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Delta-9-tetrahydrocannabinol and cannabidiol: Separating the chemicals from the "weed," a pharmacodynamic discussion

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Abstract

Cannabis is being increasingly used as a medical treatment for a variety of illnesses. However, the cannabis plant has more than 70 different phytocannabinoids with potential pharmacologic activity. Two of the most researched phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Evidence suggests CBD can decrease some of the psychomimetic effects of THC. This has led to the development of a new drug, Nabiximols, for the treatment of moderate to severe spasticity due to multiple sclerosis. A discussion of evidence supporting proposed pharmacodynamic interplay between CBD and THC is presented.

Keywords: cannabis, delta-9-tetrahydrocannabinol, cannabidiol, marijuana, Nabiximols

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Introduction

Cannabis sativa, or cannabis, is increasingly being approved as a medical treatment for a variety of illnesses, although it is still a Schedule I drug per federal law. As of June 2015, a total of 23 states and the District of Columbia had approved cannabis for medical purposes and another 4 states approved it for recreational uses. However, the cannabis plant has more than 70 different phytocannabinoids with potential pharmacologic activity.[1] Although there is interest in many of these molecules, two of the phytocannabinoids contained in cannabis, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), have been researched extensively because of their biologic effects. In this discussion, we will review the effects of each of these molecules and describe their pharmacodynamic interactions.

Endocannabinoid System

The ability of cannabis to cause physiologic effects is due to the endogenous cannabinoid or endocannabinoid system. There are two primary receptors for the endocannabinoid within the brain: cannabinoid 1 receptors (CB1Rs), which are primarily located on neurons in the central nervous system (CNS) and the peripheral nervous system, and cannabinoid 2 receptors (CB2Rs), which are located on glial cells in the CNS and in the immune and enteric nervous systems.[2-4] Other receptors (eg, GPR55 and peroxisome proliferator–activated receptor-alpha [PPAR-alpha]) in the CNS are also activated by endocannabinoids but are not considered part of the endocannabinoid system.[5] The psychotomimetic effects produced by cannabinoids, such as THC, are attributed to activation of

CB1Rs.[6] Cannabinoid 1 receptors are found on GABAergic terminals and on glutamatergic terminals in several areas of the brain, including the basal ganglia, frontal cortex, hippocampus, and cerebellum.[7,8] Cannabinoid 2 receptors are expressed in similar areas of the brain but to a much lesser extent. Although several molecules have been suggested to have effects on the endocannabinoid system, the primary endogenous agonists are anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG).[9] Endocannabinoids are released on demand from the postsynaptic sites and exert their effects through fast retrograde signaling of the CB1Rs on the presynaptic membrane.[10,11] Once bound, these G protein–coupled receptors activate inwardly rectifying K^+ channels and inhibit voltage-sensitive N-type and P/Q-type Ca^{2+} channels, thus inhibiting the release of neurotransmitters.[12] The pharmacologic term for endocannabinoid inhibition of GABA or glutamate release is *depolarized suppression of inhibition* or *depolarization of excitation*, respectively.[13] The primary catabolic pathways for AEA and 2-AG are fatty acid amide hydrolase and monoacylglycerol lipase, respectively, which have become medication targets for pharmaceutical companies for new treatments, such as those for pain, depression, and osteoarthritis.[14,15]

Delta-9-Tetrahydrocannabinol

Delta-9-tetrahydrocannabinol is a partial agonist at both the CB1R and the CB2R. The binding to the CB1R is primarily responsible for the psychotomimetic effects of cannabis. The binding to the CB2R may have other immunologic or other anti-inflammatory effects.[1] Delta-9-tetrahydrocannabinol can be administered in several formulations, including oral ingestion, sublingually, topically, vapor inhalation, smoked, mixed in food, and drunk in tea, and research studies have also administered it intravenously. It causes several potentially negative effects, including an increase in psychoactive symptoms, cognitive deficits, and an increase in heart rate.[16] The psychoactive effects are generally related to perceptual alterations (ie, changes in intensity of sounds). At higher doses, and in vulnerable individuals, THC has been associated with exacerbating psychotic symptoms, such as delusions and hallucinations. In people with schizophrenia, THC causes worsening psychotic symptoms that are not counteracted by antipsychotic medications.[17,18] It has an anxiogenic effect that in severe cases causes paranoia.

