COURSE NOTES: Understanding genetics for improving health outcomes

Course Code: CEUGH

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Course Description

The course is intended to provide the tools that holistic nutritionists can use to deliver personalized healthcare to their clients, catered to the genetic makeup of the client. Genetics plays a very robust role in nutrition, detoxification, weightloss and overall health and wellness. Furthermore, genetics can be used not only to improve the health of the clients but also to develop DNA based nutritional plans that can potentially prevent development of chronic diseases. Course participants will gain knowledge on how genetic information can be used to deliver nutritional plans, weightloss strategies, detoxification plans, hormonal balance plans along with nutritional plans to prevent development of chronic disease such as diabetes and cardiovascular diseases.

IHN has partnered with Anantlife Canada Inc., a leader in clinical grade genetic testing for healthcare providers all over the world, to offer a Certified Genetic Testing Provider Certificate upon successful completion of the course. Successful completion of the course implies that the candidates have received the education and training to not only understand genetic concepts pertaining to diet, nutrition, detoxification, fitness, hormonal health and metabolic disorders but have also been trained on interpretation of the genetic testing reports along with development of a DNA based health plan for better health outcomes.

SESSION 6:

GENETICS OF ENDOCANNABINOID PATHWAYS – UNDERSTANDING THE ROLE OF GENETICS IN REGULATING RESPONSE TO CANNABIS AND APPLICATIONS IN GENETIC TESTING

Every human has an endocannabinoid pathway which is responsible for generation/breakdown and signal transduction of cannabinoids. Cannabis contains cannabinoids which upon ingestion has an impact on the endocannabinoid system. The genetics of endocannabinoid system plays a role in determining how one reacts to cannabis including the risk of addiction, psychoses, cardiovascular complications, eating disorders along with understanding which cannabinoid is likely to have higher clinical efficacy. The readings herein are to provide an extensive understanding of the endocannabinoid system as well as how genetic variation in plays a role in determining one's response to cannabis including the risk of adverse effects.

GENETIC TESTING TO IDENTIFY PREDISPOSITION TO CANNABIS INDUCED ADVERSE EFFECTS FOR WIDESPREAD ACCEPTANCE OF MEDICAL CANNABIS IN MODERN MEDICINE

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Cannabis has been widely used as a medicinal agent in Eastern medicine with earliest evidence in ancient Chinese practice dating back to 2700 BC. Medical cannabis and cannabinoid based drugs have become a part of modern-day medicine with an ever-expanding list of diseases for which cannabis can be used as treatment. Medical cannabis is increasingly used as a treatment or adjunct treatment with different levels of efficacy in several neurological disorders or related symptoms (such as multiple sclerosis, autism, Parkinson and Alzheimer disease, Tourette's syndrome, Huntington's disease, neuropathic pain, epilepsy, headache), as well as in other medical conditions (e.g. nausea and vomiting, glaucoma, appetite stimulation, cancer, inflammatory conditions, asthma). However, at the same time cannabis associated adverse health events have been reported in addition to many neurological adverse effects from use of medical cannabis both short as well as long term. In fact, in almost 10% of users, cannabis has been associated with development of adverse effects such as cannabis dependence, cannabis induced cognitive defects, cardiovascular issues as well as eating disorders.

The widespread use of medical cannabis is impeded by the reluctance of physicians in prescribing medical cannabis due to the potential adverse effects. To put this simply, when physicians prescribe antibiotics, there is no uncertainty as they are aware in terms of what can go wrong. In contrast to an antibiotic, when they are writing a license to the patient to take medical cannabis, there is a lot of fear they have in their minds on the potential adverse impact of cannabis. As such, to further progress widespread use of medical cannabis there is a need for a testing methodology to identify whether cannabis is potentially going to be advantageous or disadvantageous for the patient. Hence, a genetic test to assess for predisposition to cannabis associated adverse effects is needed to further expedite widespread acceptance of medical cannabis as a medical treatment. Moreover, to further alleviate concerns pertaining to genetic testing, genetic information non-discrimination act has been passed in US, Europe as well as Canada which prevents genetic discrimination based on individual's genetic makeup or predisposition. Opioid epidemic claims almost 78 lives a day and medical cannabis offers a ray of hope to potential alleviate the opioid epidemic. With medical cannabis, opioid users who have been taking opioids for their pain can potentially be weaned off the opioids and be given medical cannabis. Nevertheless, prior to prescribing medical cannabis physicians need to understand how the patient's body is going to react to it as one would not want to prescribe medical cannabis to somebody who is highly predisposed to cognitive defects, perhaps even schizophrenia. In such scenarios, genetic test becomes quite powerful, in identifying individuals who are potentially the best and the worst candidates to move from opioids to medical cannabis. Research on various strains of Cannabis is moving at a rapid pace and eventually genetic testing can be coupled with recommendations to identify which strain of cannabis is likely to be more efficacious for an individual depending on their genetic makeup.

Anantlife, a Canadian Genetics company has been working with clinics all over US and Canada to offer the most comprehensive, robust and scientifically backed genetic tests for cancer, autoimmunity, brain disorders, nutrition and ethnicity specific diseases using the Next Generation Sequencing platform, targeting greater than 99% accuracy. Over the past year Anantlife has actively worked with cannabis physicians, researchers, bioinformaticians along with medical geneticists to develop the world's first genetic test aimed to identify predisposition to cannabis related adverse effects. The test is based on a robust analysis of over 20 markers identified by extensive review of clinical research carried out to date as well as data mining from our databases as well as external reputable genetic databases. In conjunction with the genetic information, the test takes into consideration the family medical history of the individual and uses a proprietary algorithm to carry out risk stratification analysis to identify if the individual has low risk, moderate risk or high risk of developing cannabis induced dependence, cognition deficits, cardiovascular complications and eating disorders. Furthermore, every two weeks, the scientific team at Anantlife performs an extensive critical review of new research developments coupled with validation through data mining to identify potentially new genetic markers which can be further incorporated into the test to increase predictive power.

Studies examining the characteristics of medical cannabis patients in the US have revealed that the majority medicate daily and consume 6–9 g of cannabis per week. In Canada, 42% of medical cannabis patients reported medicating two to three times per day, and 40% consume greater 14 g per week. In addition to patients with access to prescribed medical cannabis, there is also a huge population of users who consume cannabis recreationally or for self-defined medical reasons. Cannabis is the most commonly used illicit drug in the world, with 7% of adults in the US reporting use within the last 30 days. Interestingly, only 53% of adult cannabis users in the US consume cannabis exclusively for recreational purposes, while the other 47% of users consume cannabis "in part or entirely for medicinal purposes", with 10% using solely for medicinal purposes. Recreational use of cannabis is increasing rapidly all over the US and Canada. The onus really falls on the individual to understand how their body is going to react to regular recreational cannabis use. The genetic test can potentially offer them the information on their genetic make-up and their predisposition, which they can use to make a better decision regarding their personal recreational cannabis use.

Every person has an endocannabinoid system, just like a nervous system and digestive system. The endocannabinoid system is involved in many processes in your body, including appetite, pain-sensation, mood and memory. The two major pharmacologically active cannabinoids are phytocannabinoid Δ9-tetrahydrocannabinol (THC) and phytocannabinoid cannabidiol (CBD). Some medical ailments affect the proper functioning of the endocannabinoid system, which can lead to many of the symptoms that patients experience as part of their condition. Cannabinoids can help to treat those symptoms by supplementing the endocannabinoids normally produced in your body, and subsidizing the endocannabinoid system. However, cannabis use may also lead to addiction, binge eating, anorexia nervosa, cognitive defects, psychotic phenomena and impact brain activity which can be dependent on the genetic makeup. The human genome consists of about 25,000 genes and virtually all can exist in different forms. The variations in our genes make us unique and different from one another. Genetic variation determines how our endocannabinoid pathway metabolizes THC and CBD and determines the impact of cannabis on our physiology. The genes within the endocannabinoid system can be divided into several groups: genes encoding receptors—CNR1, CNR2, TRPV1, GPR55, OPRM1, and GABRA2; transporters and action—ABCB1, ABCG2, SLC6A4, and COMT; metabolism of cannabinoids—CYPs and UGTs; biosynthesis, bioactivation of

endocannabinoids: FAAH, MAGL, COX2, ABHD6, and ABHD12; and cannabinoid-related cellular processes: MAPK14. The genetic variation amongst these genes plays a very important role in identifying how an individual's body will respond to medical cannabis and can further dictate the predisposition of an individual towards development of cannabis associated adverse effects. Moreover, the differential effects of THC and CBD are further dependent on the genetic variation within endocannabinoid pathway. At the same time, genes involved in the cardiovascular system as well as metabolic pathways can also interact with cannabis use towards predisposing an individual to development of cardiovascular complications as well as eating disorders with long term cannabis use.

