Molecular Targets Reported for Cannabidiol

Subjects: Neurosciences

Contributor: Jorge Castillo-Arellano , Ana Canseco-Alba , Stephen J. Cutler , Francisco León

Cannabidiol (CBD) is a major phytocannabinoid present in *Cannabis sativa* (Linneo, 1753). This naturally occurring secondary metabolite does not induce intoxication or exhibit the characteristic profile of drugs of abuse from cannabis like Δ^9-tetrahydrocannabinol (Δ^9-THC) does. CBD is a complex multi-target molecule, meaning that it can exert different pharmacological effects by interacting with highly diverse molecular targets. CBD behaves as an agonist, inverse agonist, or antagonist on different receptors. CBD can also behave as an allosteric negative (NAM) or positive (PAM) modulator. CBD also exerts an effect on several enzymes, both neuro-enzymes and hepatic ones. CBD's effects have been reported to vary across concentrations and doses in vitro and in vivo models.

cannabidiol Cannabis sativa L. multi-target neurological conditions

1. Ligand-Gated Ion Channels

Glycine receptors (GlyRs) are ligand-gated chloride ion channels that mediate fast inhibitory neurotransmission [1]. GlyRs are expressed in the spinal cord and the brain stem where they are mainly involved in motor control, sensorial processing, and pain perception [2]. GlyRs are pentameric membrane proteins composed of four isoforms of the α subunits (α1–4) and a single isoform of the β subunit [3]. It has been demonstrated that high-range concentrations of CBD directly activate the strychnine-sensitive GlyRs, while at low micromolar concentration range, CBD exerts a positive allosteric modulation (PAM) of GlyRs [4]. GlyRα3 is highly expressed in the superficial layer of the spinal dorsal horn and is involved in the antinociceptive process. It has been reported that CBD can suppress persistent inflammatory and neuropathic pain by targeting these receptors in animal rodent models for pain [5].

GABA-A receptors (GABA-$_A$Rs) are ligand-gated ion channels that mobilize chlorine anion, producing hyperpolarization of cells and a subsequent reduction of neuronal activity through the actions of the amino acid GABA, which is the major inhibitory neurotransmitter in the mammalian brain. GABA-$_A$Rs are formed by combinations of 19 subunits: 6 alpha, 3 beta, 3 gamma, 3 rho, and one each of delta, epsilon, pi, or theta, thus generating a wide variety of isoforms. GABA-$_A$R exhibit multiple allosteric binding sites. Pharmacological interactions with GABA-$_A$R are extremely complex [6]. It has been described that in GABA-$_A$R transfected into *Xenopus laevis* oocytes, CBD is capable of increasing GABA-$_A$R mediated currents in a dose-dependent manner, with the β subunit being the main binding site for it. Therefore, CBD is a PAM of GABA-$_A$R in micromolar concentration ranges [7]. This mechanism of action seems to be related with the anxiolytic and anticonvulsant effects exerted by CBD [8].

The only ionotropic serotonin receptors are 5-HT_3 ionotropic serotonin receptors (5-HT_3Rs). They are ligand-gated cation channels located in the CNS and PNS [9][10]. The 5-HT_3R is expressed in regions that are involved in the integration of the vomiting reflex, bradycardia, hypotension, pain transmission, analgesia, mood disorders, and control of anxiety. Meanwhile, peripheral receptors participate in the regulation of sensory transmission and autonomic functions [11][12][13]. CBD has been reported to act as a negative allosteric modulator (NAM) for 5-HT_3R and a non-competitive inhibitor of the function of human and mice 5-HT_3R expressed in HEK293 cells [13] and *Xenopus laevis* oocytes [14].