In general it is thought that THC causes acute cognitive problems, but the most stable cognitive deficits seen with THC administration are verbal learning deficits, specifically an inability to encode new information.[19] Previously there has been debate regarding whether chronic cannabis use could result in a decrease in cognitive function. Recent evidence has suggested longer-term use of cannabis, especially if started in

adolescents, results in memory deficits. Meier et al[20] followed 1037 individuals during more than 20 years and found almost a 10-point decrease in IQ with chronic cannabis use starting in adolescents.[20] The most common physiologic effect of THC is an increase in heart rate, but this generally is time limited and does not usually cause significant sequela.[21]

Other effects of THC have been used for clinical benefit. These include antiemetic, appetite stimulation, analgesic properties, and possibly some immunologic-modulating actions.[22] Dronabinol, an oral THC product, is approved in the United States specifically for treatment of chemotherapy-induced nausea and vomiting and as an appetite stimulant. The purported effects of THC have led to states approving cannabis, which is a combination of dozens of phytocannabinoids, for a variety of diseases, including chronic pain, seizures, glaucoma, HIV/AIDS, and many other chronic medical illnesses. Several states have also approved cannabis for the treatment of posttraumatic stress disorder. Whiting et al[22] conducted a meta-analysis of cannabis and cannabinoid drugs for medical usage and discovered 79 trials thought to be of adequate quality to review. In the final analysis they found moderate levels of evidence for efficacy in chronic pain and spasticity. There was limited evidence of efficacy in several other conditions, such as chemotherapy-induced vomiting and weight gain in HIV, although in general the short-term side effect burden was very high. Common adverse events reported included dizziness (66%), dry mouth (65%), nausea (55%), fatigue (42%), somnolence (49%), euphoria (37%), vomiting (34%), disorientation (27%), drowsiness (20%), confusion (18%), loss of balance (14%), and hallucinations (14%).[22] Available data[23] suggest there are a great deal of questions related to the wisdom of marketing cannabis as a medical treatment.

Cannabidiol

Experiments with CBD started in the early 1970s, with many of the studies analyzing how CBD interacted with THC in animals and humans. In general CBD has been found to be well tolerated and have few to no psychoactive effects. The most common side effect of CDB is sedation.[24] The pharmacology of CBD is complex, because more than 20 different mechanisms of action have been described.[5] It binds to both the CB1R and CB2R but acts as an antagonist at these receptors. Another mechanism of action that has received a lot of attention is the ability of CBD to inhibit the activity of fatty acid amide hydrolase, thus increasing AEA concentrations in the body. Clinical effects of CBD are being explored in a variety of illnesses, including epilepsy, anxiety disorders, cancer, anti-inflammatory effects, and schizophrenia.[25]

Pharmacodynamic Effects of THC and CBD

Cannabidiol and THC seem to have an important interaction in both negation of detrimental effects and potentiation of positive effects. For a list of human studies investigating the interactive and opposing actions of CBD and THC, see the Table. In one of the earliest animal studies by Karniol and Carlini,[26] CBD was found to decrease many negative effects related to anxiety but potentiated the analgesic effects of THC. Another rodent study by Fernandes et al[27] found that CBD actually prolonged the effects of THC in mice, and therefore potentiates the effects of THC. A series of subsequent studies in humans found CBD had few effects in healthy adults, but when combined with THC participants reported less anxiety and psychotic symptoms.[28,29] Interestingly, one of the early studies, similar to the rodent study by Fernandes et al,[30] showed that smoked cannabis with higher concentrations of CBD prolonged the effects of THC. Although there have been some contradictive studies, most evidence suggests CBD diminishes many of the psychoactive effects of THC. An epidemiologic study investigated this by taking hair samples from 120 current cannabis smokers. In the study[31] they found individuals with CBD in hair samples reported fewer psychiatric affects then those with higher THC concentrations. This gives further credence that the laboratory findings are valid that CBD decreases psychotomimetic effects of cannabis by decreasing THC effects.