According to the most recent research, roughly 10 percent of cannabis users will develop a psychological dependence on the drug. A dependence is defined as habitual use that impedes or interferes with daily functioning. Cannabis dependence, also referred to as "cannabis use disorder" as experienced in clinical populations appears very similar as other substance dependence disorders. However, the percentage of cannabis users that become dependent tends to be lower than other drugs such as opioids. Cannabis dependent adults continue to use cannabis despite social, psychological, and physical impairments, commonly citing consequences such as relationship and family problems, financial difficulties, low energy and self-esteem, dissatisfaction with productivity levels, sleep and memory problems, and low life satisfaction. Most perceive themselves as unable to stop, and most experience a withdrawal syndrome upon cessation. Cannabis dependence also shows a very strong association with major depressive order with studies showing a very strong genetic correlation. As such individuals predisposed to development of cannabis dependence may also be predisposed towards development of major depressive disorder. One of the biggest risk factor for cannabis dependence is the individual's genetic makeup based on the genetic polymorphisms within the endocannabinoid pathway. Genetic polymorphisms in several different genes of the endocannabinoid pathway including genes encoding for receptors, transporters as well as endocannabinoid biotransformation and activation have been shown in several clinical studies to play an essential role in mediating an increased risk of developing cannabis dependence.

Clinical epidemiology studies have consistently demonstrated that cannabis use is associated with an increased subsequent risk of both psychotic symptoms and schizophrenia-like psychoses. It is well known that cannabis intoxication can cause brief psychotic symptoms like paranoia, whilst recent evidence demonstrates that heavy use of cannabis increases the risk of chronic psychoses like schizophrenia with genetic component predisposing some people to a higher risk. Numerous studies have reported marijuana-associated impairments in frontal function, most notably during tasks that require executive control, inhibition, and decision making. Furthermore, several investigations have specifically examined the role of age at marijuana onset, with results suggesting that earlier age at marijuana onset is related to impairment on measures of visual scanning, verbal IQ, and executive function. Marijuana smokers performed more poorly than healthy control subjects on tasks of executive function, including the Wisconsin Card Sorting Test (WCST) and Stroop Color Word Test (Stroop). Several genes from the endocannabinoid pathway have been shown to mediate predisposition to cannabis induced cognitive defects ranging from impact on executive function, cortical response to even brain volume deficits.

Cardiovascular diseases remain the most frequent cause of global death worldwide, and the most common is coronary artery disease, with a mortality rate of around 15%. Cannabis consumption has been shown to cause increase in heart rate, supine systolic and diastolic blood pressures, and forearm blood flow via increased sympathetic nervous system activity. These actions increase myocardial oxygen demand to a degree that they can decrease the time to exercise-induced angina in patients with a history

of stable angina. In addition, cannabis has also been associated with increasing the risk for myocardial infarctions (MIs) in young male patients. Cannabis has been shown to increase the risk of MI onset by a factor of 4.8 for the 60 minutes after marijuana consumption, and to increase the annual risk of MI in the daily cannabis user from 1.5% to 3% per year. Genetic predisposition plays a strong role in development of cardiovascular diseases since an individual predisposed to cardiovascular complications is likely to very prone to developing cardiac issues with cannabis use. As such cannabis users need to understand their risk of predisposition to cardiovascular diseases with regular cannabis use.

Eating is very pleasurable. Yet, for some people, eating can induce feelings of anxiety and fear. Food, or even the expectation of food, makes someone with anorexia nervosa feel terribly uncomfortable; the only thing that can reduce this anxiety is to avoid food completely. Bulimia shares some features with anorexia; these people alternate between a careful restriction of eating and an almost complete loss of self-control. The endogenous endocannabinoid system has an important role in signaling rewarding events, such as eating. Our brain's endocannabinoid system normally controls how much pleasure we derive from sensory experiences; it then motivates us to repeat the experience again and again. As such, exogenous cannabinoids directly impact our feeding behaviour. Research shows that mutations in several genes of the endocannabinoid system can increase the risk of eating disorders, which is of prime importance for individuals on medical cannabis. Moreover, at the same time medical cannabis is being currently used by HIV as well as cancer patients to boost appetite. However, based on genetic predisposition, it may have the opposite effect due to genetic predisposition to eating disorders and as such understanding the predisposition is of eminent importance prior to the use of medical cannabis in these individuals.

Genetic testing for predisposition to cannabis associated adverse effects will not only help alleviate physician's concerns in prescribing medical cannabis but it will also aid in helping an individual make better decisions towards using cannabis for medical or recreational purposes. At the same time with the current opioid crisis, there is a need to move individuals from opioids to cannabis for various conditions. Hence genetic testing becomes extremely powerful, in identifying who are the best and who are the worst candidates to move from opioids to medical cannabis. Overall genetic testing will help in potentially eliminating cannabis induced adverse effects which will bring to frontline the clinical benefits of cannabis and will significantly aid in acceptance of medical cannabis as a medical treatment in modern medicine.

An Introduction to the Endocannabinoid System

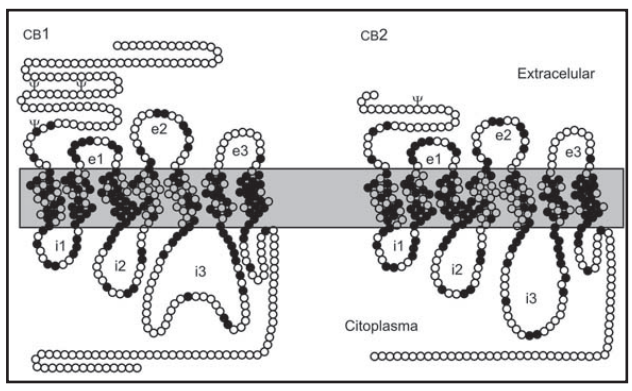
A description of the lipid signaling system essential to health, healing, and homeostasis, long excluded from the medical school curriculum

By Dustin Sulak, D.O.

Adapted from a class for doctors entering the field of Cannabis-based Medicine.

You may be wondering why, as a clinician, you've never learned about the endocannabinoid system (ECS) during any of your training. The discovery of this system is relatively new, but it's been around for 20 years, and a huge body of evidence and peer-reviewed research has been published on various aspects of the endocannabinoid system.

There are two different cannabinoid receptors, the CB1 and the CB2, which are very similar in structure. They follow the classic pattern of the G protein-coupled receptor with seven passes through the cell membrane.



CB1 and CB2 are 7-transmembrane G-coupled receptors. Lipophilic ligands outside the cell (top) activate structures within the hydrophobic layer of the membrane, leading to a response within the cell (bottom).

CB1 receptors are located primarily in the nervous system, but also found in reproductive tissues, connective tissues, adipose tissues, and other glands and organs. The CB2 receptors are found primarily in cells of the immune system, but during situations of injury or inflammation, the CB2 receptors can also be created and up-regulated in other tissues where they're not normally found.