Five classes of nicotinic receptors nAchR subunits (α, β, y, ε, δ,) lead to different functional isoforms of the homopentameric receptor or heteropentameric receptors [15]. Homomeric α7 nicotinic acetylcholine receptors (α7-nAChR) are pentameric calcium (Ca^{2+}) channels highly expressed in the nervous system and spinal cord. In the brain, α7-nAChR are distributed post- and presynaptic throughout the cortex, thalamus, and hippocampus. Both excitatory and inhibitory synaptic transmission can be modulated by these receptors [16]. In humans, a reduction in α7-nAChR expression has been associated with an increase in seizure susceptibility [17]. α7-nAChR agonists have pro-cognitive effects, and its modulation has been proposed to be relevant for the treatment of Alzheimer's disease (AD) or cognitive symptoms of schizophrenia, among others [18]. CBD can inhibit α7nAChR in a dose-dependent manner and induce reduction of acetylcholine-evoked currents amplitude in in vitro BOSC-23 cells and in ex vivo patch clamp assays using rat hippocampal slices, while Δ^9-THC does not affect this channel. Therefore, CBD acts as a NAM in the closed and desensitized states of these channels [19][20].

Voltage-gated sodium channel (VGSC or Nav) genes are relevant to epilepsy in humans. These Nav are transmembrane ion channels that allow the passage of sodium ions (Na^+) along their electrochemical gradient [21]. After the activation of these channels, Na^+ flow into the intracellular environment, with an opening of the channel for a few milliseconds, subsequently leading to its inactivation and closing of the channel, preventing a further flow of sodium ions [21]. The passage of Na^+ through Nav channels generates transient sodium currents that produce action potentials in cardiac muscle, skeletal muscle, and neurons [22]. Mutations in the VGSC SCN1 gene led to the loss of function of the $Nav_{1.1}$ channel, causing the development of DS. In a mouse model of Scn8a-associated epilepsy (encoding $Nav_{1.6}$), CBD has shown efficacyin reducing seizures frequency at a dose of 320–360 mg/kg [23]. Similarly, it is suggested that refractory epilepsies may be associated with mutations in the SCN2A gene [24]. Nav channels have been the most studied targets of CBD since, in clinical studies, CBD (20 mg/kg/day) efficacy has been shown against drug-resistant seizures in DS [22]. The inhibitory mechanism of CBD is associated with the inhibition of the Nav channels on both rest and inactivate states, which suggests that CBD does not inhibit direct interaction with a specific binding site [22]. Similarly, it has been shown in vitro that CBD had no specificity for any of Nav channels (1.1–1.7), $mNav_{1.6}$, or bacterial homomeric Nav channel (NaChBac) and voltage-gated potassium channel subunit $Kv_{2.1}$ [21][22].

T-type voltage-gated calcium channels (VGCCs) are a family of channels highly expressed in neurons where they modulate neuronal excitability and, in other tissues, low-threshold calcium spiking or cardiac pacemaker activity. These channels have been associated with the regulation of epilepsy, sleep, and pain; however, the mechanism underlaying these effects are unclear. The endogenous cannabinoid AEA has been suggested as an endogenous

inhibitor of these channels through a non-CB receptor-mediated mechanism [25]. In an in vitro model with HEK 293 cells expressing VGCC channels, it has been proposed that CBD is an inhibitor of the cation currents recorded by patch clamp for $Ca_{V3.1}$, $Ca_{V3.2}$, and $Ca_{V3.3}$ channels [25].

Voltage-dependent anion-selective channel protein 1 (VDAC1) is a mitochondrial channel expressed in the outer membrane, where it has an important role in the control of cellular energy and metabolism, by acting as a regulator of metabolite transfer between the cell cytosol and mitochondria. CBD has been proposed as a direct inhibitor of the conductance of this channel by altering cytosolic calcium homeostasis, mitochondrial morphology, and function, as well as viability, which is associated with the strong immunosuppressive response and its anticancer effects [26].

