

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 TRPV-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-

	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.

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.

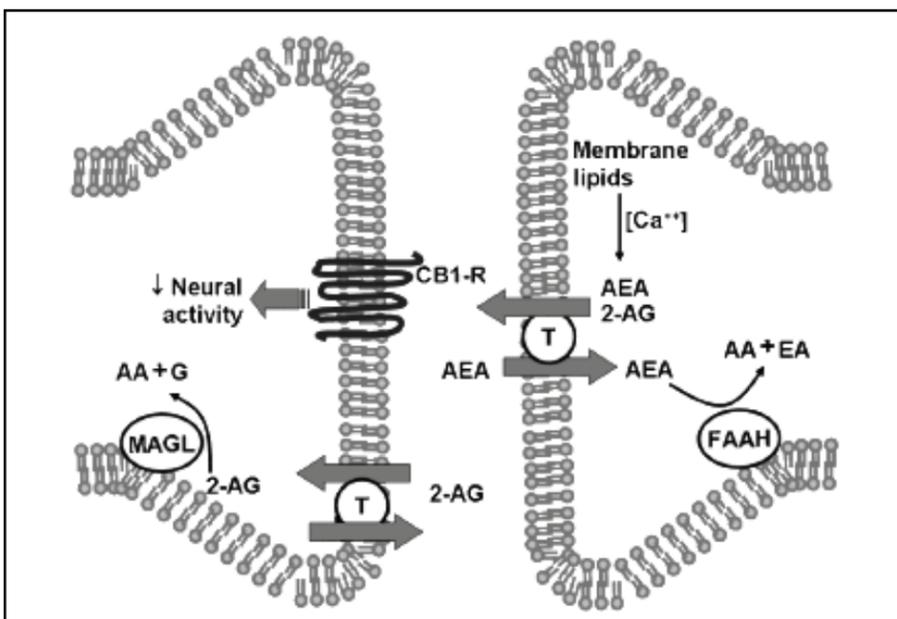
By binding to free radicals, antioxidants can break the plaque formation cycle that is associated with the progression of Alzheimer's disease. Several studies have shown that CBD blocks Alzheimer's plaque formation by a mechanism not involving the cannabinoid receptors.

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.

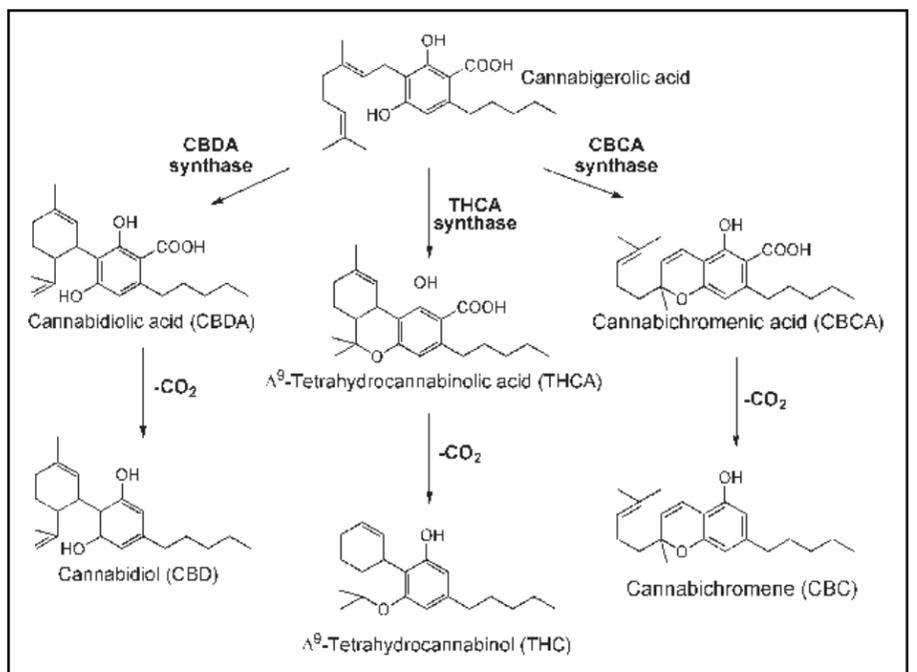
Martin A. Lee is the cofounder of the media watch group FAIR, the author of three books, including Acid Dreams, and the cofounder of Project CBD. He is currently writing a social history of cannabis, which will be published next year by Scribner's. He can be reached at martinlee@projectcbd.org

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-synaptic 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.

