The Biochemical System Controlling the Effects of Cannabis: An Introduction

Jahan Marcu, PhD, presents his 2015 article on the endocannabinoid system as it appeared in *HerbalEGram*. 2015;12(6).

In every human there are complex biological systems working to keep physiological functions in order. When these biochemical systems are functioning optimally, they maintain optimal mood and help maintain appropriate levels of immunity, proper digestion, regular sleep, and brain function. The housekeeping properties of these systems have an important role in modulating health and disease. One of these systems is the endocannabinoid system (ECS). The system is built out of G protein-coupled receptors called (CB_1 and CB_2 receptors) and the endocannabinoids that bind to them. The ECS maintains normal cerebral and physiologic function.[1]

Human clinical trials and animal studies show that stimulating this biochemical system can have both highly beneficial health effects and few negative side effects.[2,3] Basic research experiments with genetically modified mice, which are created without CB_1 or CB_2 receptors, have shown that without this biochemical system, the animals (and presumably, humans) would probably die at birth.[4-7] Studies in both humans and animals demonstrate that blocking this biochemical system can result in dreadful consequences, including, but not limited to, depression, stress, nausea, vomiting, diarrhea, anxiety, and even increased tendency for suicide.[8-11] The only antagonist drug ever to be marketed to humans that blocked the cannabinoid receptors—Acomplia® (rimonabant; Sanofi-Aventis; Paris, France)—was quickly withdrawn from the market due to its negative health consequences.[12]

How Medical Cannabis Works

Cannabis (*Cannabis sativa*, Cannabaceae; common name marijuana, among others) has been used for centuries to treat neurologic and neurodegenerative disorders such as epilepsy or spastic disorders. The medieval Arab writer Ibn al-Badri documented the use of hashish or a cannabis concentrate to cure a neurodegenerative disorder (probably epilepsy) afflicting the son of the chamberlain of the Caliphate Council in Baghdad.[2] Centuries later, Western physicians, including W.B. O'Shaughnessy and other British neurologists of the 19th century, confirmed the benefits of cannabis concentrates (hashish, hash oil, and tinctures) in the treatment of spasticity, convulsions, and related neurodegenerative disorders.[13,14] However, it was not until the discovery of the ECS in 1994 that scientists could explain these observations.

The progression of diseases such as multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and other neurodegenerative diseases is affected by neuroinflammation and neurodegeneration (brain cell death).[15] Cannabis can have a positive effect on these and related disorders in a number of ways. Delta-9-tetrahydrocannabinol (THC) from the cannabis plant stimulates CB_2 receptors, which decreases neuroinflammation by inhibiting the movement, growth, and activity of immune cells. Basically, the stimulation of the ECS by constituents from the cannabis plant results in decreasing the migration and activation of the immune cells that maintain the environment of neurodegenerative disorders, thereby disrupting the signals that sustain inflammation and cell death.[16]

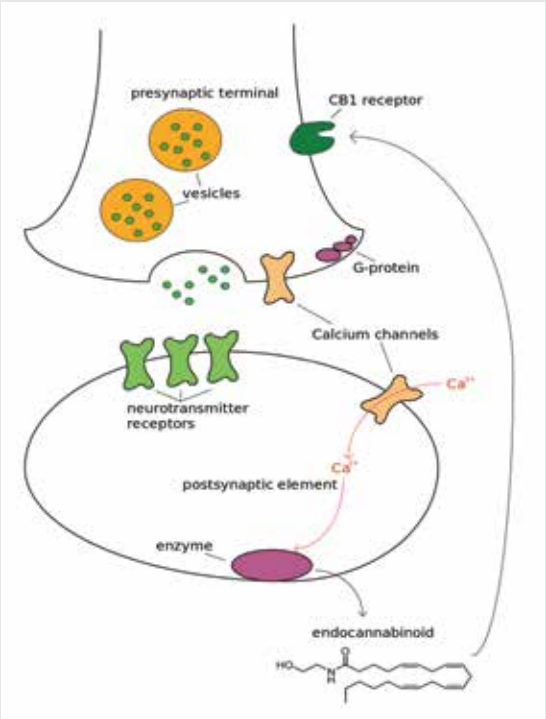
Another important aspect of neurodegenerative disorders is the irreversible death of neurons leading to progressive dysfunction. Excessive glutamate receptor activity is known to cause neuronal cell death by damaging cells and creating reactive oxygen species. The CB_1 receptors found in the brain have a direct effect on neurons by limiting glutamate release when stimulated at the presynaptic nerve terminals. (Glutamate is a key neurotransmitter, derived from glutamic acid, an amino acid.) Cannabis compounds are also potent antioxidants, reducing oxidative damage and blocking the activities of inflammatory signaling molecules like tumor necrosis factor-α. Stimulation of the ECS also has pro-survival effects on brain cells.[17,18]

