Drugs of the Future 2005, 30(7): 747-753

CCC: 0377-8282/2002
DOI: 10.1358/dof.2005.030.07.915908

Review Article

The pharmacological actions of cannabidiol

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Abstract

The major psychoactive constituent of the *Cannabis sativa* plant, Δ^9-tetrahydrocannabinol (THC), has been extensively investigated for its therapeutic and toxicological effects. Cannabidiol, another abundant but nonpsychotropic constituent of the *Cannabis* plant, has recently attracted renewed interest as a therapeutic molecule. Preliminary reports of its antipsychotic, antihyperalgesic, anticonvulsant, neuroprotective and antiemetic properties, and its ability to counteract certain effects of traditional cannabinoid receptor ligands, have been augmented by the discovery of its affinity for the vanilloid 1 receptor in the transient receptor potential family (TRPV1) and its modulation of endocannabinoid activity. This review discusses the current understanding of the mechanism of action of cannabidiol, focusing on some of the central and peripheral pharmacological effects of this exciting potential therapeutic agent.

Introduction

Cannabidiol is a nonpsychotropic constituent of the *Cannabis sativa* plant. The natural isomer is (-)-cannabidiol and its structure was first determined in 1963 by Raphael Mechoulam (Fig. 1; for review, see 1). Cannabidiol constitutes between 0.3% and 4.2% of smoked *Cannabi*s extracts (2). It rapidly reaches the brain and distributes almost equally to the various brain regions after intravenous injection in rats, without affecting the levels of radioactive Δ^9-tetrahydrocannabinol (THC) in the brain when the two drugs are coadministered (3). In humans, cannabidiol is hydroxylated to (-)-7-hydroxycannabidiol and then oxidated to (-)-7-carboxycannabidiol (4). Cannabidiol is also metabolized to form THC and cannabinol, as these naturally occurring cannabinoids have been detected in urine following cannabidiol administration (5). A high percentage of unmetabolized cannabidiol is also excreted in the feces (for review, see 6).

Cannabidiol does not produce the cannabinoid behavioral tetrad of effects characterized by hypothermia, hypomotility, catalepsy and antinociception that is usually associated with activation of cannabinoid CB_1 receptors by other cannabinoids. Indeed, (-)-cannabidiol possesses negligible affinity for and is devoid of agonist activity at CB_1 and CB_2 receptors (7-9), although it displays functional antagonism at CB_1 receptors at micromolar concentrations (9) (see below for discussion of cannabinoid receptors). Recently, it was discovered that (-)-cannabidiol binds to human vanilloid 1 receptors in the transient receptor potential family (TRPV1) with similar efficacy but lower potency than the natural vanilloid capsaicin (8) (see below for discussion of vanilloid receptors). It is also a

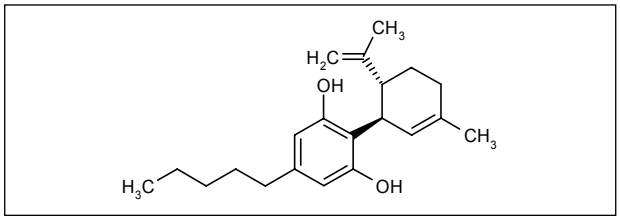

Fig. 1. Chemical structure of cannabidiol.

substrate for the putative anandamide membrane transporter and inhibits the cellular uptake of the endocannabinoid anandamide (8).

Cannabidiol metabolites and synthetic derivatives have been investigated for their functional activity. Analogues of (-)-cannabidiol have been shown to have little affinity for cannabinoid CB_1 or CB_2 receptors and to possess similar functional characteristics to (-)-cannabidiol (8, 10), while (+)-cannabidiol and several analogues, such as (+)-7-OH-DMH-CBD and (+)7COOH-CBD, possess affinity for CB_1 and CB_2 receptors and display functional properties related to these receptors (8, 10). Abnormal cannabidiol counteracts the effects of cannabidiol in some assays and is thought to act at a non-CB_1, non-CB_2 and non-TRPV1 receptor. For the purposes of this review, cannabidiol refers to (-)-cannabidiol unless specified, and the majority of the pharmacological effects of cannabidiol discussed will refer to (-)-cannabidiol.

An understanding of the pharmacology of cannabinoid receptors, TRPV1 receptors, endovanilloids and endocannabinoids is essential in clarifying the role of cannabidiol as a potentially clinically effective drug, as some effects of cannabidiol are thought to be mediated by TRPV1 receptors or by enhancement of the activity of anandamide, which subsequently activates TRPV1, CB_1 or CB_2 receptors.

