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Beyond the CB1 Receptor: Is Cannabidiol the Answer for Disorders of Motivation?

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Keywords

cannabidiol, Δ^9-tetrahydrocannabinol, THC, reward, addiction, anxiety, depression

Abstract

The *Cannabis sativa* plant has been used to treat various physiological and psychiatric conditions for millennia. Current research is focused on isolating potentially therapeutic chemical constituents from the plant for use in the treatment of many central nervous system disorders. Of particular interest is the primary nonpsychoactive constituent cannabidiol (CBD). Unlike Δ^9-tetrahydrocannabinol (THC), CBD does not act through the cannabinoid type 1 (CB1) receptor but has many other receptor targets that may play a role in psychiatric disorders. Here we review preclinical and clinical data outlining the therapeutic efficacy of CBD for the treatment of motivational disorders such as drug addiction, anxiety, and depression. Across studies, findings suggest promising treatment effects and potentially overlapping mechanisms of action for CBD in these disorders and indicate the need for further systematic investigation of the viability of CBD as a psychiatric pharmacotherapy.

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INTRODUCTION

Since antiquity, various preparations of the plant *Cannabis sativa* have been used for medicinal and religious purposes. Widespread across ancient Asia, cannabis served as an antiemetic, anticonvulsant, antibiotic, anti-inflammatory, analgesic, anesthetic, antispasmodic, diuretic, digestive, appetite stimulant, antitussive, expectorant, and aphrodisiac (Zuardi 2006). With origins as far back as 4000 BC, Chinese pharmacopoeias documented the medicinal use of cannabis, outlining its effectiveness in the treatment of pain, constipation, menstrual cramps, and malaria (Li 1978). However, these sources noted that, when taken in excess, cannabis could yield "visions of devils" (Li 1978, p. 18). Its psychoactive properties were also described in ancient India, where they were associated with religious rituals, and the sacred text *Atharva Veda* included cannabis as one of the five sacred plants for its ability to convey "happiness," "joy," and "freedom" (Touw 1981, p. 25). Additionally, it is well documented that people used cannabis to alleviate symptoms of mood disorders such as anxiety, depression, mania, and hysteria (Mechoulam et al. 1970, Russo & Guy 2006).

Medical interest in the plant spread throughout Europe and North America in the nineteenth century (Grinspoon & Bakalar 1995), but despite the apparent therapeutic potential of cannabis for affective disorders and innumerous other ailments, its use in Western medicine decreased significantly in the early twentieth century (Zuardi 2006). The decline of medicinal cannabis was largely due to several factors. In particular, researchers may have had difficulty in achieving reliable therapeutic effects, as drug extracts were made from different strains of the plant and with varying methods of preparation (Fankhauser 2002). Because the active constituents of cannabis had not been isolated, other medications replaced cannabis for its recommended uses, and it was eventually removed from Western pharmacopoeias. Finally, concerns regarding the psychoactive effects of cannabis and its potential impairment of learning and memory prompted many legal restrictions, obstructing academic research on the plant (Zuardi 2006, Hill et al. 2012).

pCB: phytocannabinoid

THC: Δ^9-tetrahydrocannabinol

CBD: cannabidiol

Systematic quantitative research on the active constituents of cannabis did not begin in earnest until modern separation techniques made it possible to distinguish among the closely related molecular compounds within the plant (Mechoulam & Parker 2013). Although scientists eventually isolated over 60 phytocannabinoids (pCBs), the two major active constituents identified were Δ^9-tetrahydrocannabinol (THC) (Gaoni & Mechoulam 1964) and cannabidiol (CBD) (Mechoulam & Shvo 1963). THC is the prominent psychoactive pCB of the plant and mediates

the rewarding properties of cannabis (Huestis et al. 2001); CBD, in contrast, does not have reinforcing effects and has low abuse potential (Katsidoni et al. 2013, Parker et al. 2004). Despite these differences in psychoactivity, THC and CBD are produced by codominant alleles of the same gene locus and segregate according to simple Mendelian inheritance, yielding three cannabis chemovariants in a 1:2:1 ratio of pure THC, mixed THC/CBD, and pure CBD (de Meijer et al. 2003). Currently, although the chemovariants containing predominantly THC are used primarily for recreational purposes, synthetic THC (e.g., dronabinol, nabilone) has been approved for the alleviation of nausea and vomiting as well as for appetite stimulation in cancer and HIV/AIDS patients (Hill et al. 2012). Perhaps of greater therapeutic interest are the chemovariants containing a 1:1 ratio of THC to CBD or those containing predominantly CBD. As the first licensed medicinal whole cannabis extract [in Canada, the United Kingdom (UK), Germany, Spain, Denmark, and New Zealand], Sativex® (GW Pharmaceuticals, UK) has indications for pain and spasticity associated with multiple sclerosis (Barnes 2006, Perras 2005) and an approximate 1:1 ratio of THC to CBD. Importantly, this ratio reduces the unwanted central actions of THC (Russo & Guy 2006) and minimizes abuse liability (Schoedel et al. 2011). This has renewed interest in investigation of synergistic or "entourage" effects of pCBs administered together (Ben-Shabat et al. 1998, Mechoulam & Ben-Shabat 1999) and highlighted the need for systematic examination of pCBs other than THC.