CBDiary from previous page



JAMAICAN LION

June 26

CBD-rich Cannabis Gets its own Category At High Times MMJ Cup

The High Times Medical Cannabis Cup has instituted a new award category: "CBD-rich." First place (9.23% CBD) went this year to a strain called "Alaskan Thunderfuck," entered by the Master Control Unit Collective. The MCUC is at an undisclosed location, on the lam from the Word Police.

Second place went to "Jamaican Lion," entered into the competition by Elemental Wellness of San Jose. "Jamaican Lion comes from Rock Bud, which won the Cannabis Cup in 2003," the grower told Project CBD, "crossed with Lion Heart, which comes from Almighty Seeds out of Quebec. It produced Mountain Lion, the mother of this plant. The Jamaican Yarders were brought straight from Jamaica. It's a Sativa that grows about 15 to 18 feet tall. They also call them 'darker,' because it gets a really dark color to it. I took the fastest flowering, most vigorous male, crossed it with my best female and had one mother left when I moved here from the East Coast three years ago."

Since no Jamaican Lion male plant exists, the grower is now crossing his Lionesses with several strains of interest, including an Omrita Rx3 from Miguel.

At the High Times Cup



Ringo with Jaime of Resin Seeds.



Debby Goldsberry, Melissa Balin



Caroline Francesc (in straw hat) at the Harborside booth.



LIFETIME AWARD WINNERS MICHELE AND MICHAEL ALDRICH

The Release of Omrita Rx3

Miguel has decided to "share the genetics" of the CBD-rich strain now known as Omrita Rx3. (See page 12 regarding its origins.)

This spring Miguel used the pollen from his one male plant to fertilize branches from his CBD-rich females. He germinated 20 seeds in sustainable coco coir and 11 turned out to be vigorous females, which he grew out. These 11 phenotypes varied widely in CBD:THC content.

In mid-August Miguel provided Omrita clones to several participants in Project CBD —WAMM, Harborside Health Center, and the Berkeley Patients Group. Trusted growers will now produce clones so that patients will be able to grow their own Omritas by next spring, for sure.

By allowing others to grow out the plants —instead of remaining the sole source of Omrita flowers— Miguel gives up the opportunity to charge top dollar for his herb and products made from it.

Based on anecdotal reports reaching Project CBD, demand for Omrita will be strong. It is said to quell pain and intestinal disorders, while sharpening focus.

"Giving it away seemed like the right thing to do," says Miguel. "Of course I need to make a living, but if something is helping people this much, it needs to be available."

Miguel is 38 and does not have a family to support (yet). His dream is to have some arable land to farm.

Clones are also being provided to edible- and tincture makers. "The more patients that use CBD and report the effects, the more we'll know what it's good for," says Miguel.

Miguel has sought advice from California Botanicals laboratory about creating Omrita-based tinctures and salves. He has already created one for veterinary use.

This spring Miguel's beloved 12-year-old Chocolate Labrador Retriever, Samantha, was diagnosed with a cancerous mass in her jaw. It had eaten away the main TMJ joint and the vet didn't recommend chemo because if the mass shrank, there wouldn't be anything to hold the jaw in place. There have been no studies examining the effectiveness of CBD on cancer in dogs, but Miguel thought it couldn't hurt to give his Omrita a try.