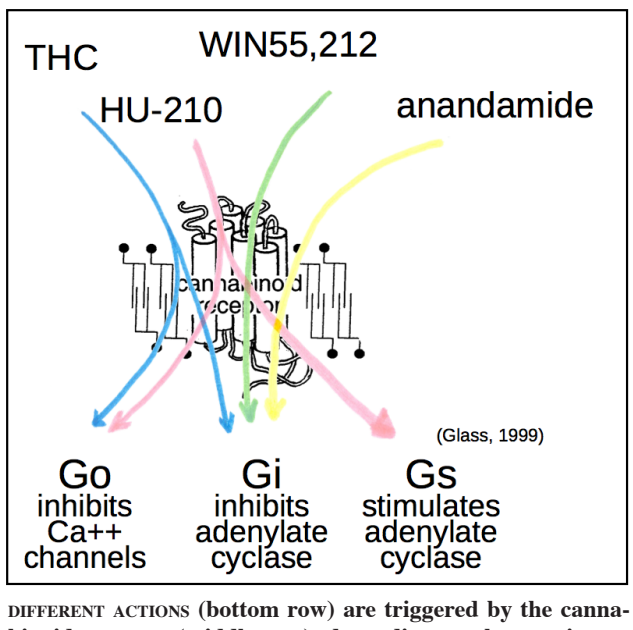
The cannabinoid system is extremely old. Phylogenetic studies suggest the cannabinoid receptors evolved some 600 million years ago. Insects don't have any cannabinoid receptors.

Very primitive animals like sea squirts and nematodes have a cannabinoid receptor that's almost identical to the human CB1 receptor. This high level of evolutionary conservation suggests that this receptor and receptor system is very important for the function of life.

G protein receptors

G protein-coupled receptors can open or close the ion channels and they can inhibit or stimulate the formation of adenylate cyclase, which will have other downstream effects in the cell.

"Agonist trafficking" means that the function of the cannabinoid receptor depends on which agonist actually activates that receptor, which adds another layer of complexity to the ECS. This is analogous to an assortment of keys opening the same lock. But depending on which key is used, the door will open into different rooms.



Different actions (bottom row) are triggered by the cannabinoid receptor (middle row), depending on the agonist activating it (top row). THC is from the plant. WIN55,212 and HU-210 are synthetics, and anandamide is made by the body.

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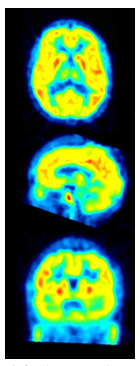
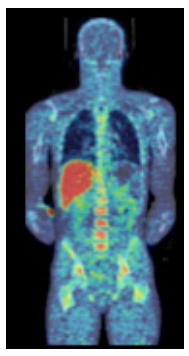




CB1 receptors *(scans at left)* are distributed throughout the central nervous system, with highest densities shown in red. CB2 receptors *(scan at right)* are found throughout the periphery, with especially high density in the liver.

Endogenous Cannabinoids and Their Targets

The endogenous (endo-) cannabinoids are molecules our bodies make to interact with the cannabinoid receptors. The two most well-known are anandamide and 2-arachidonoyl glycerol (2-AG). Anandamide is named after the Sanskrit word *ananda*, which means bliss.

The endocannabinoids are arachidonic acid derivatives synthesized on demand from precursors in the cell membrane. They act as "retrograde messengers." Elsewhere in the body these endocannabinoids function as autocrine (within cells) and paracrine (cell-to-cell) mediators.

When the endocannabinoids have finished their signaling role, they're degraded by enzyme hydrolysis; FAAH (fatty acid amide hydrolase) degrades anandamide and MAGL(monoaglycerol lipase) degrades 2-AG.

Several other endogenous cannabinoids, less well understood than anandamide and 2-AG, play a significant role in the function of the endocannabinoid system.

The endocannabinoids also have other targets in the body besides the CB1 and CB2 receptors. For example, G-protein receptor 55 (or GPR55) is a post-synaptic membrane receptor involved in hyperalgesia and endocannabinoid production. Stimulating this receptor likely signals the cell to cease the production of endocannabinoids.

The TRPV1 receptor (also know as the capsaicin receptor) is another target of endocannabinoids. It has implications in pain, inflammation, respiratory, and cardiovascular disorders.

Peroxisome proliferator-activated receptors (or PPARs) are nuclear membrane receptors located inside the cell that are also targets of endocannabinoids. They regulate the translation of genes that are involved in metabolism, energy homeostasis, cell differentiation, and inflammation. PPAR agonists tend to have anti-inflammatory, cardioprotective, and neuro-protective properties.

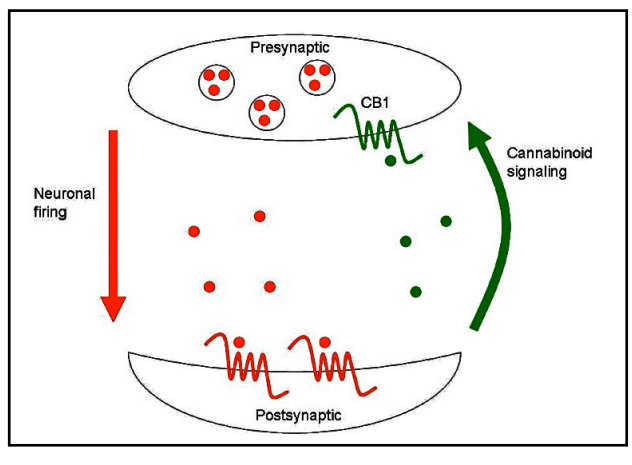
Furthermore, endocannabinoids can control voltage-gated ion channels and ligand-gated ion channels.

Canabinoid function in the nervous system

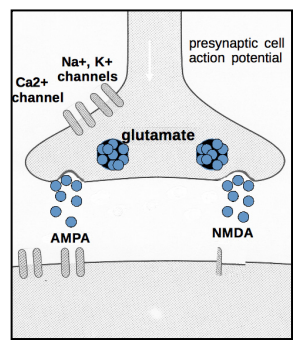
The CB1 receptor is the most common G-protein receptor found in the human brain. The highest densities of CB1 are found in the hippocampus, the cerebral cortex, the cerebellum, the amygdala nucleus, and the basal ganglia —areas of the brain involved with short-term memory, cognition, mood and emotion, motor function, and nociception.

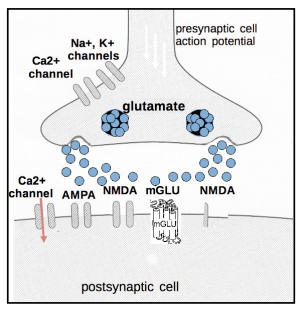
Cannabinoid receptors are virtually absent in brainstem cardiorespiratory centers. This is why that there is no lethal overdose of cannabinoids.

Below is a simplified diagram of the "retrograde signaling" activity of cannabinoids in the nervous system. At the top you see the presynaptic cell with neurotransmitters inside of vesicles. Upon nerve depolarization, these neurotransmitters are released, and they move across the synapse to stimulate a receptor on the post-synaptic cell. Cannabinoids follow the opposite path. They're produced on the cell membrane of the post-synaptic cell and travel retrograde across the synapse to interact with the CB1 receptor on the pre-synaptic nerve terminal.



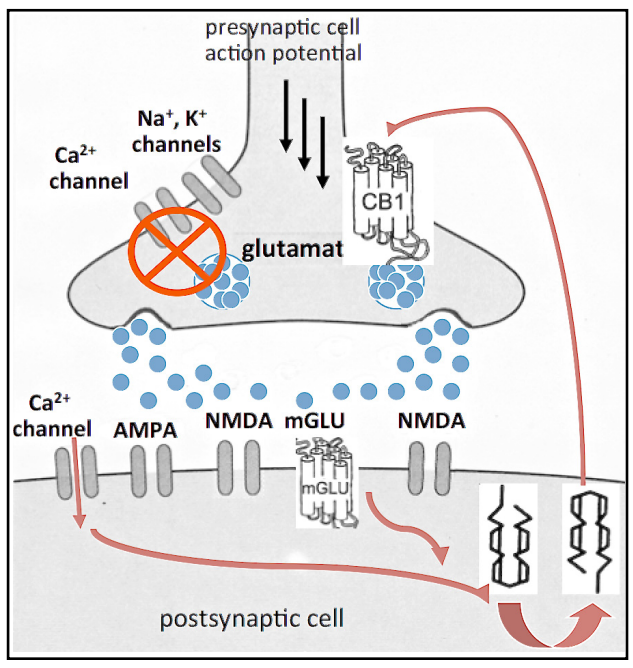
Retrograde signaling is the process by which cannabinoids made on a postsynaptic cell travel across the synapse (upwards in graphic) to modulate the neurotransmitter release of the presynaptic cell.