Whether CBD could affect other clinical effects of THC has still been questioned. A study in 46 adults found oral CBD 600 mg given 3.5 hours before intravenous THC (1.5 mg) reduced verbal memory deficits to a greater extent than placebo when administered with THC. Furthermore, CBD reduced psychotic symptoms from THC as measured by the Positive and Negative Symptom Scale (PANSS).[32] Emotional perception is altered in many people with cannabis use disorder. Hindocha et al[33] conducted a randomized, crossover, double-blinded study during 4 days to examine the effects of oral THC (8 mg) and oral CBD (16 mg) and placebo in 48 participants, regarding the ability of participants to recognize emotional facial affect from pictures. Although the test participants reported no difference of feeling "stoned" with THC or THC + CBD, the THC test day resulted in more errors in emotion facial recognition that were corrected when CBD was given concurrently.[33] The authors concluded that CBD reverses the deficits in emotional processing caused by THC.

It is unclear if the attenuation of effects is due to only pharmacodynamic effects or if pharmacokinetic effects are also involved. THC concentrations in the blood do not seem to be altered by CBD, but CBD may prevent THC from being converted into a more psychoactive metab-olite, 11-hydroxy-THC.[34] Bhattacharyya et al[35] performed a functional magnetic resonance imaging (fMRI) study in which 15 individuals performed a series of cognitive tasks after given oral THC, CBD, or placebo during 3 different study days. They found THC and CBD had opposing neurobiologic effects on blood oxygen level–dependent responses, with CBD generally showing an increase in activation relative to placebo, and THC showing a decrease. In a second phase of the study they gave 6 individuals oral CBD or placebo before intravenous THC on 2 different test days and found that, similarly to previous studies, CBD diminished the psychotomimetic effects of THC. Several subsequent imaging studies from this group have consistently shown that CBD has opposing biologic effects in the brain,[36] suggesting many of the effects are pharmacodynamic.

Nabiximols (Sativex®)

Nabiximols, a THC and CBD combination medication, has been approved in Europe for the treatment of symptomatic improvement in adult patients who experience moderate to severe spasticity due to multiple sclerosis.[37] Pharmaceutical companies have been pursuing development of a selective CB_2 agonist for their therapeutic action in areas of analgesia, inflammatory, and cancer. Given that the THC component acts as an agonist at CB_1 and CB_2, risking the CNS side effects, CBD was added since it is an antagonist at CB_1. This mechanism would potentially neutralize the adverse CNS effects from the THC component, rendering this product to act as if it were selective for the CB_2 receptor.[38]

Nabiximols is available as an oromucosal spray that contains 2.7 mg THC and 2.5 mg CBD per 100 mL spray. Patients are initially required to titrate nabiximols over an approximated 14-day period in order to achieve the desired dose. In clinical trials, the average therapeutic dose was 8 sprays per day in two-divided doses.[37] Of note, the maximum dose is 12 sprays per day in two divided doses, though clinical trials have studied up to 48 sprays per day.[37] Once desired total daily dose is achieved, patients are allowed to spread individual sprays across a 24-hour period based on individual tolerability and response. Given this, nabiximols is available as either three 10-mL spray bottles, or four 5.5-mL spray bottles for a total quantity of 30 mL and 22 mL respectively. These quantities would provide a 25 and 18-day supply, respectively, for patients taking the maximum recommended dosage of 12 sprays per day. Currently, nabiximols is undergoing phase 3 clinical trials in the United States for the treatment of cancer pain, although there has not been any regulatory application submitted for multiple sclerosis spasticity.

