacerbated by dysfunction of the T helper type 2 lymphocyte–M2 macrophage pathway

"Nutritional zinc deficiency leads to immune dysfunction and aggravates inflammation."...

"Zinc deficiency-induced aggravated inflammation is related to Th2 lymphocytes and followed by the association with loss of GATA-3, IL-4 and anti-inflammatory M2 macrophages. Importantly, IL-4 injection or zinc supplementation can reverse the effects of zinc deficiency on immune function."

-Department of Public Health and Environmental Medicine, The Jikei University School of Medicine, Tokyo, Japan,
-Department of Tropical Medicine, The Jikei University School of Medicine, Tokyo, Japan,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6418430/

# #

2-Arachidonoylglycerol (2-AG)

"2-Arachidonoylglycerol (2-AG) is a signaling lipid in the central nervous system that is a key regulator of neurotransmitter release. 2-AG is an endocannabinoid that activates the cannabinoid CB1 receptor. It is involved in a wide array of (patho)physiological functions, such as emotion, cognition, energy balance, pain sensation and neuroinflammation."…

-Department of Molecular Physiology, Leiden Institute of Chemistry, Leiden University, CC Leiden, The Netherlands.
-Department of Medicine, Campus Bio-Medico University of Rome, Rome, Italy
-European Centre for Brain Research/IRCCS Santa Lucia Foundation, Rome, Italy
https://www.sciencedirect.com/science/article/pii/S0163782717300619

"Like AEA, 2-AG is found in both the brain and periphery, although in the brain it is found at concentrations approximately 150 times that of AEA (Bisogno et al., 1999). 2-AG is found at high levels in

the brainstem, hippocampus, striatum and medulla in rats, showing a correlation with AEA but not CB1 localization [Bisogno et al., 1999]. 2-AG is an agonist at CB1 and also CB2, where its potency is greater than that of AEA; while this has been taken to suggest that 2-AG may be the endogenous ligand for CB2, this finding could equally be due to greater stability of 2-AG than AEA [Mechoulam et al., 1995; Gonsiorek et al., 2000; Sugiura et al., 2000]."

-Centre for Brain Research and Department of Pharmacology, University of Auckland, Auckland, New Zealand
-Department of Anatomy and Cell Biology, Centre for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931550/

The endocannabinoid 2-arachidonoylglycerol activates human platelets through non-CB1/CB2 receptors.

"The endocannabinoid 2-arachidonoylglycerol (2-AG) is an endogenous lipid that acts through the activation of G-protein-coupled cannabinoid receptors and plays essential roles in many physiological contexts. In the cardiovascular system 2-AG is generated by both activated endothelial cells and platelets, and participates in the regulation of inflammation and thrombosis. Although human platelets actively metabolize endocannabinoids, 2-AG also binds to platelet surface and leads to cell activation"

…"2-AG can be considered a new physiologic platelet agonist able to induce full platelet activation and aggregation with a non-CB(1)/CB(2) receptor-mediated mechanism."

-Department of Clinical and Experimental Medicine, University of Eastern Piedmont, Novara, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/18647220

■■■

…"In the cardiovascular system 2-AG is generated by both activated endothelial cells and platelets, and participates in the regulation of inflammation and thrombosis."…

-Department of Clinical and Experimental Medicine, University of Eastern Piedmont, Novara, Italy.
https://www.ncbi.nlm.nih.gov/pubmed/18647220

■■■

"2-AG is a derivative of arachidonic acid conjugated with glycerol. It can be formed from arachidonic acid-containing membrane phospholipids or lysophosphatidic acid. Once 2-AG is formed, it can diffuse through the plasma membrane and target the CB receptors of the same cell where it was formed or it can activate CB receptors of other identical or different cell types

after being released to the extracellular fluid. In addition, 2-AG can be transported inside the cells, possibly by a specific uptake system. Despite the increasing number of experimental data from pharmacological studies [8], little is known concerning the molecular properties of the purported 2-AG transporter. Anyway, **2-AG is rapidly metabolized by different cell types to yield arachidonic acid** and glycerol. The most important mechanism of degradation of 2-AG is catalyzed by a monoacylglycerol lipase [9, 10] but 2-AG can also be hydrolyzed by fatty acid amide hydrolase [11].

Because of its wide distribution throughout the body, 2-AG physiologically plays essential roles in diverse biological systems. For example, several lines of evidence indicate that 2-AG plays an important role as a retrograde messenger molecule in the regulation of synaptic transmission [12]. 2-AG is also involved in the regulation of various types of inflammatory reactions and immune responses. In fact, many inflammatory cells and immune-competent cells, such as macrophages [9] and dendritic cells [13], generate 2-AG when stimulated, and release 2-AG into the extracellular fluid. The released 2-AG then binds to the CB2 receptor expressed on other inflammatory cells or immune-competent cells, increases the production of chemokines [14] and triggers direct migration of macrophage-like cells [15], dendritic cells [16], B lymphocytes [17], eosinophils [18] and natural killer cells [19], thereby stimulating inflammatory reactions and immune responses. Several types of cells, such as human vascular endothelial cells and human platelets, generate 2-AG when stimulated [20, 21]. It is noteworthy that human platelets seem to be particularly active in metabolizing endocannabinoid molecules. In fact, anandamide membrane transporter and fatty acid amide hydrolase are present and active in human platelets [22, 23]. Moreover, 2-AG was found to be released from activated platelets during hemostasis and inflammation as well as in association with different vascular diseases. Hence, 2-AG may participate in the regulation of platelet response and function.