Let's look at the function of retrograde signaling in a little more depth, beginning with depolarization-induced suppression of excitation. In the illustrations at right we see an excitatory glutamatergic nerve releasing its glutamate neurotransmitter into the synapse. This occurs after an action potential arrives at the accent terminal and opens voltage-gated calcium channels. The glutamate diffuses across the synapse to interact with receptors in the post-synaptic cell. Cannabinoids are produced in the post synaptic membrane and act on the presynaptic cell to halt this excitatory process.

The same model applies to inhibitory GABAnergic neurons. In the illustration below we see 2-AG diffusing retrosynaptically to a presynaptic CB1 receptor, closing calcium channels and preventing the release of GABA into the synapse. This is called depolarization-induced suppression of inhibition.



Neuroplasticity

The function of the endocannabinoid system in the nervous system is more than just homeostatic prevention of too much excitation or too much inhibition. There is a significant protective and repair function, and the endocannabinoid system is heavily involved in neuroplasticity.

Neuroplasticity involves the sprouting and pruning of synapses, changes in dendritic spine density, and changes in neurotransmitter pathways. It gives rise to all types of adaptive learning, including recovering from a stroke, the conscious act of gaining a new skill, and the unconscious acquisition of a new emotional response. It is also involved in pathological processes such as central sensitization to pain.

There are multiple mechanisms by which cannabinoids modulate neural plasticity, including neurogenesis (the formation of new neurons), long-term potentiation and long-term depression.

Research in humans has shown that the administration of exogenous cannabinoids can cause neuroplastic changes. One study that looked at volunteers who were heavy cannabis users found neuroplastic changes in the nucleus accumbens and amygdala. These are two areas of the brain that are involved in the enjoyment of activities such as eating and sex, and also involved in addiction.

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Endocannabinoid System *from previous page*

Other studies have shown that cannabinoids can enhance a process called fear extinction. Fear extinction is a neuroplastic event that's essential for preventing and recovering from post-traumatic stress.

Anandamide and 2-AG are also endogenous neuroprotective agents, produced by the nervous system in response to both chemical and mechanical trauma. Other phytocannabinoids and synthetic cannabinoids have been shown to decrease glutamate excitotoxicity in a situation of a seizure or a stroke.

When neurons become injured or ill, they tend to release their contents. Excitatory neurons release levels of glutamate that become toxic to the surrounding cells, and we see a domino effect of excitotoxicity. Cannabinoids have been shown to halt that process.

The United States Department of Health and Human Services actually owns a patent on the use of cannabinoids as anti-oxidants and neuroprotectants. The authors of this patent discuss the potential benefit of using cannabinoids in neurodegenerative conditions such as multiple sclerosis, Alzheimer's, Parkinson's, Huntington's, and more.

Cannabinoids also affect autonomic tone. In the sympathetic nervous system, CB1 receptor stimulation will inhibit noroepinephrine release. It will dampen sympathetically mediated pain and modulate the hypothalamic-pituitary-adrenal axis and the hypothalamic locus coerulius-norepinephrine axis.

Depending on the situation, stimulation of the CB1 receptors could increase or decrease heart rate and contractility.

Cannabioid receptors also have peripheral activities that affect autonomic tone: For example, myocardial CB1 receptors, when activated, cause vagally mediated biphasic effects in heart rate and cardiac contractility. Depending on the situation, stimulation of the CB1 receptors could increase or decrease heart rate and contractility.

In vascular tissues CB1 activation causes vasodilation, which leads to an anti-hypertensive effect that has been demonstrated in humans.

Some rodent studies suggest that cannabinoid receptor activation has a protective role in myocardial ischemia.

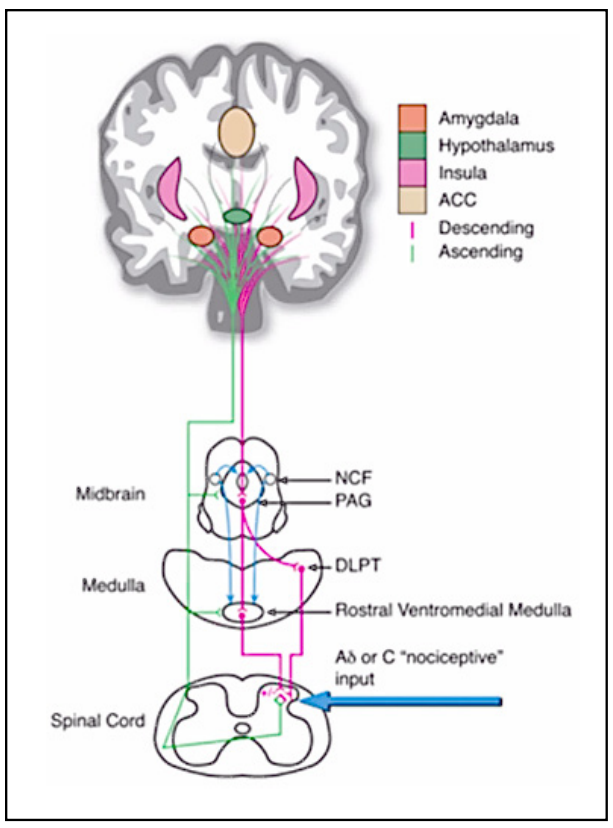
The parasympathetic nervous system also has CB1 receptors, which will reduce parasympathetic activity when stimulated. And this is likely providing the anti-emetic effect of cannabinoids.

Pain signaling

The endocannabinoid system is heavily involved in pain signaling. Pre-clinical models have shown that endocannabinoid activation causes antinociceptive effects in the three major types of pain: acute pain, persistent inflammatory pain, and neuropathic pain.

The antinociceptive effects of cannabinoids involve many mechanisms in different parts of the body, including the central nervous system's periaqueductal gray, ventroposterior lateral nucleus of the thalamus, and rostral ventromedial medulla), as well as the spinal cord, the peripheral nervous system, and the peripheral tissues.

One mechanism by which cannabinoids are able to decrease nociception and decrease the perception of pain involves the descending pain inhibitory pathway depicted below. This pathway has components in the mid-brain, the medulla, and the spinal cord that decrease the nociceptive signals that make it to pain areas in the brain.



'Descending pain inhibitory pathway' is enhanced by cannabinoids to decrease pain signaling to the brain.

In the dorsal horn of the spinal cord there are inhibitory interneurons that release GABA and actually suppress this descending pain inhibitory pathway. Cannabinoids will suppress these GABA-releasing interneurons, thus enabling the descending pain pathway to do its work in decreasing the amount of pain experienced.

Cannabinoids also decrease pain associated with injury via the homeostasis of activators and sensitizers. When we experience an injury, activators and sensitizers cause peripheral sensitization including hyperalgesia and eventually allodynia. These activators and sensitizers come from a variety of sources including the damaged tissue itself, the leukocytes, leukocyte-activated platelets, the neighboring autonomic nerves, and the nociceptive nerves themselves. All can release activators and sensitizers, leading to peripheral sensitization, which elicits a homeostatic response by the endocannabinoid system.

As peripheral sensitization begins after an injury, the function of the endocannabinoid system provides the first line of defense against pain. CB1 receptors will decrease the release of activators and sensitizers around the site of the tissue injury. CB1 receptors on the nociceptor will also open potassium channels and cause the nociceptor to hyperpolarize, making it less likely to fire. At the same time, CB2 receptor signaling decreases the release of activators and sensitizers from the neighboring immune cells.

As noted, CB2 receptors are found not only in immune cells but also in other tissues, especially during situations of injury. CB2 receptors have been found, for example, in painful neuromas. And CB2 agonists produce anti-nociceptive effects in pre-clinical models of inflammatory and nociceptive pain.

Cannabinoid-opioid interaction

Opioids and cannabinoids share several pharmacologic effects including antinociception. In animal studies, the crosstalk between these two signaling pathways has shown promise for combination pain therapy and novel treatments for opioid addiction and abuse.

The spinal administration of various cannabinoids with morphine produces a greater-than-additive anti-nociceptive effect in mice. The "tail-flick test" enables researchers to assess pain levels. The rodent is positioned with its tail on a hot plate and the heat is gradually increased until the animal feels the pain and flicks its tail.