Cannabinoid receptors

Two cannabinoid receptors have been cloned to date: CB_1 and CB_2. While the CB_2 subtype is located in the periphery on immune cells and has also been located in microglial cells in the central nervous system, CB_1 is one of the most abundant receptors in the brain (11), with dense localization in the cerebral cortex, hippocampus, basal ganglia and cerebellum, moderate expression in the hypothalamus and amygdala, and low expression in the brainstem (12). It is a 7-transmembrane domain protein and its receptor signal transduction occurs via Gi/o proteins and various second messenger pathways, such as inhibition of adenylyl cyclase, activation of potassium channels, inhibition of voltage-gated L-, N-, P- and Q-type Ca^{2+} channels and activation of mitogen-activated protein kinase (MAPK) (13). The major psychoactive constituent of *Cannabis*, THC, acts as an agonist at the CB_1 receptor, albeit with lower efficacy than synthetic cannabinoid agonists, elicits the cannabinoid behavioral tetrad of effects and also produces euphoria at lower doses and delusions, hallucinations, paranoia and sedation at high doses. Endocannabinoids including anandamide and 2-arachidonylglycerol bind to the presynaptically located CB_1 receptor following on-demand synthesis in the postsynaptic terminal and diffusion across the postsynaptic cleft (14), resulting in inhibition of the release of neurotransmitters such as GABA and glutamate. Endocannabinoid metabolism is regulated by the enzymes fatty acid amide hydrolase (FAAH), yielding arachidonic acid and ethanolamide, and lipoxygenase, which leads to the formation of products such as 12-(*S*)-hydroperoxyeicosatetraenoic acid (HPETE) ethanolamide, which itself is an FAAH inhibitor (for review, see 15).

Vanilloid receptors

Vanilloid receptors belong to the family of transient receptor potential proteins. The best characterized of these proteins, the TRPV1 receptor, has 6 transmembrane domains and is an outwardly rectifying channel with a central pore (16, 17). Activation of this channel occurs in response to protons, heat above 43 °C and the hot chili pepper component capsaicin, and results in depolarization of the cell membrane and inward flow of Ca^{2+} ions. The strength of this activation is modulated by pH and intracellular phosphatidylinositol-4,5-bisphosphate (PIP_2) (18). TRPV1 channels are located on the terminals of primary afferent nerve fibers projecting from the dorsal root and trigeminal ganglia, and play an integrative role in pain signaling pathways. Vanilloid compounds such as capsaicin produce nociceptive, inflammatory and hypothermic effects via TRPV1 channels, but also desensitize these channels and reduce heat hyperalgesia produced by inflammation or tissue injury (for review, see 16). Other natural vanilloid compounds such as piperine, a black pepper constituent, do not desensitize the receptor but do produce a pungent response; conversely, the synthetic agonist olvanil produces desensitization without an initial painful stimulus.

The TRPV1 channel may also play a role in the development of pathological conditions in the brain (motor disorders), inner ear, skin, mucosal protection in the gastrointestinal tract, urinary tract, airways and circulation (for review, see 19). The discovery of TRPV1 protein expression in the central nervous system in the cortex, hippocampus, amygdala, striatum, hypothalamus, cerebellum, olfactory bulb, mesencephalon and hindbrain (20) has heralded further interest in the involvement of these channels in neurotransmission and cognitive processes, such as emotion, learning and satiety.

Endogenous ligands for the TRPV1 receptor, or endovanilloids, have not yet been conclusively identified. Anandamide is thought to be a suitable endovanilloid candidate, however, as it activates TRPV1 receptors (21) and its synthesis and metabolism are under sufficient control to act as a regulatory molecule (22). Extracellular anandamide activity at CB_1 receptors is terminated by cellular uptake via an as yet unidentified transporter molecule, which can be inhibited by synthetic ligands such as olvanil (23) and AM-404 (24). The activation of TRPV1 by anandamide, however, requires facilitated transport across the cell membrane by this putative anandamide transporter molecule, suggesting that the binding site for anandamide on this receptor is intracellular (25). The inhibition by cannabidiol of the anandamide membrane transporter may potentiate anandamide activity at extracellular binding sites such as the CB_1 receptor, particularly as

cannabidiol also inhibits FAAH-mediated anandamide hydrolysis (8); however anandamide activation of TRPV1 at the intracellular binding site may be reduced, suggesting complementary activation pathways as a means of mutual regulatory control. Indeed, CB_1 and TRPV1 proteins are expressed in similar areas of the central nervous system, including the brain and spinal cord (26-28).

