CBD: How It Works

By Martin A. Lee

Cannabidiol, a non-psychoactive component of the cannabis plant, has generated significant interest among medical scientists in recent years, but researchers are still sorting out how CBD exerts its therapeutic impact on a molecular level.

CBD and FAAH

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

Anandamide is an endogenous cannabinoid compound that activates the CB1 receptor, which is concentrated in the mammalian brain and central nervous system. Less FAAH means more anandamide is present for longer duration in the body. And more anandamide means greater CB1 signaling.

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, a major endogenous cannabinoid compound 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, it directly interacts with other G-protein-coupled receptors to confer a medicinal effect. CBD binds to the TRPV-1 receptor, which mediates pain perception, inflammation and body temperature.

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

Capsaicin, the pungent compound in hot chili peppers, also activates the TRVP-1 receptor.

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. Vanilla contains eugenol, an essential oil that has antiseptic and analgesic properties that also helps to unclog blood vessels. The vanilla bean has been used as a folk cure for headaches.

Adenosine receptor

CBD exerts an 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.

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

5-HT serotonin receptor

At high concentrations, CBD directly activates the 5-HT1A(hydroxytryptamine) serotonin receptor, thereby conferring an anti-depressant effect. This receptor is implicated in a range of biological and neurological processes, including anxiety, addiction, appetite, sleep, pain perception, nausea and vomiting.

5-HT1A 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 an intracellular cascade of chemical messages to produce an excitatory or inhibitory response. CBD triggers an inhibitory response that slows down 5-HT1A signaling.

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-HT1A serotonin receptor, CBD functions 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.

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 a 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 attenuates bone reabsorption and cancer cell proliferation. This is one of many molecular pathways through which CBD exerts an anti-cancer effect.

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.

A potent anti-oxidant

CBD is a potent anti-oxidant that mitigates the negative effect of free radicals. 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 the organism to protect itself against free-radical-induced inflammation and oxidative stress, which 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 causative agents. Free radicals are implicated in the formation of protein amyloid plaques, which attack neural synapses and prevent normal chemical and electrical signaling activity in the brain.

By binding to free radicals, antioxidants can break the plaque formation cycle that is associated with the progression of Alzheimer's disease. Several studies have shown that CBD blocks Alzheimer's plaque formation by a mechanism not involving the cannabinoid receptors.

The antioxidant properties of CBD exceed the antioxidant potency of vitamins C and E. When combined with THC, the antioxidant properties of cannabis are even stronger.

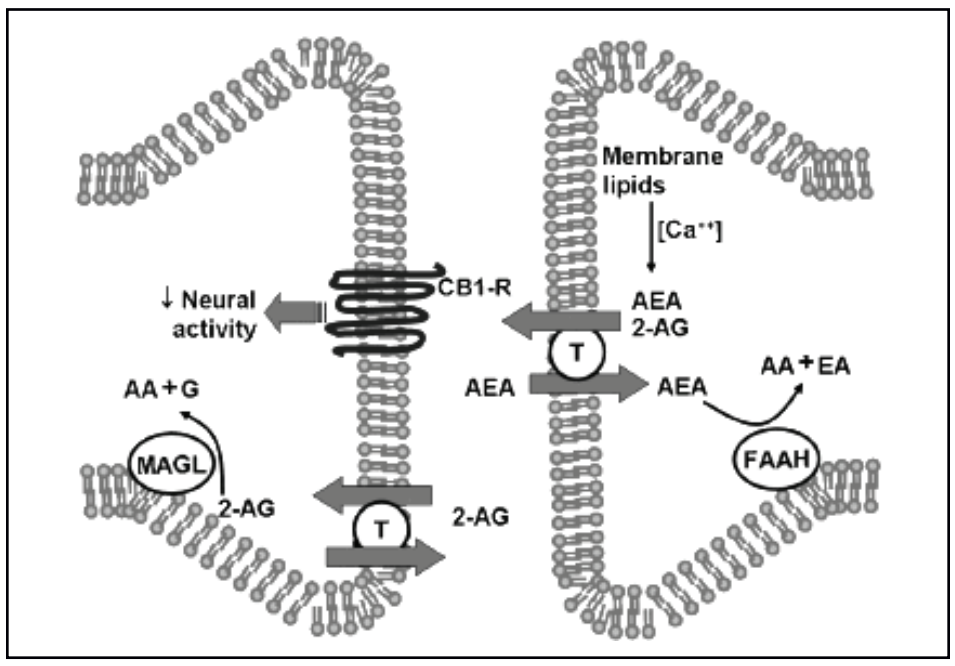
Once again, whole-plant cannabis therapeutics is greater than the sum of the herb's individual medicinal components.