TABLE: Human studies evaluating the effects of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

Authors, Year	Participants/Design	Cannabinoid, Dose/Route		Outcome
		THC	CBD	
Bhattacharyya et al,[39] 2015	15 healthy males 3-day randomized crossover study comparing THC, CBD, and placebo on fMRI effects	10 mg, PO	600 mg, PO	fMRI: opposite effects of THC and CBD on functional connectivity between dorsal striatum, prefrontal cortex, and hippocampus.
Hindocha et al,[33] 2015	24 heavy cannabis smokers (18 males) 24 light cannabis smokers (16 males) 4-day randomized crossover study comparing THC, CBD, placebo, and THC + CBD on facial recognition	8 mg, inhaled	16 mg, inhaled	CBD improves recognition of emotional facial affect and attenuates impairments caused by THC
Englund et al,[40] 2013	CBD: 22 (13 males) Placebo: 26 (14 males) Participants were randomized to receive placebo or CBD 210 min before THC 1.5 mg IV and rated on cognition and symptoms	1.5 mg, IV	600 mg, PO	CBD resulted in decreased PANSS scores and paranoia. Verbal memory is improved with CBD.
Bhattacharyya et al,[41] 2012	15 healthy men with minimum history of previous cannabis use 3-day randomized crossover study comparing THC, CBD, and placebo on symptoms, fMRI effects	10 mg, PO	600 mg, PO	THC increases PANSS positive symptoms. fMRI: THC attenuated activation of right caudate, which was inversely correlated with severity of psychotic symptoms. CBD resulted in opposite effects in comparison to THC on task-related changes.
Martin-Santos et al,[42] 2012	16 healthy males 3-day randomized crossover study comparing THC, CBD, and placebo on symptoms	10 mg, PO	600 mg, PO	THC increases PANSS symptoms, anxiety, sedation, dysphoria
Stadelmann et al,[43] 2011	20 healthy controls (10 males) 3-day randomized crossover study of THC, THC + CBD, and placebo examining finger tapping	10 mg, PO	Cannabis extract: 10 mg of THC and 5.4 mg of CBD; PO	ERP: >10/>10 genotype of CNR1 gene is associated with significant decrease of P300 amplitude and significant prolongation of P300 latency with THC but not cannabis extract. For pure THC, the higher the number of AAT repeats, the smaller the amplitude of P300 and the longer the latency.
Winton-Brown et al,[44] 2011	14 healthy males 3-day randomized crossover study comparing THC, CBD, and placebo on symptoms, physiology, biochemical effects, and fMRI	10 mg, PO	600 mg, PO	THC increases PANSS symptoms, anxiety, sedation, intoxication. fMRI: THC attenuates, whereas CBD activates, temporal areas related to processing of information.
Bhattacharyya et al,[36] 2010	First study: 15 healthy men 3-day randomized crossover study comparing THC, CBD, and placebo on fMRI effects	10 mg, PO	600 mg, PO	fMRI: opposite effects of THC and CBD on striatum, hippocampus, amygdala, superior temporal cortex, occipital cortex
	Second study: 6 healthy controls (3 males) 3-day randomized crossover study comparing THC, CBD, and placebo on symptoms	1.25 mg	5 mg, PO	THC increases PANSS positive symptoms

TABLE: Human studies evaluating the effects of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (continued)