Central effects of cannabidiol

Antipsychotic and anxiolytic effects

Animal models of psychotic behavior ranging from tests of dopaminergic receptor activation to measurement of sensorimotor gating (the filtering of sensory information to produce an appropriate motor response) by prepulse inhibition (PPI) of the startle response have been used to predict the efficacy of potential antipsychotics. Cannabidiol and the clinically effective antipsychotic haloperidol reversed the incidence of stereotypical behavior and decrease prolactin levels induced by the dopaminergic D_1 and D_2 receptor agonist apomorphine (29). Unlike the haloperidol-treated animals, however, there was no catalepsy observed in the cannabidiol-treated animals. A later study showed that cannabidiol and haloperidol increased the expression of the proto-oncogene *c-fos* in the rat nucleus accumbens, indicating neuronal activation in this area. Cannabidiol, unlike haloperidol, did not increase *c-fos* expression in the dorsal striatum (30). Both of these studies suggest that cannabidiol may have antipsychotic efficacy without motor side effects as a result of neuronal activation in extrapyramidal areas.

Cannabidiol (30 and 60 mg/kg i.p.) inhibits hyperlocomotion induced by the psychotomimetic drugs amphetamine and ketamine in mice (31). In our laboratory, cannabidiol (5 mg/kg i.p.) reversed disruption of PPI induced by the NMDA receptor antagonist MK-801 in mice (32). This effect was reversed by the TRPV1 receptor antagonist capsazepine, suggesting for the first time a possible role for TRPV1 receptors in the regulation of sensorimotor gating and in the mechanism of action of cannabidiol in the central nervous system.

There are few studies investigating the antipsychotic potential of cannabidiol in humans. A case study from Brazil reported that a female schizophrenic patient administered cannabidiol at up to 1500 mg/day orally experienced reduced psychotic symptoms such as suspicion and thought disturbance, as well as greater efficacy and fewer side effects compared to previous haloperidol treatment (33). The synthetic THC analogue nabilone (1 mg orally) impaired binocular depth inversion in humans, a model of illusionary perception, while cannabidiol (200 mg orally) had no effect. However, when administered in conjunction with nabilone, cannabidiol reduced the impairment in binocular depth inversion experienced with nabilone alone (34). Thus, there is clearly a need to investigate cannabidiol in a controlled clinical trial for the treatment of psychosis.

Cannabidiol has also been observed to counteract some of the psychotropic effects of other natural cannabinoids. In humans, anxiety and euphoria induced by THC were reversed by cannabidiol (35, 36). Unlike THC, cannabidiol also elicited an increase in elevated plus-maze open arm entries in rats (37) and mice (38), indicating an anxiolytic effect. This functional antagonism is likely to be due to activity at a non-CB_1/CB_2 receptor, as cannabidiol has low affinity for these receptors and does not block CB_1-mediated hypothermia and other physiological effects produced by THC (39).

Antihyperalgesic effects

Natural and synthetic cannabinoid ligands have been investigated for their nociceptive activity. While THC was reported to reduce formalin-evoked nociceptive behavior in a rat model of persistent pain, cannabidiol did not affect nociception on its own (5 and 50 mg/kg i.p.), nor did it affect the antinociception produced by THC (40), suggesting that it may not interfere with the therapeutic effects of other *Cannabis* constituents while counteracting some unwanted effects. Clinical studies investigating *Cannabis* extracts containing a 1:1 THC:cannabidiol ratio (Sativex®) reported efficacy in alleviating pain associated with nerve damage at a comparable level to extracts containing THC alone, but with fewer reports of intoxication (41), as well as in reducing symptoms of multiple sclerosis such as spasticity and tremor (42). Another clinical study reported statistically significant decreases in patients' reporting of central neuropathic pain symptoms resulting from brachial plexus aversion after administration of Sativex®, although these changes did not meet the predetermined criteria for a clinically significant effect (43). Thus, while cannabidiol may not have analgesic activity *per se*, it may be useful in neuropathic pain conditions where hyperalgesia is a feature. Furthermore, it may be a useful adjunct to THC as an analgesic, counteracting some of the unwanted psychotropic effects produced by THC.

Recently, it was shown that TRPV1 channels may mediate the antihyperalgesic effects of cannabidiol. Acute inflammation induced by intraplantar injection of carrageenan in rats resulted in hyperalgesia, which was abolished by administration of cannabidiol (10 mg/kg orally); this effect was reversed by the TRPV1 antagonist capsazepine, but not by a CB_1 or CB_2 receptor antagonist (44).