At the present time, the evidence of the ECS as an appropriate target to treat neurodegenerative and other diseases does not come solely from the limited approved studies on marijuana from the US National Institute on Drug Abuse. The information comes from a wealth of new information about stimulating this biological system and the mechanisms explaining the central role of this system in health. The ECS is inherent to proper human functioning; in fact,

every physiologic system that has ever been studied is positively modulated by it.[19] Recent reports suggest that cannabis, cannabis extracts, and mixtures of the plant's active ingredients are useful for treating epilepsy (ie, Dravet syndrome), traumatic brain injury, cancers, post-traumatic stress disorder, HIV, wasting, glaucoma, Crohn's disease, multiple sclerosis, autism, and other diseases and symptoms.[20]

Since the isolation and structure elucidation of the main ingredient found in cannabis (THC) in the 1960s, several research groups have explored THC and other cannabinoids for therapeutic effects (anti-epileptic effects, palliative care) in adults and children.[21-23] Also, since the elucidation of THC's structure, more than 100 other plant cannabinoids have been documented.[24-29] The efficacy of THC can be increased with other phytocannabinoids and plant compounds such as cannabidiol (CBD) and various terpenes, respectively.[30-34] THC and CBD are both psychoactive but have very different therapeutic mechanisms of action; THC directly stimulates CB_1 and CB_2 receptors, whereas CBD appears to interact with receptors of other important neurotransmitters, serotonin and adenosine.[33,35] When the distinct mechanisms of THC and CBD are combined, they can trigger an enhancement of activity. For example, experimentally derived combinations of THC and CBD have been documented to synergistically inhibit cancer cell growth in Petri dish experiments on human grade IV glioma cells by increasing activity in a specific molecular pathway when co-applied.[34] When a 1:1 combination is used clinically, it proves effective at treating multiple sclerosis without causing intoxication.[36-38]

In mammals, the ECS is modulated during disease or injury; for example, CB_2 receptor density is increased during inflammation or bone injury.[39-42] This upregulation or modulation during disease or injury is associated with increases in both levels of endocannabinoids and the expression of the cannabinoid receptors on the cell membrane.[1,43,44] Modulation of the ECS may be an attempt by the body to reduce or abolish unwanted effects or to slow the progression of various disorders. There is evidence supporting a modulation of this biochemical system in a number of disease models.[2] Additionally, a number of genetic mutations and polymorphisms of the ECS (eg, CB_1 and/or CB_2 receptor mutations) in the human genome are associated with diseases in human populations, such as anorexia, bulimia, migraines, chronic pain, gastrointestinal disorders, mental disorders, alcoholism, and other treatment-resistant conditions.[45-50] A mutation or fault in the ECS that may underlie a disease or condition has been termed the clinical endocannabinoid deficiency syndrome.[47]



Retrograde signal in endocannabinoid.
Photo credit: *Kenneth Han.*

Conclusion

In addition to anecdotal reports and more than 30,000 basic scientific studies with cannabinoids, there are also more than 100 published clinical studies that have looked at the effect of a variety of cannabis-based medicines (including inhaled whole-plant material, oral THC capsules, and cannabis extracts) on the treatment of a wide range of disorders.[3,36,51]

The data generated from these clinical trials suggest that cannabis and its various preparations interact with the ECS to result in improvements in spasticity, muscle spasms, pain, sleep quality, tremors, appetite, and the patient's general condition.[3,51] Most of these clinical trials have focused on either THC as the primary therapeutic ingredient or a 1:1 ratio of THC to CBD, but there is a paucity of clinical studies examining pure CBD for a therapeutic outcome.

Animal and human research also demonstrates a potential for synergizing or enhancing certain therapeutic effects when cannabinoids and/or terpenes are applied in an appropriate

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combination. The therapeutic rationale for combining THC and CBD, and other cannabis plant components in fixed ratios, can result in a decrease in unwanted side effects and an enhancement of therapeutic benefits.[33,37]

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