Various doses of morphine can be given to rodents to plot the dose response curve of antinociception in the tail flick test. When very low doses of THC —doses that are marginally active in a tail-flick test— are added to morphine, the dose response curve of morphine shifts to the left by four-to-12-fold.

The same is true in the opposite experiment. When low doses of morphine are added to the THC trial, we see the dose response curve shifting to the left again. This points to an analgesic synergy beyond just the additive effects of morphine plus THC.

Adding cannabinoids to opioids will potentiate analgesia but will not increase the risk of cardio-respiratory suppression or fatal overdose.

THC has also been shown to trigger the release of endogenous opioids, which stimulate both the delta and kappa opioid receptors. Combination treatment with cannabinoids and opioids is surprisingly safe. The cannabinoid and opioid receptors are both found in areas of the brain and spinal cord that control pain signaling. But because the cannabinoid receptors have such low densities in the brainstem's cardio-respiratory center, adding cannabinoids to opioids will potentiate the analgesia but will not increase the risk of cardiorespiratory suppression or fatal overdose. Therefore, combination therapy actually increases the therapeutic index of opioids.

We all know that, clinically, treating chronic pain with opioids is a major problem due to tolerance building and the need for dose escalation. Cannabinoids, when co-administered with opioids, can prevent tolerance building to the opioids. Opioid receptor proteins are upregulated in the spinal cord of animals treated with both cannabinoids and opioids. Mice treated with low doses of THC and morphine in combination showed avoidance of tolerance to the opioids while retaining their anti-nociceptive effects.

CB1 and MU opioid receptors are also co-localized in the areas of the brain that are important for morphine abstinence, such as the nucleus accumbens.

Endocannabinoids and connective tissue

In bone, both osteoblasts and osteoclast produce anandamide and 2-AG, and both express the CB2 receptor. Stimulation of this receptor leads to decreased osteoclast activity and increased osteoblast activity, thus increasing bone formation.

There are CB1 receptors on the sympathetic nerve terminals close to the osteoblasts. These nerves release norepinephrine, which restrains bone formation. Retrograde CB1 signaling will inhibit the release of the norepinephrine and alleviate this tonic sympathetic restraint, thus allowing bone to form.

Cells in other connective tissues —fibroblasts, myofibroblasts, chondrocytes, and synoviocytes— express both CB1 and CB2 receptors, and the enzymes used to metabolize endocannabinoids.

CB1 receptors have been found to be upregulated after exposure to inflammatory cytokines and equiaxial stretching of fibroblasts in models of stress.

Cannabinoids also modulate fascia remodeling via fibroblast focal adhesions.

Cannabinoids have been shown to prevent cartilage destruction by inhibiting chondrocyte expression of cytokines and metalloproteinase enzymes.

Cannabinoids have also been shown to decrease connective tissue inflammation. Animal models of atherosclerosis demonstrate that CB2 receptor activation on macrophages within atherosclerotic plaques can decrease atherosclerosis.

ECBs in the immune system.

In contrast to the drug war propaganda that cannabinoids are immunosuppressive, researchers have found that cannabinoids modulate the immune system, just as they modulate other bodily systems. Cannabinoids have been shown to decrease Th1 cytokine levels, increase the levels of Th2 cytokines, and increase certain subsets of B, T, and NK (natural killer) cells.

Phytocannabinoids also have other immune-mediating mechanisms that are separate from cannabinoid receptors. For example, THCa, the acidic form of THC, can inhibit the release of tumor necrosis factor-alpha from macrophages.

Neoplasm

As clinicians, when we think of cannabinoids and cancer, we tend to think of the management of cancer symptoms and the side effects of chemotherapy. Many clinicians are surprised to discover that cannabinoids also have direct oncologic effects.

The animals treated with cannabinoids tend to have much slower growing tumors than the animals treated with a control vehicle.

Cannabinoids have been shown to inhibit tumor growth in multiple cell lines. This is a hot area of research. Numerous human cancer cells lines have been xenografted to immunosuppressed rodents and treated with cannabinoids.

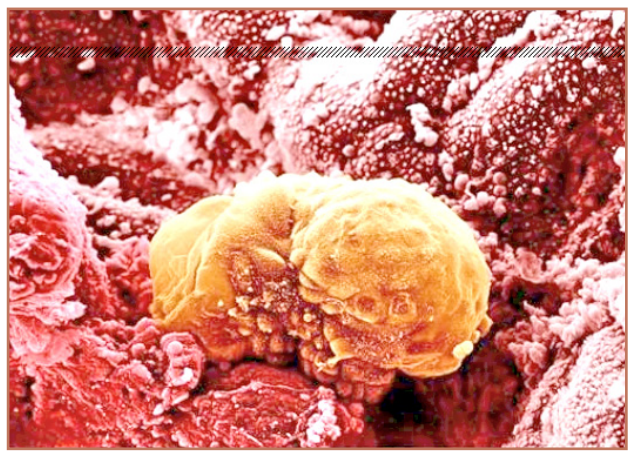
The animals treated with cannabinoids tend to have much slower growing tumors than the animals treated with a control vehicle. Cannabinoids affect neoplasm via multiple mechanisms of action, including cytostatis, apoptotis, antiangiogenesis, and antimetastesis.

Cannabinoids are selective anti-tumor compounds that can kill cancer cells without injuring healthy cells at the same dosage. This makes cannabinoids much less toxic than traditional chemotherapy agents.

Cannabinoids in embryology

Cannabinoids are also heavily involved in embryology and cell growth and differentiation. CB1 receptors have been detected in mouse embryos as early as the second day of gestation. Blastocyst implantation into the endometrium, which is thought of as the first suckling function, requires suitable levels of anandamide.

The proliferation and differentiation of neural stem cells are shaped by extracellular cues provided by endocannabinoids. Adult neurogenesis is regulated by many of these



Six-day-old human embryo, known as a blastocyst, implanting itself onto the wall of the mother's womb, a process mediated in part by the endocannabinoid system in mother and child. False colors show the blastocyst in orange and the womb (endometrium) in pink.

continued on next page

Endocannabinoid System *from previous page*

same embryonic endocannabinoid mechanisms.

Endocannabinoids in the Gastrointestinal System

In the digestive system, CB2 receptors are found in the lamina propria, the plasma cells, activated macrophages, and in the myenteric and submucosal plexus ganglia in the human ilium. CB2 receptor signaling likely involves the inhibition of inflammation, visceral pain, and intestinal motility in the inflamed gut.

The Endocannabinoid System In The Liver

The liver expresses both CB1 and CB2 receptors at low levels. The CB1 receptors are mostly found in endothelial cells and hepatocytes, and the CB2 receptors are mostly found in Kupffer cells.

Anandamide and 2-AG are present at substantial levels in the liver, along with the enzymes needed to break down the endocannabinoids.

Liver injury is associated with an increased endocannabinoid tone in several pathologic settings. During injury or inflammation, CB1 receptors are induced in hepatocytes, hepatic myofibroblasts, and endothelial cells. CB2 receptors are induced in Kupffer cells as well as the hepatic myofibroblasts. Levels of 2-AG also increase in hepatic stellate cells and hepatocytes during liver injury.

The Kupffer cells are involved in our response to early liver injury via the production of tumor necrosis factor-alpha. This signals the stellate cells to synthesize collagen and cause fibrosis. Fibrosis will eventually lead to cirrhosis or loss of liver function.