Although CBD is the second most common pCB, there has been a shortage of experimental inquiry into its mechanisms of action and therapeutic effects. When administered along with THC, CBD reduces subjective ratings of intoxication (Robson 2011, Schoedel et al. 2011), ameliorates cognitive and behavioral impairment (Wade et al. 2004), and reverses THC-induced anxiety (Zuardi et al. 1982). However, CBD might be worth investigating not just for its ability to antagonize the effects of THC but in its own right as a pharmacological agent. Early preclinical studies demonstrate promising treatment effects of CBD for seizure disorders (Devinsky et al. 2014), and along with the development of CBD-based pharmacotherapies (e.g., Epidiolex®, GW Pharmaceuticals), clinical trials are under way to evaluate the strength of its treatment effects for medically intractable pediatric epilepsy (Cilio et al. 2014, Devinsky et al. 2014). The potential for wide-ranging therapeutic action of CBD in central nervous system disorders extends from emerging evidence of its diversity of receptor targets, including those beyond the endocannabinoid (eCB) system. Here, we review the pharmacological actions of CBD that may make it suitable as a treatment for an array of motivational and affective disorders such as drug addiction, anxiety, and depression.

eCB: endocannabinoid

GPCR: G protein–coupled receptor

CB1 receptor: cannabinoid type 1 receptor

CB2 receptor: cannabinoid type 2 receptor

AEA: *N*-arachidonoylethanolamine or anandamide

BRIEF OVERVIEW OF THE ENDOCANNABINOID SYSTEM

Following the isolation of THC from cannabis (Gaoni & Mechoulam 1964), researchers discovered that it binds to two different G protein–coupled receptors (GPCRs), the cannabinoid type 1 (CB1) (Devane et al. 1988) and CB2 (Munro et al. 1993) receptors. Whereas the CB2 receptor is distributed primarily in immune cells, the CB1 receptor is found throughout the CNS (Herkenham et al. 1990). It is the most abundant GPCR in the brain (Mechoulam & Parker 2013), and consistent with its role in reward and cognition, its highest densities are in the basal ganglia, substantia nigra, globus pallidus, hippocampus, and cerebellum (Herkenham et al. 1990). Sharing 48% sequence homology, both receptors couple to inhibitory G_i/G_o proteins and have the ability to activate several signal transduction mechanisms to inhibit voltage-gated calcium channels and adenylyl cyclase as well as activate potassium channels and MAP kinase (Bidaut-Russell et al. 1990, Henry & Chavkin 1995, Hoffman & Lupica 2000, Twitchell et al. 1997). The endogenous ligands *N*-arachidonoylethanolamine (AEA) or anandamide (from the Sanskrit word ananda, meaning bliss) (Devane et al. 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam et al. 1995, Sugiura et al.

1995) were identified shortly thereafter. Unlike classical neurotransmitters, eCBs function as retrograde messengers in several brain regions, including the nucleus accumbens (NAc) and ventral tegmental area (VTA) (Melis et al. 2004, Robbe et al. 2002, Wilson & Nicoll 2001); they are not stored in vesicles but rather are synthesized on demand within the postsynaptic cell in response to large increases in intracellular calcium levels during periods of sustained neural activation (Freund et al. 2003). Once synthesized, they cross the plasma membrane and activate CB1 receptors on presynaptic terminals, thereby inhibiting neurotransmitter release (Wilson & Nicoll 2001). Thus, the retrograde action of eCBs permits postsynaptic neurons to adjust their synaptic input as a function of their relative level of activation and may play an important role in regulating synaptic plasticity (Alger 2009).