Authors, Year	Participants/Design	Cannabinoid, Dose/Route		Outcome
		THC	CBD	
Bhattacharyya et al,[35] 2009	15 healthy males 3-day randomized crossover study comparing THC, CBD, and placebo on symptoms, fMRI effects	10 mg, PO	600 mg, PO	THC increases PANSS symptoms, anxiety, sedation, intoxication. fMRI: THC augments activation of PHG and attenuated ventrostriatal activation—correlated with psychotic symptoms.
Roser et al,[45] 2009	24 healthy right-handed controls (12 males) 3-day randomized crossover study of THC, THC + CBD, and placebo examining finger tapping	10 mg, PO	Cannabis extract: 10 mg of THC, 5.4 mg of CBD; PO	THC reduced right-handed tapping frequencies
Fusar-Poli et al,[46] 2009	15 healthy males 3-day randomized crossover study comparing THC, CBD, and placebo on symptoms, skin conductance, and fMRI	10 mg, PO	600 mg, PO	THC increased PANSS symptoms, anxiety, and skin conductance. CBD decreased skin conductance. fMRI: CBD reduced amygdala and anterior and posterior cingulate activity in response to fearful faces THC modulated activity in frontal and parietal regions.
Borgwardt et al,[47] 2008	15 healthy males 3-day randomized crossover study comparing THC, CBD, and placebo on symptoms, physiology, biochemical effects, and fMRI	10 mg, PO	600 mg, PO	THC increases PANSS positive symptoms, sedation, intoxications, anxiety. fMRI-THC attenuated activation in right inferior frontal and anterior cingulate. CBD deactivated left temporal cortex and insula.
Roser et al,[48] 2008	20 healthy controls (10 males) 3-day randomized crossover study of THC, THC + CBD, and placebo examining EEG effects with an auditory P300 task	10 mg, PO	Cannabis extract: 10 mg of THC, 5.4 mg of CBD; PO	THC reduced P300 amplitude, and it was not corrected by CBD
Juckel et al,[49] 2007	22 healthy controls (11 males) 3-day randomized crossover study of THC, THC + CBD, and placebo examining EEG auditory MMN	10 mg, PO	Cannabis extract: 10 mg of THC, 5.4 mg of CBD; PO	Increased amplitude of MMN with THC + CBD but not with THC
Ilan et al,[50] 2005	23 healthy cannabis users (12 males) 4-day randomized crossover study with placebo, and differing doses of combined THC, CBD, and CBC, and placebo on subjective, physiologic, neurobiologic, and EEG outcomes	1.8% or 3.6%, smoking	0.2% or 1.0%, smoking	THC decreased amplitude of ERP and reduced EEG power. CBD and CBC did not affect any outcomes.
Leweke et al,[51] 2000	9 healthy males 3-day randomized crossover study examining nabilone, CBC, or nabilone + CBD on binocular depth inversion	1 mg of nabilone, PO	200 mg, PO	CBD reduced effects of nabilone on binocular depth inversion

TABLE: Human studies evaluating the effects of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (continued)

| Authors, Year | Participants/Design | Cannabinoid, Dose/Route | | Outcome |
		THC	CBD	
Zuardi et al,[29] 1982	8 healthy controls (6 males) 5-day randomized crossover study looking at the individual effects of THC, CBD, THC + CBD, placebo, and diazepam 10 mg PO on subjective effects	0.5 mg/kg, PO	1 mg/kg, PO	CBD reduced THC-induced feelings of anxiety
Karniol et al,[28] 1974	40 healthy males Participants were randomized to receive THC, CBD, THC + CBD, placebo	30 mg, PO	15, 30, or 60 mg; PO	CBD blocked most of the effects of THC, including anxiety, causing people to report more pleasurable effects

BPRS = Brief Psychiatric Rating Scale; CBC = cannabichromene; EEG = electroencephalogram; ERP = event-related potential; fMRI = functional magnetic resonance imaging; IV = intravenous; MMN = mismatch negativity; PANSS = Positive and Negative Syndrome Scale; PHG = parahippocampal gyrus; PO = oral.

Conclusion

During the past 25 years we have gained a much better understanding of the endocannabinoid system and the effects of phytocannabinoids, such as THC and CBD. Evidence is accumulating that when CBD is administered with THC, CBD has the ability to diminish the psychoactive symptoms induced by THC through pharmacodynamics and possible pharmacokinetic interplay. Despite diminishing the psychoactive effects of THC, it is thought that CBD reserves the potential for THC to exert possible therapeutic action among many different disease states. It is with these findings that novel medications containing a combination of THC and CBD are being explored for potential clinical benefit.

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