Anticonvulsant effects

Cannabidiol was reported to be anticonvulsant in a mouse electroconvulsive model as early as 1973 (45). In 1982, it was reported that cannabidiol prevented seizures in mice induced by electroshock or by GABA antagonists, but it did not prevent strychnine-induced seizures (46), suggesting that its anticonvulsant effect does not extend

to glycine antagonist-induced seizure activity. Later studies showed that while THC and WIN-55212-2 exerted anticonvulsant activity via CB_1 receptors in a maximal electroshock animal model, the anticonvulsant activity of cannabidiol was not CB_1 receptor-mediated (47).

Patients with epileptic seizures no longer controlled by previous antiepileptic medication were administered cannabidiol at doses of approximately 200-300 mg/day for up to 4.5 months, as an adjunct to previous medication. Cannabidiol reduced seizure activity in 50% of the patients and was well tolerated in both the epileptic patients and in a group of healthy volunteers receiving oral doses of 3 mg/kg/day for 30 days (48).

Neuroprotective effects

Cannabidiol protected against glutamate-induced neurotoxicity and reactive oxygen species-induced cell death in cortical neuronal cultures in a cannabinoid receptor-independent manner (49). Glutamate toxicity associated with NMDA, AMPA and kainate receptors was reduced without directly blocking NMDA receptors, suggesting the possibility of reduced side effects associated with noncompetitive NMDA receptor antagonists. In serum-deprived fibroblasts, cannabidiol prevented cell death via an antioxidant effect (50), and it also reduced infarct size in a rat model of ischemic stroke (51). The neuroprotective effect of cannabidiol has also been shown to involve peroxynitrite in retinal neurons, implicating its use as a novel treatment for glaucoma (52). Cannabidiol protected against neurotoxicity in a model of ethanol binge drinking; this toxicity is considered to be mediated via NMDA receptors, as well as oxidative stress (53). Cannabidiol (3 mg/kg/day i.p. for 2 weeks) protected against neurotoxicity induced by injection of 6-hydroxydopamine into the medial forebrain bundle (54), which may be relevant in Parkinson's disease.

Antiemetic effects

Unlike THC and another nonpsychotropic *Cannabis* constituent, cannabinol, cannabidiol did not decrease gastrointestinal motility or transit time (55). However, it suppressed nausea in a conditioned rejection rat model of nausea (56). Cannabidiol reversed lithium chloride- and cisplatin-induced vomiting in the shrew at low doses (5 and 10 mg/kg), but it potentiated vomiting at higher doses (24 and 40 mg/kg); these effects were not reversed by the CB_1 receptor antagonist SR-141716 (57, 58). Interestingly, this biphasic dose-response relationship has been reported in other assays of cannabidiol activity (37, 59), as well as for endogenous cannabinoids such as anandamide (60) and natural and synthetic cannabinoid ligands (61, 62). Further work is necessary to investigate phases of nausea that may not be responsive to the current 5-HT_3 receptor antagonists, such as anticipatory vomiting following chemotherapy and delayed emesis (57), in which cannabidiol and other cannabinoids may be more effective. Derivatives of (+)-cannabidiol tend to be centrally inactive but display peripheral activity such as inhibition of gastrointestinal motility (63), a good pharmacological profile for use in disorders such as cystic fibrosis and inflammatory bowel disease that primarily involve peripheral systems (10).

Motor effects

Cannabidiol (100 mg/kg i.p.), unlike SR-141716, did not reverse cerebellar motor disturbances induced by the cannabinoid agonists THC, WIN-55212-2 and CP-55940, as measured by bar slips and observations of hypotonia and hyperreflexia (64). Cannabidiol was reported to be clinically ineffective in relieving symptoms of Huntington's chorea in a clinical trial measuring chorea severity and other motor and emotional indicators. Despite the lack of therapeutic effect, the drug was well tolerated and produced no apparent toxicity when administered to patients at doses of 700 mg/day (65). The motor effects of traditional cannabinoids are mediated by CB_1 receptors, which are densely expressed in the basal ganglia (66). Thus, cannabidiol, with its low affinity for these receptors, is less likely to affect motor function.

Peripheral effects of cannabidiol

Cardiovascular effects

Despite the affinity of cannabidiol for TRPV1 receptors and the known involvement of TRPV1 receptors in mediating the cardiovascular effects of both capsaicin and anandamide, cannabidiol does not produce vasodilatation and hypertension when administered alone and does not alter hypotension or reflex hyperventilation induced by anandamide, or hypotension induced by the cannabinoid agonist HU-210 (67, 68). Although this most likely reflects the lack of CB_1/CB_2 receptor activity of cannabidiol, it might have been expected that cannabidiol would potentiate the activity of anandamide on blood pressure given its ability to block the hydrolysis of anandamide by FAAH. Cannabidiol also blocks the vasodilatation produced by the behaviorally inactive cannabidiol analogue abnormal cannabidiol, which has been suggested to be due to the antagonism of an as yet unidentified non-CB_1, non-CB_2 Gi/Go-coupled receptor which produces vasodilatation by a nitric oxide-independent mechanism, possibly via the release of endothelium-derived hyperpolarizing factor (EDHF) (67, 69).

