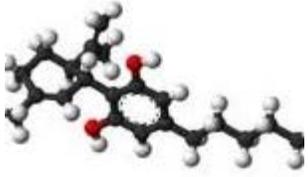


## Martin A. Lee in O'Shaughnessy's, Autumn 2011



CANNABIDIOL (CBD), a non-psychoactive component of the marijuana plant, has generated significant interest among scientists and physicians in recent years – but how it exerts its therapeutic impact on a molecular level is still being sorted out.

### **CBD and FAAH**

Unlike psychoactive THC, CBD has little binding affinity to either the CB1 or CB2 cannabinoid receptors. Instead, CBD indirectly stimulates endogenous cannabinoid signaling by suppressing the enzyme fatty acid amide hydroxylase ("FAAH") – the enzyme that breaks down anandamide.

Whereas the cannabinoid molecules found in cannabis are considered "exogenous ligands" to the cannabinoid (CB) receptor family, anandamide is an "endogenous" cannabinoid ligand – meaning it binds to one or more cannabinoid receptors and is found naturally inside the body. Anandamide favors the CB1 receptor, which in mammals is concentrated in the brain and central nervous system. Because FAAH is responsible for breaking down anandamide, less FAAH means more anandamide remains present in the body for a longer duration. More anandamide means greater CB1 activation.

By inhibiting the enzyme that metabolizes and destroys anandamide, CBD enhances the body's innate protective endocannabinoid response. At the same time, CBD powerfully opposes the action of THC at the CB1 receptor, thereby muting the psychoactive effects of THC. CBD also stimulates the release of 2-AG, another endocannabinoid that activates both CB1 and CB2 receptors – CB2 receptors are predominant in the peripheral nervous system and the immune system.

### **The Vanilloid Receptor**

Whereas CBD does not bind to either of the two known cannabinoid receptors with particular affinity, it has been shown to directly interact with other, so-called "G-protein-coupled" receptors to confer its medicinal effect. CBD, for example, binds to the TRPV-1 receptor, which is known to mediate pain perception, inflammation and body temperature.

TRPV is the technical abbreviation for "transient receptor potential cation channel subfamily V." Scientists also refer to it as the "vanilloid receptor," named after the flavorful vanilla bean. Capsaicin — the pungent compound in hot chili peppers — is a well known activator of the TRPV-1 receptor. Vanilla contains eugenol, an essential oil that has antiseptic and analgesic properties, that also helps to unclog blood vessels. Historically, the vanilla bean has been used as a folk cure for headaches.

CBD is a TRPV-1 "agonist" or stimulant. This is likely one of the reasons why CBD-rich Cannabis may be a particularly effective treatment for neuropathic pain.

### **The Adenosine Receptor**

CBD may exert its anti-anxiety effect by activating adenosine receptors. Adenosine receptors play significant roles in cardiovascular function, regulating myocardial oxygen consumption and coronary blood flow. The

adenosine (A2A) receptor has broad anti-inflammatory effects throughout the body.

Adenosine receptors also play a significant role in the brain. They down-regulate the release of other neurotransmitters such as dopamine and glutamate.

## **The Serotonin Receptor**

Jose Alexandre Crippa and his colleagues at the University of San Paulo in Brazil and at the King's College in London have conducted pioneering research into CBD and the neural correlates of anxiety.

At high concentrations, CBD directly activates the 5-HT<sub>1A</sub> (hydroxytryptamine) serotonin receptor, thereby conferring an anti-depressant effect. This receptor is implicated in a range of biological and neurological processes, including, but not necessarily limited to, anxiety, addiction, appetite, sleep, pain perception, nausea and vomiting.

5-HT<sub>1A</sub> is a member of the family of 5-HT receptors, which are activated by the neurotransmitter serotonin. Found in both the central and peripheral nervous systems, 5-HT receptors trigger various intracellular cascades of chemical messages to produce either an excitatory or inhibitory response, depending on the chemical context of the message.

CBD triggers an inhibitory response that slows down 5-HT<sub>1A</sub> signaling. In comparison, LSD, mescaline, magic mushrooms, and several other hallucinogenic drugs activate a different type of 5-HT receptor that produces an excitatory response.

## **GPR55**

Whereas cannabidiol activates the TRPV-1 vanilloid receptor and 5-HT<sub>1A</sub> serotonin receptor, some studies indicate that CBD may also function as an antagonist that blocks, or deactivates, another G protein-coupled receptor known as GPR55.

GPR55 has been dubbed an "orphan receptor" because scientists are still not sure if it belongs to a larger family of receptors. Some researchers postulate that GPR55 may actually be a third cannabinoid receptor type.

GPR55 is widely expressed in the brain, especially in the cerebellum. It is involved in modulating blood pressure and bone density. GPR55 promotes osteoclast cell function, which facilitates bone reabsorption. Overactive GPR55 receptor signaling is associated with osteoporosis.

GPR55, when activated, also promotes cancer cell proliferation, according to 2010 study by researchers at the Chinese Academy of Sciences in Shanghai. This receptor is expressed in various types of cancer.

CBD is a GPR55 antagonist, as University of Aberdeen scientist Ruth Ross disclosed at the 2010 conference of the International Cannabinoid Research Society in Lund, Sweden.

By blocking GPR55 signaling, CBD might act to decrease both bone reabsorption and cancer cell proliferation. This is one of many molecular pathways through which CBD exerts an anti-cancer effect.

## **Combination Most Effective – CBD and THC Synergy**

Dr. Sean McAllister's research at the Pacific Medical Center in San Francisco indicates that CBD reduces breast cancer cell proliferation, invasion and metastasis by inhibiting Id-1 gene expression. Best results were obtained when CBD was administered in combination with THC.

Several other studies underscore the therapeutic advantages for combining CBD and THC. CBD has been shown to be a potent anti-oxidant that mitigates the negative effects of oxygen free radicals. These highly reactive free radical chemicals are produced when animals use oxygen to burn food for fuel.

A great deal of data suggests that many problems associated with aging stem from the inability of an organism to protect itself against free-radical-induced inflammation and oxidative stress. This provides a fertile ground for the development of neurodegenerative and other age-related illnesses.

Cardiovascular, autoimmune, neurological disorders, cancers, and the aging process itself are all thought to have free radicals as a causative agent. Further, they are implicated in the formation of protein amyloid plaques — plaques that can attack neural synapses and prevent normal chemical and electrical signaling.

By binding up these free radicals, antioxidants can minimize the plaque formation cycle associated with the progression of Alzheimer's disease. Accordingly, several studies have shown that CBD blocks Alzheimer's plaque formation by a cannabinoid-receptor-independent mechanism.

The antioxidant properties of CBD exceed the antioxidant potency of either vitamin C or E. When combined with THC, the antioxidant properties of CBD grow even stronger. Once again, whole-plant Cannabis therapeutics has been shown to be far greater than the sum of the herb's individual medicinal components.

**Martin A. Lee** is the author of [\*Smoke Signals: A Social History of Marijuana – Medical, Recreational and Scientific\*](#) (Scribner, August 2012). He is the cofounder of the media watch group FAIR, director of Project CBD, and a contributor to BeyondTHC.com. He is also the author of *Acid Dreams* and *The Beast Reawakens*.