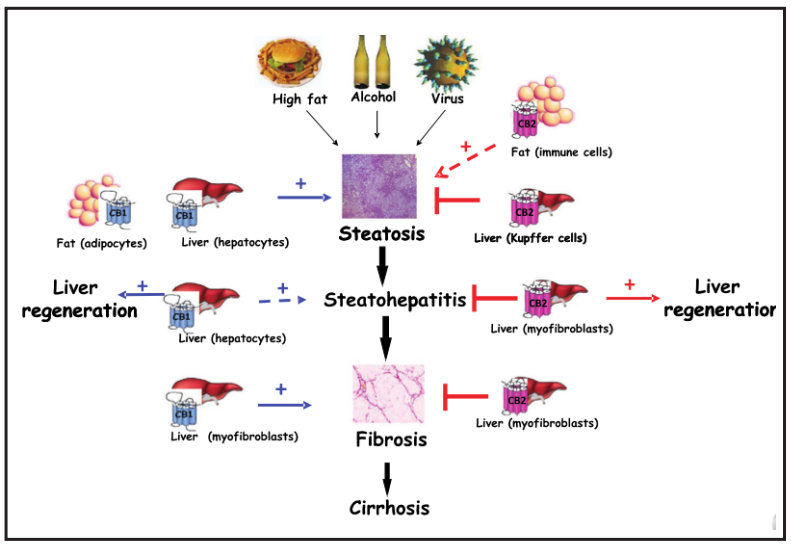
As we can expect from a signaling system that has homeostatic properties, the cannabinoid system can both increase and decrease liver fibrosis via different mechanisms of CB1 and CB2. It's been shown that stimulation of the CB1 receptor can enhance fibrogenesis, while stimulation of the CB2 receptor counteracts the progression of fibrosis. It's important to note that effective antifibrotic treatments are not available in humans yet. And numerous efforts are being directed at the development of liver-specific antifibrotic therapies to treat liver disease and prevent cirrhosis.

CB1 and CB2 receptors have opposite effects on liver fibrosis (see figure below). At the top of the figure we have three typical liver insults: a high fat diet, alcohol, and a virus such as hepatitis C. Early liver injury leads to steatosis, which is enhanced by CB1 receptor activation on hepatocytes and on adipocytes, but inhibited by CB2 receptor activation on the Kupffer cells. Prolonged steatosis will lead to liver inflammation and steatohepatitis. Again, this process is enhanced by CB1 signaling on the hepatocytes and this time inhibited by CB2 signaling on the myofibroblasts. Both CB1 signaling and CB2 signaling can promote liver regeneration at this step. Prolonged inflammation, however, will lead to fibrogenesis, as mentioned previously. This process is enhanced by CB1 signaling in myofibroblasts and inhibited by CB2 signaling in the same cells.

The endocannabinoid system also helps control both hunger and feeding. Human breast milk contains endocannabinoids, and newborn mice that are given a CB1 receptor antagonist stop suckling and die.

The endocannabinoid system modulates cellular metabolism via many other hormones include ghrelin, leptin, orexin, and adiponectin. In obesity, adipocytes produce excessive levels of endocannabinoids which can drive CB1 receptors into a feed-forward dysfunction, contributing to metabolic syndrome. Interestingly, long-term heavy recreational cannabis use is inversely associated with both obesity and Type 2 diabetes.

It has been suggested that blocking CB1 receptor activation could reduce hunger and be a treatment for obesity. A drug that blockes CB1 receptors, Rimonanbant, was approved in Europe, but was later withdrawn from the market because it was found to cause severe psychiatric side effects such as suicide. The endocannabinoid system is incredibly complex and simply blocking a CB receptor is unlikely to offer health benefits without significant side effects in other systems.



CB1 AND CB2 PLAY OPPOSITE ROLES PLAY OPPOSITE ROLES during liver inflammation and injury. CB1 promotes fibrosis (scarring), while CB2 counteracts fibrosis. Both CB1 and CB2 can stimulate liver regeneration.

Potential Disregulations

Although cannabinoid deficiency syndromes have not yet been clearly defined in humans, there is some pre-clinical evidence and some human evidence that dysregulation of the endocannabinoid system is associated with several conditions. Endocannabinoid deficiencies have been implicated in schizophrenia, migraine, multiple sclerosis, Huntington's, and Parkinson's, irritable bowel syndrome, anorexia, motion sickness, fibromyalgia, menstrual symptoms, and other conditions that involve hyperalgesia and abnormal sensitization to pain. Several polymorphisms [differing forms] have been identified in the genes that code for the cannabinoid receptors. And some of these polymorphisms have been associated with clinical outcomes, such as a tendency towards happiness or depression, and the likelihood of developing a post-traumatic stress disorder.

Cannabinoid hyperemesis syndrome is an interesting example of endocannabinoid dysregulation. The precise mechanism of action is unknown, but it may involve endocannabinoid system dysfunction in both the central nervous system and the digestive system. It's a rare condition characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and hot bathing.

Cannabinoid hyperemesis syndrome shares several similarities with cyclic vomiting syndrome, and the two conditions are often confused. This occurs in individuals with long-term, high-dose cannabis use histories. And the onset of the hyperemesis syndrome is often years after initiating cannabis use. The acute treatment for cannabinoid hyperemesis syndrome is hot showers, and patients with this condition are often found compulsively bathing. The long-term solution to this syndrome is cannabis abstinence, which likely allows the endocannabinoid system to return to its homeostatic role in a more balanced manner.

Effects of Exogenous Cannabinoids

Delta-9 THC is the most well known phytocannabinoid. It mimics the activity of anandamide and 2-AG by acting as a partial agonist at CB1 and CB2 receptors. As a partial agonist, THC is usually stimulating the CB1 and CB2 receptors, but it may play the role of an antagonist at CB2 receptors and when the endocannabinoid system is down regulated. There may be advantages of cannabinoid receptor antagonism, for example in the situation of obesity, where the endocannabinoid system is dysregulated and hyperactive endocannabinoid synthesis is contributing to the problem via a feed-forward dysfunction at the CB1 receptor.

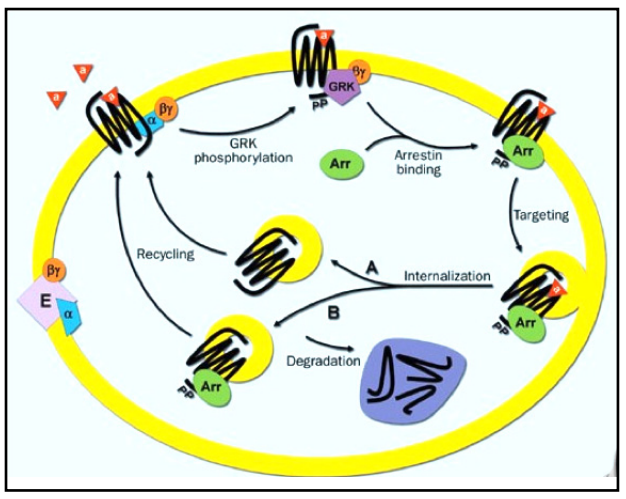
Low doses and acute doses of THC have been shown to cause upregulation within the endocannabinoid system. THC has been shown to increase the production of endocannabinoids, to upregulate CB1 receptors, to increase the receptor affinity, and to enhance the pain relief imparted by endocannabinoids. This suggests that cannabinoid treatments can actually widen their own therapeutic window by enhancing the endocannabinoid system and upregulating the receptor production and receptor sensitivity.

Tolerance to THC develops due to endocannabinoid system down regulation.

In the clinical setting, patients often find that when their cannabis use is below a certain dose threshold, they actually sensitize to cannabis over time and require a lower dose with greater therapeutic benefits. Once the patient exceeds a certain threshold dosage, they begin building tolerance to THC and other exogenous cannabinoids. Tolerance to THC develops due to endocannabinoid system downregulation.

When the cannabinoid receptors are persistently agonized they become phosphorylated, bound by arestin, and pulled into clatherin-coated pits inside the cell, making the receptors unavailable for stimulation. This CB receptor down-regulation and resulting drug tolerance occurs at varying rates and magnitudes in different brain regions. It occurs faster and more dramatically in the hippocampus, which regulates memory, than in the basal ganglia, which mediates the euphoric effect of THC. This difference may explain why memory loss decreases among frequent cannabis users, but the euphoric effect remains. The therapeutic window of cannabinoids can also be widened over time by faster tolerance-building to adverse effects than benefits

In most clinical situations, I recommend using the lowest dose of exogenous cannabinoids and keeping the endocannabinoid system finely tuned and sensitive. However, building tolerance with a cannabinoid receptor agonist —especially when it's needed at higher doses— can actually be advantageous because over time the user will experience less side effects.