Antiinflammatory effects

Cannabidiol blocked the synthesis and release of the inflammatory cytokine interferon and decreased the amount of IL-1α and tumor necrosis factor (TNF) in

human peripheral blood mononuclear cells (70). The therapeutic potential of cannabidiol in an animal model of rheumatoid arthritis was subsequently investigated. Cannabidiol administered both orally and intraperitoneally reversed symptoms of collagen-induced arthritis (CIA) in mice and reduced inflammatory and immune responses associated with the disease in both *ex vivo* and *in vitro* studies (59). These effects were suggested to be the result of a disruptive effect of the lipophilic cannabidiol on cell membranes, or due to the effect of a metabolite of cannabidiol on CB_2 receptors; the contribution of TRPV1 receptors was not investigated. More recently, cannabidiol was shown to reduce the neuronal death-induced migration of microglial cells which is stimulated by the endocannabinoid 2-arachidonylglycerol, possibly by inhibiting the as yet uncharacterized abnormal cannabidiol receptor (71).

Genitourinary effects

Cannabidiol reduced the ability of the CB_1 and CB_2 agonists WIN-55212-2 and CP-55940 to inhibit electrically evoked contractions in the mouse vas deferens in a competitive, surmountable manner at a concentration (10 μM) lower than the published values for binding to CB_1 receptors. The mechanism of the effect of cannabidiol is not postjunctional, as it did not enhance the contractile effects of α-adrenoceptor agonists and P2X agonists, and in fact it selectively decreased the contractility in response to noradrenaline, but not to β, γ-methylene-ATP (72). Subsequently, a derivative of cannabidiol, (-)-7-OH-DMH-CBD, was shown to reduce electrically evoked contractions in the same tissue preparation in a similar manner to WIN-55212-2; this effect was attenuated by cannabidiol administration and was suggested to be due to an effect at a non-CB_1, non-TRPV1 receptor target (73).

Ocular effects

Cannabidiol reduced intraocular pressure in cats in comparison to untreated controls, without producing toxic effects such as conjunctival erythema and corneal opacity that were observed with THC administration (74). These side effects were also observed upon administration of *Cannabis* extract containing THC, but to a lesser extent, perhaps due to the presence of cannabidiol in the extract.

Conclusions

In summary, cannabidiol is a nonpsychoactive *Cannabis* constituent that has affinity for TRPV1 receptors and modifies the cellular uptake and metabolism of the endocannabinoid/putative endovanilloid anandamide. Further studies into the interesting physiological implications of these actions in combination with an expanding understanding of the endocannabinoid neurotransmitter system will provide valuable insight into the pharmacological and potential clinical effects of this drug.

Cannabidiol represents a promising therapeutic agent for the treatment of psychosis, hyperalgesia, stroke and seizures, with a favorable side effect profile. Therapeutic effects are reported across a wide dose range, and further studies are necessary to confirm appropriate doses for conditions for which cannabidiol may be a potential treatment. *Cannabis* plant preparations have long been smoked or consumed orally by patients wishing to alleviate a number of pathological conditions, including pain associated with cancer, multiple sclerosis and other chronic disorders. The *Cannabis*-induced increase in appetite colloquially known as the 'munchies' may be harnessed to beneficial effect in cancer and AIDS sufferers where cachexia and anorexia lead to significant deterioration of health. Transdermal delivery is being investigated as a means of improving the bioavailability of cannabidiol, with good absorption observed using ethosomal delivery (a eutectic mixture of cannabidiol and the phospholipid phosphatidylcholine) (75) and transdermal patches with coadministration of ethanol (76). However, *Cannabis* users have often reported that the whole plant is more effective than pure THC extracts such as dronabinol, particularly as smoking may produce more rapid and extensive bioavailability. Some reports suggest that THC may not be essential for some of the observed therapeutic effects of the *Cannabis* plant, such as anticonvulsant activity (77). Opportunistic exploitation of other *Cannabis* constituents, such as cannabidiol, which, in addition to its own therapeutic potential, is able to counteract some of the psychotropic effects of cannabinoids such as THC, represents a valuable clinical opportunity. Administration of *Cannabis* extracts rich in cannabidiol and low in THC, or coadministration of cannabidiol with therapeutic doses of cannabinoid receptor agonists, may result in clinical efficacy without incurring undesirable side effects.

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