To better understand the role of 2-AG in the regulation of platelet functionality we investigated the molecular mechanisms by which 2-AG interacts with human platelets in the absence of plasma. We found that 2-AG activated platelets through non-CB1/CB2 cannabinoid receptors and induced a massive thromboxane A2 generation, which in turn caused cytoplasmic Ca2+release, granule secretion and full platelet aggregation."…

-Department of Clinical and Experimental Medicine, University of Eastern Piedmont, Novara, Italy.
https://onlinelibrary.wiley.com/doi/full/10.1111/j.1538-7836.2008.03093.x

Definitions

agonist - a substance which initiates a physiological response when combined with a receptor.[1]

analgesic - (of a drug) acting to relieve pain.[2]

antineoplastic - Acting to prevent, inhibit or halt the development of a neoplasm (a tumor). An agent with antineoplastic properties. For example, oxaliplatin (Eloxatin) is an antineoplastic used in the treatment of metastatic colon cancer.[3]

arachidonic acid - is an unsaturated, essential fatty acid. It is found in animal and human fat as well as in the liver, brain, and glandular organs, and is a constituent of animal phosphatides. It is formed by the synthesis from dietary linoleic acid and is a precursor in the biosynthesis of prostaglandins, thromboxanes, and leukotrienes. [4]

antitumorigenic - inhibits tumor growth

CB1 & CB2 - Cannabinoid receptor [1 / 2] are located through out the body and make up the endocannabinoid system (ECS)

chemopreventive - The use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the development or recurrence of, cancer.[5]

docosahexaenoic acid - is an omega-3 fatty acid and primary structural component of the human brain, cerebral cortex, skin, and retina thus plays an important role in their development and function. [6]

Dysbiosis - is any perturbation of the normal microbiome content that could disrupt the symbiotic relationship between the host and associated microbes, a disruption that can result in diseases, such as inflammatory bowel disease and other gastrointestinal (GI) disorders, including gastritis, peptic ulcer disease, irritable bowel syndrome, and even gastric and colon cancer [3–6].[7]

eicosanoids - are bioactive lipid mediators derived from oxygenated polyunsaturated fatty acids.[8]

endogenous - (abbr. endo) - having an internal cause or origin.[9]

eicosapentaenoic acid (EPA) - a polyunsaturated fatty acid found especially in fish oils. In humans it is a metabolic precursor of prostaglandins.[10]

hyperlipidemia - an abnormally high concentration of fats or lipids in the blood.[11]

hypomethylation - DNA hypomethylation refers to the loss of the methyl group in the 5-methylcytosine nucleotide. Methylation is a natural modification of DNA, and mainly affects the cytosine base (C) when it is followed by a guanosine (G) in mammals (Methylation).[12]

hypoalgesia - An increased sensitivity to feeling pain and an extreme response to pain.[13]

KN38-72717 - synthetic cannabinoid which targets activates cannabinoid type 1 & 2 receptors[14]

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[1] Oxford Languages / Google

[2] Oxford Languages / Google

[3] MedicineNet - https://www.medicinenet.com/script/main/art.asp?articlekey=22631

[4] U.S National Library of Medicine / ChemID Plus - https://pubchem.ncbi.nlm.nih.gov/compound/Arachidonic-acid

[5] National Cancer Institute - https://www.cancer.gov/publications/dictionaries/cancer-terms/def/chemoprevention

[6] U.S National Library of Medicine - https://pubchem.ncbi.nlm.nih.gov/compound/Docosahexaenoic-acid

[7] The Microbiota in Gastrointestinal Pathophysiology, 2017

[8] https://www.nature.com/articles/nri3859

[9] Oxford Languages / Google

[10] Oxford Languages / Google

[11] Oxford Languages / Google

[12] https://link.springer.com/referenceworkentry/10.1007%2F978-3-642-16483-5_2923

[13] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/791321

[14] https://www.ncbi.nlm.nih.gov/pubmed/23069763

Recent Updates

- 3-29-2021
  - Added 3 quotes to COVID-19
  - Added Fat Life Cycle Category
  - Add Silent Inflammation Category
- 4/3/2021 - 2nd Edition
  - Minor Fixes
  - Added Developmental Disorders, Fluoride, Vitamin B6
  - Updated Introduction Section, Insulin Resistance, Blood Cancers, Cannabinoids, Stress, Cannabidiol
- 4/14/2021 - 3nd Edition
  - Updated Exercise & Training
- 7/9/2021 - 8/21/2022 4th edition
  - Added 2 quotes at the beginning of book
  - Fixed a few issues under B section
  - Fixed Alopecia Areata category as there was duplicates, and merged the two
  - Fixed Colitis and added a couple quotes
  - Fixed a quote under Fasting
  - Added to categories: Autism, Endocannabinoid System, Multiple Sclerosis, Kidney Inflammation, Omega-6 (arachidonic acid) , Prostaglandins, Kidney Disease, Skin, Synthetic Cannabinoids & Derivatives
  - New Categories: Alopecia, Amyotrophic Lateral Sclerosis (ALS), Exhale, HIV, Infant, Traumatic Axonal Injury, Neurological Disease, Ultraviolet Radiation, Respiratory Diseases, Oligodendrocyte Dysfunction
  - Updated TBI, Brain Injury , Multiple Sclerosis (MS)

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You can contact me at inflammation.life@gmail.com if you have any questions or concerns.

Check online at inflammation.life for future updates.

Thank you