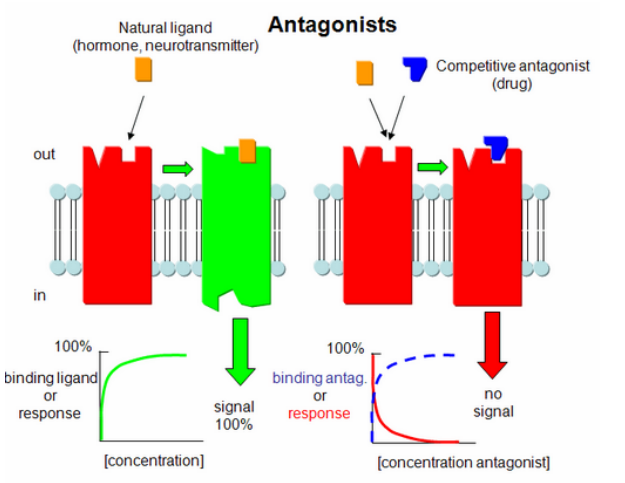


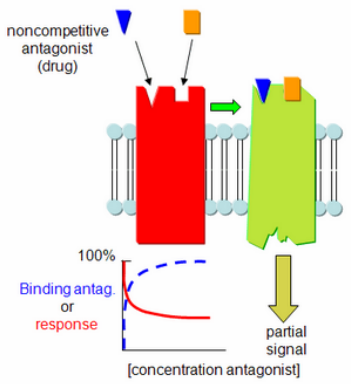
OVER-STIMULATING THE CB RECEPTORS will trigger the cell to internalize the receptor and prevent further activation, a mechanism of tolerance-building to cannabinoids.

Cannabidiol (CBD) is another plant cannabinoid that has been getting a lot of attention for its variety of therapeutic effects. CBD has very low affinity for both the CB1 and CB2 receptors and tends to antagonize other agonists of the CB1 and CB2 receptor. It has been described as "a non-competitive inverse agonist" that modulates the affinity of cannabinoid receptors for their other ligands.

But in addition to the effects on the cannabinoid receptors themselves, cannabidiol has several other mechanisms of action. It antagonizes GPR55, alpha-1 adrenergic receptors, and mu-opioid receptors while activating the 5HT serotonergic receptors and the TRPV1 and TRPV2 vanilloid receptors.

CBD can inhibit the uptake of a variety of neurotransmitters, including noradrenaline, dopamine, serotonin,





CBD has a very low affinity for CB1 and CB2 receptors. It is thought to act as a "non-competitive inverse agonist," de- creasing the receptors' affinity for agonists like THC without completely blocking the receptor's activity. This illustration compares the non-competitive activity of CBD (bottom) with the competitive antagonism of Rimonobant (top). In the bottom model, CBD is represented by the blue triangle, and THC by the orange rectangle.

GABA, and anandamide (the endocannabinoid) by inhibiting the activity of fatty acid amide hydrolase. CBD also has effects on the mitochondria, on voltage-gated calcium channels, and the inhibitory glycine receptor.

Synthetic cannabinoids developed for use in animal research have had clinical application in humans for decades. Dronabinol (Marinol), a synthetic THC, was approved as a schedule 2 drug in 1986 and was moved to schedule 3 in 1999. Nabilone, a THC analog, was also approved by the FDA and finally marketed in the U.S. in 2006. Nabilone is approximately twice as strong as THC. Both these drugs are indicated for chemotherapy-induced nausea and

continued on next page

Endocannabinoid System *from previous page*

vomiting, and as an appetite stimulant for AIDS patients.

Ultra-potent synthetic cannabinoids have much stronger psychoactive effects and a worse side effect profile compared to herbal cannabinoids. One of the disturbing results of cannabis prohibition has been the marketing of herbal products that look like cannabis and have been sprayed with synthetic cannabinoids. These products are sold over the counter —"K2," "Spice," et al— and can land patients in the emergency room with severe psychiatric side effects.

Other influences on the endocannabinoid system

Some common medications have endocannabinoid system activity. For example NSAIDS, both ibuprophen and ketorolac, block the hydrolysis of anandamide by inhibiting FAAH.

COX-2 inhibitors also have cannabinoid effects by potentiating synaptic 2-AG, release thus enhancing CB1 signaling.

Acetaminophen is deacetylated in the liver to its metabolite P aminophenol, which is then conjugated with arachidonic acid in the CNS to form N-arachidonoyl phenylamine, or NAP. NAP has several cannabinoid effects, including preventing the breakdown of anandamide by FAAH, inhibiting COX-1 and COX-2, and acting as a TRPV-1 receptor agonist. The analgesic activity of acetaminophen in rats has been blocked by CB1 and CB2 receptor antagonists, confirming a cannabinoid mechanism of action of acetaminophen for analgesia.

Glucocorticoids also have cannabinoid effects. Pre-clinical rodent studies have shown that acute glucocorticoid administration enhances the activity of endocannabinoids. Corticosteroid mania may have a cannabimimetic component. Chronic exposure to glucocorticoids down regulates the endocannabinoid system, which is scenario consistent with chronic stress. CB1 receptors have also shown to play a pivotal role in the anxiolytic action of benzodiazepines. And many antidepressant, antipsychotic, anxiolytic, and anesthetic agents have demonstrated effects on the endocannabinoid system.

Probiotics have been shown to upregulate CB2 receptor expression in colonic epithelium cells in mice. Administering probiotics can decrease pain behavior following colonic distension with butyrate, a model of Irritable Bowel Syndrome. This effect is reversed by CB2 antagonists, so we know that some of the benefits of priobiotics are due to a CB2 mechanism.

Ethanol can dampen the effects of the endocannabinoid system. Chronic alcohol consumption and binge drinking likely desensitize or down-regulate the CB1 receptor and impair endocannabinoid signaling, except perhaps in areas of the brain involved in reward and motivation to self-administer the substance of abuse.

Several herbal medicines also have endocannabinoid system activity. Curcumin, the active component of the yellow spice turmeric, for example, elevates endocannabinoid levels and brain nerve growth factor in a brain region specific fashion. Pre-treatment with a CB1 receptor antagonist blocks the effects of curcumin on endocannabinoids and brain nerve growth factor.

Echinacea, an herb well known for its use in balancing and stimulating the immune system, contains alkylamides which are potent agonists of the CB2 receptor. These do not interact with the CB1 receptor, and this is why Echinacea doesn't have psychoactive effects. Copal is in the Boswellia family, which has traditional uses for anti-inflammatory and analgesic purposes. Copal incense contains a pentacyclic triterpene that has high affinity for both CB1 and CB2 receptors. Beta-caryophyllene is the principal terpenoid in black pepper and is also found in cannabis and elsewhere in the plant kingdom. Beta-caryophyllene is a CB2 agonist and has demonstrated protective effects in colitis and cisplatin-induced nephrotoxicity via a CB2 mechanism.

Lifestyle Factors

Several lifestyle factors have also been shown to affect the endocannabinoid system. For example, medium to high intensity voluntary exercise increases endocannabinoid system signaling via increased levels of anandamide and potentially increased CB1 receptor expression. The "runner's high" —the euphoria after vigorous exercise that was previously attributed to endorphins— is most likely a cannabimimetic effect.

On the other hand, forced exercise doesn't increase anandamide levels and can actually decrease CB1 signaling! Forced exercise is seen by the endocannabinoid system as a type of stress.

Stress and social play have an impact on the endocannabinoid system. Chronic stress has been shown to impair the ECS via decreased levels of both anandamide and 2-AG. Social play in rats, on the other hand, increases CB1 phosphorylation, which is a marker of CB1 activation in the amygdala. It enhances anandamide levels in the amygdala and the nucleus accumbens, again, areas of the brain that are responsible for enjoyment of pleasurable activities.

Several non-pharmacologic therapeutic treatments have also been shown to work via cannabinoid mechanisms. Electro-acupuncture, for example, causes increased levels of anandamide in the skin via a CB2 receptor mechanism. It also upregulates the expression of the CB2 receptors in the skin, and may have central effects that are mediated by CB1 receptors.