2. Transient Receptor Potential Channels (TRP)

TRP channels are present in mammals and expressed in multiple body tissues, being of great importance in peripheral neurons to transmit nerve impulses produced by chemical and physical stimuli to the brain [27]. Such stimuli can be mechanical stress, heat, variation in pH, osmotic pressure, and compounds derived from plants that lead to the activation of these receptors and the consequent mobilization of cations such as K^+, Na^+, Mg^{2+}, and Ca^{2+} [28][29]. TRP channels are classified into six families with 27 different channels, being canonical (TRPC), ankyrin (TRPA), polycystin (TRPP), mucolipin (TRPML), melastatin (TRPM), and vanilloid (TRPV) [30]. Six of these channels, TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, and TRPM8, are of importance because they are activated or inhibited by cannabinoids and have been called ionotropic CBR [29]. These six channels are involved in important physiological processes such as immune function, regulation of neurotransmitter release, temperature sensation, and pain [31].

Transient receptors potential vanilloid (TRPV), and especially type 1 (TRPV1), is the most studied of the TRP channels, which was discovered to be activated by vanilloid agonists such as capsaicin, which subsequently leads to channel desensitization and a quiescent analgesic effect [30][32], which earned its discoverer the 2021 Nobel Prize in Medicine. CBD is a full, but not potent, agonist of this type of channel [27][30][32]. This mechanism of action is related to the anxiolytic, anti-hyperalgesic, and anti-inflammatory effects of CBD in animal models [12]. In addition, CBD activates the phagocytic capacity of microglia concentration-dependent (0.1–10 µM) by mobilizing Ca^{2+} dependent on TRPV1 and TRPV2. The latter has been proposed as an advantage in favoring the clearance of β-amyloid and reducing problems in patients with AD [33]. TRPV2 shares a sequence identity of 50% and similar desensitization with TRPV1. However, this receptor is insensitive to capsaicin and acts as a heat sensor: activating above 52 °C, it is associated with chronic pain and inflammation [30]. It has recently been suggested that CBD activates TRPV2 by binding in a small hydrophobic gap between the S5 and S6 helices of adjacent subunits, which have not been identified in other TRP channels [34][35]. TRPV3 is also a warm temperature sensor that activates in the range of 33–39 °C. This channel is widely expressed in the brain, skin, and tongue. It has been described that CBD produces a similar response in TRPV3 to that of its agonist carvacrol since it activates the channel but subsequently desensitizes it [36]. However, the response of CBD to TRPV3 is lower than for TRPV1 and TRPV2. It has been suggested that differences in sequence homology at the putative CBD binding site could be responsible for the low response [30]. TRPV4 is also a warm temperature sensor in the range of 25–34 °C. This channel is

present in the skin where it has an important role in barrier functions and nociception. CBD has a poor response compared to the three previously mentioned TRPV channels [30][32][36].

Transient receptors potential ankyrin type 1 (TRPA1) is a sensor of low temperatures (<17 °C). It is present in the PNS, where it plays a role as a response sensor to cold, as well as hypersensitivity to cold and hyperalgesia to cold, so this receptor is important for detection of inflammatory and pain stimuli [31]. The canonical agonists of TRPA1 are isothiocyanates that are present in onions, mustard, and garlic [31]. CBD has been shown a more potent agonist than allyl isothiocyanate [30][32][36]. It was previously demonstrated in dissociated vagal afferent neurons that CBD generated its response to increasing intracellular calcium through TRPA1 [37].

Transient receptors potential melastatin 8 (TPRM8) is a temperature sensor that is activated at ~27 °C and is expressed in sensory neuron subpopulations of the PNS, where it has been found to act in the development of neuropathic pain and migraines [38]. TRPM8 agonists include icilin, eucalyptol, and menthol, which have been suggested to activate the channel at different sites [30][31]. However, CBD is an effective TPRM8 antagonist regardless of the type of agonist used [30][31] (**Table 1**).

Table 1. CBD such as an antagonist, NAM, or inverse agonist of receptors in the nervous system.