NAc: nucleus accumbens

VTA: ventral tegmental area

GABA: gamma-aminobutyric acid

PHYTOCANNABINOIDS AND DISORDERS OF MOTIVATION: MECHANISMS OF ACTION

Δ^9-Tetrahydrocannabinol

Self-administration of THC (Justinova et al. 2008) and the positive subjective effects of smoked marijuana (Huestis et al. 2001) are blocked by administration of the CB1 receptor inverse agonist rimonabant, suggesting that the characteristic reinforcing or pleasurable effects of cannabis are mediated by the CB1 receptor. THC is a partial agonist of the CB1 receptor (Pertwee 2008), and similar to most other drugs of abuse, it modulates the mesolimbic dopamine system. This neural pathway is composed of dopamine cells originating in the VTA of the midbrain that project rostrally to the NAc in the ventral forebrain and to the prefrontal cortex (Wise & Bozarth 1985). The rewarding properties of all known drugs of abuse are thought to arise from dopamine release in the NAc (Di Chiara & Imperato 1988, Roberts et al. 1977, Volkow & Morales 2015, Wise & Bozarth 1985). Importantly, administration of THC or cannabinoid agonists increases the baseline firing rate (Cheer et al. 2000, French et al. 1997) and burst firing (Cheer et al. 2003, Diana et al. 1998, French et al. 1997) of VTA dopamine neurons and stimulates phasic dopamine release in the NAc (Cheer et al. 2004) in a CB1 receptor–dependent manner. However, dopamine neurons do not express CB1 receptors (Herkenham et al. 1991, Julian et al. 2003), and current data support a CB1 receptor–mediated increase in dopamine neuron activity due to local disinhibitory mechanisms (Lupica & Riegel 2005). During periods of burst firing, VTA dopamine neurons synthesize and release eCBs onto presynaptic GABAergic terminals expressing CB1 receptors, suppressing GABA-mediated inhibition and initiating a disinhibitory feedback loop that enhances dopamine cell firing (Alger & Kim 2011, Lupica & Riegel 2005, Melis et al. 2004, Riegel & Lupica 2004).

Although these actions on the mesolimbic dopamine system and associated abuse liability inherently limit the use of THC as a medicinal agent, its mechanism of action at the CB1 receptor reveals an opportunity to target the reward circuitry for therapeutic purposes. Indeed, CB1 receptor antagonism was investigated for a possible role in attenuating aberrant reward-seeking behavior. Preclinical animal work demonstrated significant reductions in abused drug–induced phasic dopamine release (Cheer et al. 2007), drug-seeking behavior (Cippitelli et al. 2005, Cohen et al. 2004, De Vries et al. 2001, Fattore et al. 2005, Justinova et al. 2008), and feeding behavior (Di Marzo & Matias 2005, Rinaldi-Carmona et al. 2004) due to functional antagonism of the CB1 receptor by the inverse agonist rimonabant. Owing to its effects on appetite and reward seeking, rimonabant was approved and marketed for the treatment of metabolic syndrome in obese patients (Christensen et al. 2007, Ward & Raffa 2011) and went to advanced clinical trials for smoking cessation (Cohen et al. 2004, Gelfand & Cannon 2006). However, even with psychiatric

Δ^9-TETRAHYDROCANNABIVARIN

In addition to CBD, other pCBs may exhibit novel therapeutic effects in the treatment of psychiatric disorders of motivation. Of particular interest is Δ^9-tetrahydrocannabivarin (THCV). THCV is a pCB with multitarget pharmacological effects as a neutral antagonist of the CB1 receptor as well as a partial agonist of the CB2 receptor (McPartland et al. 2015). Neutral antagonism of the CB1 receptor may allow THCV to therapeutically target the mesolimbic reward circuitry and avoid the negative psychiatric side effects of CB1 receptor inverse agonists such as rimonabant (Riedel et al. 2009, Ward & Raffa 2011, Tudge et al. 2015). Similarly, the actions of THCV as a CB2 receptor partial agonist may engender it with additional therapeutic potential for dysregulated reward-motivated behaviors. Recent work revealed the expression of CB2 receptors in VTA dopamine neurons (Zhang et al. 2014), and activation of these receptors reduced dopamine firing and cocaine self-administration (Xi et al. 2011, Zhang et al. 2014). Given these promising results, additional research on the medicinal value of pCBs such as THCV in disorders of reward and motivation is warranted.

exclusions, clinical trials revealed adverse side effects of high doses, including anxiety, depression, and suicidal ideations (Christensen et al. 2007). Part of the failure of rimonabant is thought to be due to its action as an inverse agonist of the CB1 receptor, producing an effect intrinsically opposite to that of the classical agonist (Ward & Raffa 2011). Currently, neutral antagonists for the CB1 receptor are under investigation for their effects on food intake and reward seeking (see sidebar, Δ9-Tetrahydrocannabivarin) (Riedel et al. 2009, Tudge et al. 2015, Ward & Raffa 2011). Nevertheless, these results emphasize the critical involvement of the CB1 receptor in motivation for reward and highlight the need for alternative receptor targets for the treatment of motivational disorders.