He used ethanol to make an extract with a 3:1 CBD-to-THC ratio. He gave her one

California Botanicals											Berkeley, Ca. 415.260.2889		
Sample Submission Form						Results							
Client ID Number	Material Type	Sample Name	Jar Number	THCA (%g/g or mg/mL)	THC (%g/g or mg/mL)	Total THC (%g/g or mg/mL)	CBDA (%g/g or mg/mL)	CBD (%g/g or mg/mL)	Total CBD (%g/g or mg/mL)	Total CBN (%g/g or mg/mL)	Total CBG (%g/g or mg/mL)		
Omrita Rx3 by Design	Flower	Rx3	1	6.34%	0.97%	8.29%	2.91%	0.30%	8.99%	0.03%	0.18%		
	Flower	BB3	2	18.10%	0.52%	17.20%	0.07%	1.03%	1.15%	0.01%	1.34%		
"7 weeks"	Flower	BB3	5	18.80%	0.27%	15.00%	0.05%	0.70%	0.77%	0.01%	1.18%		
"7 weeks"	Flower	BB5	4	4.03%	0.10%	3.66%	8.45%	0.92%	6.33%	0.02%	0.41%		
	Flower	BB7	5	14.00%	0.76%	13.04%	0.09%	0.72%	0.49%	ND	ND		
"7 weeks"	Flower	BB7	8	13.50%	0.12%	12.00%	0.07%	0.17%	0.43%	0.03%	0.38%		
	Flower	BB9	7	6.51%	0.65%	6.44%	8.19%	0.16%	7.35%	ND	ND		
"7 weeks"	Flower	BB9	8	6.51%	0.09%	5.80%	7.35%	0.14%	6.60%	0.02%	0.24%		
	Flower	G1	9	5.13%	0.14%	4.68%	12.40%	0.88%	10.00%	0.02%	0.43%		
"7 weeks"	Flower	G1	10	5.52%	0.10%	4.95%	11.20%	0.72%	10.50%	0.04%	0.57%		
	Flower	G2	11	4.23%	0.12%	3.82%	9.15%	0.07%	4.60%	0.00%	0.08%		
"7 weeks"	Flower	G6	12	7.21%	0.12%	6.44%	7.47%	0.12%	6.67%	ND	ND		
	Flower	G6	13	7.17%	0.14%	6.43%	8.47%	0.13%	7.56%	0.07%	0.19%		
"7 weeks"	Flower	P2	14	7.30%	0.06%	6.40%	4.60%	0.03%	13.30%	0.07%	0.26%		
	Flower	P2	15	0.52%	0.05%	0.60%	3.06%	1.06%	12.51%	ND	ND		
	Flower	P5	16	2.34%	0.16%	7.47%	8.35%	0.13%	7.47%	ND	ND		

CANNABINOID CONTENTS OF OMRITA Rx3 (TOP ROW) AND OFFSPRING as reported by California Botanicals to Miguel A. The lab uses high-pressure liquid chromatography, which does not involve heating samples. THC Acid and CBD Acid are measured and THC and CBD totals projected. Flowers from 11 different plants were tested; five were tested twice, at seven weeks and at harvest (8-9 weeks). One sample, P2, had a CBD:THC ratio of 20:1. Three others are in the range of 1:20 (very high THC). In the middle range are four samples with approximately equal CBD and THC contents, and three are approximately 1:2. The remarkable P2 strain is being grown out for use in a tincture, Miguel says, and to cross with other plants in an effort to reduce THC content even further.



LOVELY OMRITA Rx3

dose (15 milligrams CBD, 5 THC) per day in her food, and occasional sublingual doses. These, he says, "definitely onset

much quicker than digestive. Her behavior while medicated is similar to humans —seeking out crumbs of food, kind of like the munchies... Hiding out in long-lost corners... playful and energetic."

The vet is aware of Miguel's unusual treatment plan and impressed by the big old Lab's response. Dogs with sarcomas don't usually have Samantha's healthy appetite, or high energy and spirits, he told Miguel. Miguel advises that Omrita grows well from cuttings, both outdoors in soil and indoors in coco, and he suggests using "Less nutrients and a slightly higher pH than normal."

Omrita is a very stout plant with strong side branching and large colas.



The Return of Stinky (Pink) Purple

In the winter of 2009/10, Steep Hill lab tested a sample of "Stinky Purple" for Harborside Health Center and found it to contain 9.3% CBD and only 1.2% THC —the highest CBD-to-THC ratio yet observed, by far. According to Karen Byars, who had brought it in to Harborside, the breeder had not kept a mother plant.

This was very disappointing news, because Stinky Purple seemed uniquely lacking in psychoactivity. An SCC doctor treating a terminal cancer patient who disliked — and was very sensitive to— the effects of THC, was able to tolerate Stinky Purple, and used it beneficially on several occasions. (This patient had not been able to tolerate two other CBD-rich strains.)

Earlier this year, the breeder, Mark Thies of Dos Rios, located some seeds of the type that had produced his exceptional plant in '09. He sprouted them and gave four females to Byars to grow out. She arranged for Pure Analytics lab to test them when they were 16 weeks old.

"Three of the four show CBD dominance," Byars' reports. She hopes that one will equal in CBD:THC ratio the one that got away in '09. She intends to use the plants as mothers and to have flowers, tinctures and clones to distribute through her newly formed "CBD-Rich Collective" by the spring of 2012.

This is growing a male and a female for seed production. One of the parents was "Stinky Pink," he says. His cross is dubbed "Stinky Pink Purple."



STINKY PINK PURPLE female will be pollinated by "a male counterpart that looked exactly like her, with deep purple stems holding up the fan leaves," according to breeder Mark Thies.

reprint courtesy of cannabisclinicians.org

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