Receptor Type	Activity	IC_{50} (μM)	Disease Model	Tissue Expression	Cited
$5\text{-}HT_{3A}$	NAM	0.6	LiCl-induced nausea in rats.	CNS and PNS.	[12] [39]
α7nAChR	Antagonist	11.3	Inflammation in mice.	PNS, CNS (cortical, thalamic, and hippocampal regions), and skeletal neuromuscular junction.	[20] [40]
$Na_{V1.1–1.7}$	Antagonist	1.9–3.8	Drug-resistant seizures in DS models.	CNS and peripheral neurons.	[22] [41]
Kv2.1	Antagonist	3.0	Epilepsy in humans and microcephaly induced in zebrafish.	Hippocampal and cortical pyramidal neurons.	[22] [42] [43]
GPR3	Inverse agonist	1	-	-	[44]
GPR6	Inverse agonist	0.1	-	-	[44]
GPR12	Inverse agonist	10	-	-	[44]
$Ca_{V3.1}$	Antagonist	0.82	-	Widespread expression in neuronal and other tissue.	[25]

Receptor Type	Activity	IC_{50} (μM)	Disease Model	Tissue Expression	Cited
$Ca_{V3.2}$	Antagonist	0.78	-	Widespread expression in neuronal and other tissue.	[25]
$Ca_{V3.3}$	Antagonist	3.7	-	Widespread expression in neuronal and other tissue.	[25]
TRPM8	Antagonist	0.06	Rat behavioral model of headache and hind paw and cutaneous facial allodynia.	Sensory neuron subpopulations of the PNS, and circuits related to migraine pathogenesis.	[38] [45]
CB_1R	NAM	0.2 **	Seizures in cobalt-epileptic rats.	Amygdala, olfactory bulb, cerebellum, hippocampus, basal ganglia, and neocortex.	[41] [46]
CB_2R	NAM	0.24 **	-	Cells of the immune and hematopoietic system.	[41] [46]
μ-OPR	Antagonist	8–12	Drug abuse, mood disorders, and pain perception models.	Amygdala, spinal cord, substantia nigra, hypothalamic nuclei, hippocampus, and dorsal root ganglia.	[41]
δ-OPR	NAM	-	Drug abuse, mood disorders, and pain perception models.	Amygdala, spinal cord, substantia nigra, hypothalamic nuclei, hippocampus, and dorsal root ganglia.	[41]
GPR55	Antagonist	0.44	Epilepsy in mouse model of DS.	Excitatory neurons of dentate gyrus in hippocampus.	[41]

CNS = Central nervous system; PNS = Peripheral nervous system; DS = Dravet syndrome; LiCl = Lithium chloride; NAM = Negative allosteric modulator. ** Ki for human CB_1 and CB_2.

Cannabinoid receptors (CB_1R and CB_2R) share 44% of their molecular structure, and both are coupled to Gi/o protein, which negatively modulates adenylyl cyclase. However, they differ in their specificity, function, and their pattern of distribution, as well as in cellular expression. CB_1R is highly expressed in the brain; meanwhile, CB_2R is found predominantly in immune cells, although recent evidence demonstrates that CB_2R is expressed in microglia and also in neurons in the brain [47][48][49][50][51][52]. These receptors mediate the physiological actions of the endocannabinoids and the behavioral effects of the phytocannabinoid Δ^9-THC [53]. It has been reported that CBD has a weak binding affinity for CBR (Ki ≥ 10 μM) [54], but it seems that CBD is capable of modulating some of its actions. It has been reported that CBD behaves as a non-competitive NAM of CB_1R and CB_2R, reducing the efficacy and potency of Δ^9–THC and other cannabinoid receptors agonists, such as synthetic cannabinoids, CP–55,940 and WIN55,212 and of the endocannabinoids, AEA and 2-AG [55][56][57][58][59].