Osteopathic manipulative treatment (OMT), one of my favorite healing modalities, can also have a cannabimimetic effect. In subjects receiving the OMT, serum levels of anandamide after the treatment more than doubled compared with the pre-OMT levels. No change was seen in the control subjects. Other studies have shown cannabinoid effects of other types of bodywork as well.

In summary, the endocannabinoid system is widely distributed throughout the body. The primary function of the endocannabinoid system is cellular homeostasis. Our understanding of the endocannabinoid system is currently incomplete, still emerging, and suggests significant complexity. Manipulation of the endocannabinoid system may provide effective treatments for a wide variety of conditions.

Dustin Sulak, DO, is the founder and medical director of Maine Integrative Healthcare in Manchester, Maine, and Integr8 Health, LLC in Falmouth Maine. This article is based on Sulak's presentation for the Society of Cannabis Clinicians' CME course, which can be accessed via ***cannabisclinicians.org.***

A Discovery By Inference

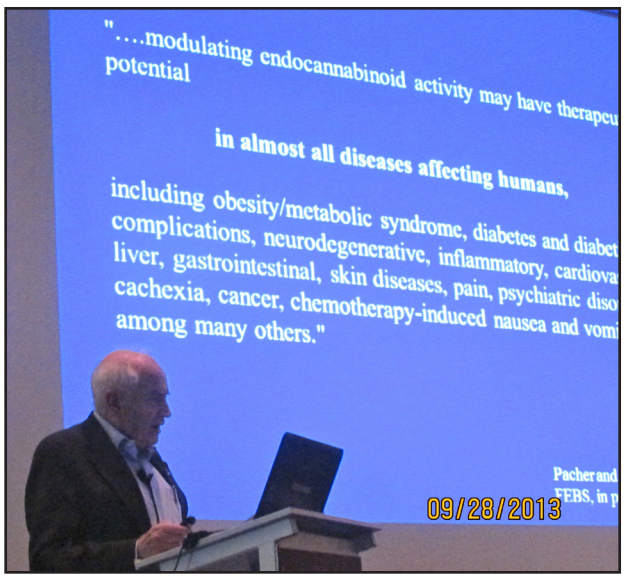
By Fred Gardner

While studies reported in journals help keep scientists and doctors abreast of recent developments, conferences offer a preview of ongoing research and a chance to question and network with the investigators. Scientists who attend meetings of researchers in other fields remark the unusually non-competitive, collegial openness at get-togethers of cannabinoid researchers.

The International Association for Cannabinoid Medicines grew out of a group founded in 1997 by a German physician, Franjo Grotenhermen, the "Association for Cannabis as Medicine." (Similarly, the C-word in the International Cannabinoid Research Society's name has been changed from "Cannabis.")

At the September 2013 IACM meeting in Cologne, Raphael Mechoulam recounted a hypothesis published by Pal Pacher and George Kunos in *FEBS (The Journal of the Federation of European Biochemical Societies)*: "modulating endocannabinoid activity may have therapeutic potential in almost all diseases affecting humans."

Tod Mikuriya, MD, had posited essentially the same hypothesis in 1996, based on his reading of the medical literature and histories he'd taken from patients at the San Francisco Cannabis Buyers Club.

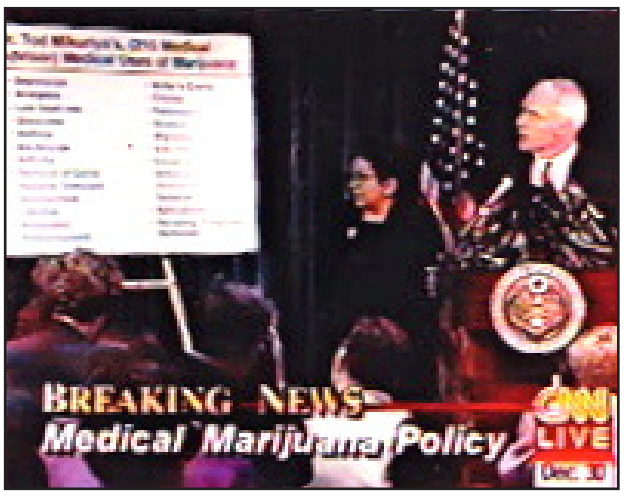


Professor Raphael Mechoulam, at the 2013 meeting of the IACM, admiringly quoted a statement by Pacher and Kunos, "modulating endocannabinoid activity may have therapeutic potential in almost all diseases affecting humans." A slide provided a partial list of conditions involving the endocannabinoid system.

Mikuriya, who died in 2007, was a psychiatrist with a practice in the East Bay, and a scholar who had compiled an anthology of the pre-prohibition medical literature devoted to cannabis. It was he, with the support of organizer Dennis Peron, who insisted that California's medical marijuana initiative legalize its use in treating not just a short list of grave illnesses, but also "any other condition for which marijuana provides relief.

Mikuriya's finding that cannabis alleviates a very wide range of symptoms —and his inference that compounds in the plant act on many physiological systems— were met with contempt by federal officials. At a press conference in December 1996, Drug Czar Barry McCaffrey scoffed that Mikuriya practiced "Cheech and Chong medicine," and Attorney General Janet Reno threatened to revoke the licenses of physicians who approved marijuana use by patients.

Hearing Mechoulam refer matter-of-factly in 2013 to "endocannabinoid involvement in a myriad of bodily processes," I couldn't help thinking that Tod (co-founder of *O'Shaughnessy's*) had reached the same conclusion from a different direction. An insightful doctor can discern things about a drug's mechanism of action. Pharmacology is not the only route to the truth, although as "hard science," it commands more respect than the clinician's craft.



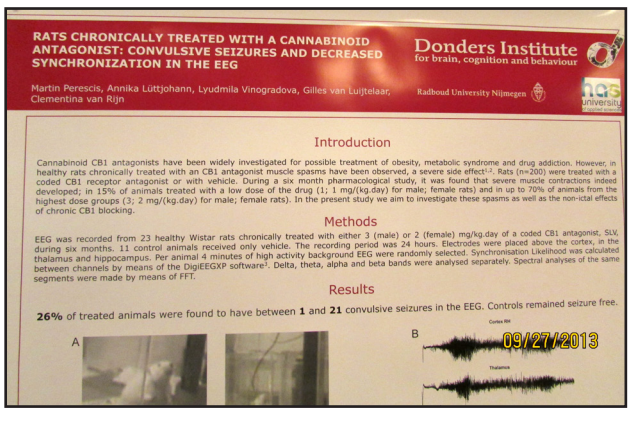
Drug Czar Barry McCaffrey, at a press conference in December 1996, ridiculed Dr. Tod Mikuriya's finding that marijuana provides relief for a very wide range of conditions. A partial list of treatable conditions, culled from a website and attributed to Mikuriya, was blown up for display on an easel.

Pharmacology is not the only route to the truth, although as "hard science," it commands more respect than the clinician's craft.

Another IACM presentation that Tod anticipated, in a sense, linked Rimonabant to epileptic seizures. Rimonabant is a cannabinoid-antagonist drug that Sanofi-Aventis marketed for treating metabolic syndrome. It was approved by European regulatory authorities in 2006 but had to be withdrawn when it led to a spate of suicides.

Tod had written a letter to the U.S. Food and Drug Administration urging that Rimonabant be rejected because any drug blocking the CB1 receptor would very likely cause a wide range of adverse effects —not just mood-related ones. This is an important point because drug manufacturers still dream of marketing synthetic cannabinoid antagonist drugs, and some would have us believe that suicidality was the one and only problem with Rimonabant.

An IACM poster by Dutch researcher Martin Perescis described a study in which he and his team treated 200 rats with either an antagonist drug or placebo for six months. "Severe muscle contractions developed in 15% of animals treated with a low dose of the drug... and in up to 70% of animals from the highest dose groups." Video recordings showed that over the course of 24 hours, "26% of animals treated with this CB1 antagonist were found to have between 1 and 21 convulsive seizures in the EEG, whereas controls remain seizure free."



Cannabinoid antagonist drugs can induce seizures in rats, according to an IACM poster by Martin Perescis and colleagues in the Netherlands. Their findings put the lie to the oft-repeated assertion that the only adverse effect of the antagonist drug Rimonabant was suicidal ideation.

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