Martin A. Lee is the cofounder of the media watch group FAIR, the author of three books, including Acid Dreams, *and the cofounder of Project CBD. He is currently writing a social history of cannabis, which will be published next year by Scribner's. He can be reached at martinlee@projectcbd.org*

	Serotonin 5HT1A	Vanilloid TRVP-1	Adenosine 2A2	GPR55	FAAH inhibition	antioxidant
Agonist	★	★	★			
Antagonist				★		
Receptor-Independent					★	★
Regulates	depression sleep appetite	pain inflammation body temperature	cardio-vascular other neuro-transmitters	bone density blood pressure cancer cell proliferation	ECB tone	Neuro-protection

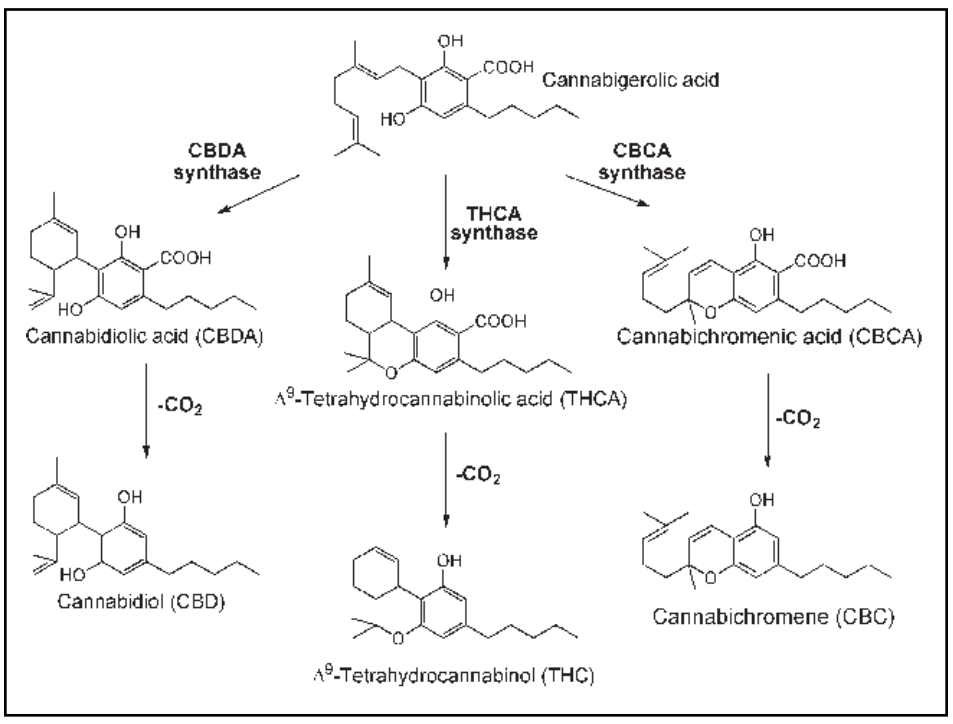
CANNABIDIOL'S MECHANISM OF ACTION: a summary of what scientists have learned.

Endocannabinoid Synthesis



ENDOCANNABINOID SIGNALING ACROSS SYNAPSE (gap between nerve cells) is depicted. Anandamide and 2-AG are synthesized from membrane lipids in postsynaptic neuron (right) after calcium (CA++) increase. They diffuse and activate pre-synpatic CB1 receptors that induce intracellular cascades, inhibiting neural activity and neurotransmitter release in the pre-synaptic neuron (left). Anandamide (AEA) undergoes re-uptake and hydrolysis (breakdown) by fatty acid amide hydrolase —FAAH); 2-AG is broken down by monoacylglycerol lipase (MAGL).

Phytocannabinoid Synthesis



CANNABIGEROLIC ACID (CBGA) IS THE COMMON PRECURSOR to CBD, THC, and CBC. As the Cannabis plant matures, CBGA is turned into CBD acid, THC acid, and CBC acid by enzymes called synthases. Mutations resulting in excess CBDA synthase or reduced THCA synthase would result in CBD-rich offspring.