Serotonin receptors are classified into seven families ($5\text{-}HT_{1\text{-}7}R$) with at least 14 distinct receptor subtypes. Except for the ligand-gated ion channel $5\text{-}HT_3R$, all serotonin receptors are classical seven-transmembrane GPCRs that mediate their effects on different secondary messenger enzymes via activation of distinct G-proteins [60]. Serotonin receptors are widely expressed in multiple brain regions, and specific neurons can express several different serotonin receptors. They play a role in many physiological processes, including thermoregulation, respiration, circadian rhythm (sleep-wake cycle), vascular function, emesis, cognition, and regulation of emotion [61]. Evidence has shown that CBD interacts with 5-HTRs, in particular, with $5\text{-}HT_{1A}R$ and $5\text{-}HT_{2A}R$ [62]. The $5\text{-}HT_{1A}R$ is located

presynaptically and postsynaptically and therefore can act as autoreceptor and heteroreceptor, where they exert their effects through $G_{\alpha i/o}$ proteins to inhibit adenylyl cyclase. Studies have shown that CBD acts as an agonist with modest affinity at the human 5-HT_{1A}R [62]. One of the most conclusive pieces of evidence of the pharmacological effects of CBD is its anxiolytic property, because CBD produces the anxiolytic response through a wide range of concentrations. One of the proposed mechanisms is the interaction with the $5HT_{1A}$R [62][63][64][65][66]. Anxiolytic effects of CBD are induced with a bell-shaped dose–response curve when administered directly into the dorsolateral periaqueductal gray, an effect mediated by the $5HT_{1A}$R [63]. On the dorsal raphe nucleus, CBD acts as an indirect agonist of the somatodendritic 5-HT_{1A} autoreceptors, contributing to the anti-emetic effect [67]. The 5-HT_{2A}R is expressed mainly in the cerebral cortex, olfactory bulb, and brainstem nuclei. These receptors are coupled via Gq and are known as presynaptic and postsynaptic on serotoninergic terminals. CBD acts as a partial antagonist of 5-HT_{2A} [62].

Adenosine produces its physiological response by activating four G-protein coupled receptors (A_1, A_{2A}, A_{2B}, and A_3 receptors), and they are found widely distributed in most of the body tissues, participating in a large variety of pathophysiological responses, such as vasodilation, pain, and inflammation [68]. It has been demonstrated that CBD activates the A_{1A}R; this mechanism is related to the capacity of CBD to suppress ischemia-induced ventricular arrhythmias [69].

Opioidergic compounds interact with opioid receptors (μ, δ, and κ receptors) and play an important role in diverse physiological and pathophysiological processes, including analgesia, respiratory depression, and psychiatric illness. They are also expressed in the cardiovascular and immune system [70]. CBD behaves as PAM at and δOPR, and it is capable of accelerating μOPR mu agonist dissociation from the binding site, thus reducing its activity (demonstrated by kinetic binding studies) [71][72].

GPR55 is a receptor that is commonly expressed in association with CBR in the brain, PNS, and other tissues such the immune system cells and microglia [73]. This receptor has been associated with different diseases such as vascular functions, motor coordination, metabolic disorders, bone physiology, pain, and cancer. Its endogenous ligand is lysophosphatidylinositol (LPI). Once activated, GPR55 can interact downstream with Gαq/11, Gα12, Gα13, or Gα12/13, depending on the tissue or cell type [74]. CBD is an antagonist of GPR55 since it can block the effect of CP55940 in cells transfected with GPR55 in vitro [74]; CBD also acts in other tissues [75][76]. GPR18 has shown low sequence homology concerning CB_1R, CB_2R, and GPR55 receptors; its endogenous agonist is *N*-arachidonoyl glycine (NAGly). GPR18 has been described in various tissues such as lymphoid tissue, brain, lungs, ovary, and testis, where it has been associated with sperm physiology, metabolism, and with diseases such as cancer, intraocular pressure, and pain [77]. CBD acts as an antagonist of GPR18, shown to inhibit the migration of BV-2 microglia and transfected HEK293-GPR18 cells induced by NAGly and Δ^9-THC [78]. GPR3, GPR6, and GPR12 are three receptors with about 60% molecular sequence similarity to the CB_1 and CB_2 receptors. These three receptors are expressed in the reproductive system and the brain and constitutively activate adenylate cyclase through Gαs proteins. These receptors are involved in the formation of synaptic contacts as well as in differentiation and neuronal growth [79]. The GPR3 is expressed in the nervous system: in dorsal root ganglia neurons, hippocampus, amygdala, cortex, and habenula [79]. Additionally, GPR3 is expressed in the ovary, testis,

skin, adipose tissue, heart, liver, breast, and eye. GPR3 has been shown to prevent apoptosis in neurons and is associated with the development of neuropathic pain, emotional disorders, and morphine-induced antinociception [80]. Similarly, GPR12 is expressed in the limbic system and associated with emotion, behavior, and memory [79]. CBD has been shown to act as an inverse agonist for all three receptors: GPR3, GPR6, and GPR12 [81]. Although, CBD showed a weak to moderate response to GPR3 [80].

4. Nuclear Receptor: Peroxisome Proliferator-Activated Receptor γ (PPARγ)

PPARγ has been identified in adipose tissue and macrophages and has been involved in glucose energy metabolism and lipid storage [82]. In general, PPARγ ligands have shown anti-inflammatory activity, and CBD acts as an agonist of this receptor [82][83][84][85]. CBD has been shown to activate PPARγ in multiple sclerosis (MS) models [86]; also, CBD prevents neurodegeneration in a rat model of AD by reducing pro-inflammatory molecules and stimulating hippocampal neurogenesis [83]. CBD also reduces VCAM-1 level and the permeability produced by ischemia in a model of the blood–brain barrier [85].

5. Enzymes

Between the neuro-enzymes that have been shown interaction with CBD, the researchers can highlight (**Table 2**) acetylcholinesterase (AChE), butyrylcholinesterase (BChE), fatty acid amide hydrolase (FAAH), and arylalkylamine *N*-acetyltransferase (AANAT). Current medications to treat patients with AD are based on blocking cholinesterase enzymes. However, these drugs have been shown to have side effects such as vomiting and nausea, as well as limitations by not being able to control neuroinflammation, oxidative stress, and amyloidogenesis [87]. CBD and Δ^9-THC can inhibit AChE, while CBD only inhibits BChE.

FAAH is a membrane protein belonging to the serine hydrolases family; this enzyme is part of the endocannabinoid system, and its main role is terminating the signaling of bioactive lipids known as fatty acid amides (FAAs) present in the CNS and peripheral tissues; this includes hydrolysis of the AEA [88]. Inhibition of FAAH activity leads to an increase in the concentration of AEA, which, when interacting with its receptors, increases neuronal transmission to reduce pain, neuroinflammation, anxiety, and depression and counteracts nicotine addiction [88]. CBD is reported to inhibit the activity of the FAAH enzyme [45][54], although this inhibition is moderate [89].

Hepatic enzymes that include cytochromes P450 (CYP) are part of a large family of hemeprotein liver enzymes classified into families or subfamilies depending on their amino acid sequence homology and are the enzymes responsible for the first step in the metabolism and biotransformation of endogenous substrates, chemicals, and drugs [90]. It has been described that CBD inhibits cytochrome P450-mediated drug metabolism; for instance, CBD increases the plasma half-life of drugs such as hexobarbital, which is metabolized by CYP2C9 in patients. CBD has recently been reported to inhibit the catalytic activity of the liver enzymes CYP1A1-2, CYP1B1, CYP1B6,

CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4-5, CYP3A7, UGT1A9, and UGT2B7 in in vitro models [91][92][93][94][95][96][97][98].

Table 2. Neuro and hepatic enzymes inhibited for CBD.

Enzyme Type	Activity	IC_{50} (μM)	Cited
AChE	Antagonist	48.1	[87]
BChE	Antagonist	36.8	[87]
FAAH	Antagonist	15.2–27.5	[45][54]
AANAT	Antagonist	<1.0	[99]
CYP1A2	Antagonist	<1.0	[91]
CYP2B6	Antagonist	1.0	[91]
CYP2E1	Antagonist	1.0	[91]
CYP3A4	Antagonist	<1.0	[91]

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