Cannabidiol

Although the pCBs share structural similarities, they vary significantly in their receptor interactions. In contrast to THC, CBD does not target CB1 and CB2 receptors directly (McPartland et al. 2015), does not increase VTA dopamine cell firing (French et al. 1997), and does not have inherent rewarding properties (Katsidoni et al. 2013, Parker et al. 2004). Although early studies indicated that CBD was a CB1 receptor inverse agonist similar to rimonabant (Pertwee 2008, Thomas et al. 2007), a recent review of the literature does not support this conclusion (McPartland et al. 2015). Rather, accumulating evidence reveals that CBD has low binding affinity for the CB1 receptor (Bisogno et al. 2001, Jones et al. 2010, Pertwee 2008) and fails to elicit measurable activity in efficacy assays (Breivogel et al. 2001, Thomas et al. 2007), making CBD unlikely to convey the negative psychiatric side effects of rimonabant (McPartland et al. 2015). However, additional studies have demonstrated indirect CBD-mediated agonism and antagonism of the CB1 receptor (**Table 1**). Various in vivo effects of CBD are absent in CB1 receptor knockout mice (Wolf et al. 2010), suggesting that CBD may act as an indirect agonist. This conclusion is reinforced by data demonstrating CBD-induced increases in AEA levels due to inhibition of fatty acid amide hydrolase (FAAH), the hydrolytic enzyme of AEA (Bisogno et al. 2001, De Petrocellis et al. 2011), and inhibition of AEA uptake by the putative AEA transporter (Bisogno et al. 2001). Furthermore, CBD noncompetitively antagonizes CB1 receptor agonists in in vitro assays by an unknown mechanism (Thomas et al. 2007). Taken together, these findings suggest that although CBD is not a primary ligand of the CB1 receptor, it may influence CB1 receptor transmission by augmenting eCB tone or by other indirect methods.

FAAH: fatty acid amide hydrolase

Table 1 Cannabidiol receptor targets with potential for modulating symptoms of motivational disorders

Receptor system	Mechanism	Potential therapeutic application	References
eCB	FAAH inhibitor	Intestinal motility; augmenting eCB tone; addiction; depression	Bisogno et al. 2001, Ligresti et al. 2006, Capasso et al. 2008, Leweke et al. 2012, Campos et al. 2013, Panlilio et al. 2013, Blanco et al. 2014, Chauvet et al. 2014
	AEA uptake inhibitor	Augmenting eCB tone; addiction; depression	Rakhshan et al. 2000, Bisogno et al. 2001, Ligresti et al. 2006, Scherma et al. 2008, Gamaleddin et al. 2011, Leweke et al. 2012, Campos et al. 2013
	Antagonist of CB1/CB2 receptor agonists	Reduction of THC effects	Thomas et al. 2007, Pertwee 2008
Expanded eCB	GPR55 antagonist	To be determined	Pertwee 2007, Ryberg et al. 2007, Rahimi et al. 2015
	TRPV1 agonist	Schizophrenia; analgesia	Costa et al. 2007, De Petrocellis et al. 2008, Santos et al. 2008, Terzian et al. 2009, Adamczyk et al. 2012, Heng et al. 2014
	TRPV2 agonist	Vasodilation	Qin et al. 2008
	TRPA1 agonist	Analgesia	De Petrocellis et al. 2008
	TRPM8 antagonist	Analgesia; prostate cancer	De Petrocellis et al. 2008
Serotonin	5-HT_{1A} agonist	Addiction; anxiety; depression; schizophrenia	Russo et al. 2005, Alex & Pehek 2007, Campos & Guimarães 2008, Resstel et al. 2009
	5-HT_{2A} agonist	Addiction; schizophrenia	Russo et al. 2005, Alex & Pehek 2007
	5-HT_3 agonist	Addiction	Alex & Pehek 2007, Xiong et al. 2012
	Tryptophan degradation inhibitor	Addiction; anxiety; depression; pain; inflammation	Jenny et al. 2009, Ross 2009
Adenosine	Adenosine uptake inhibitor and indirect A_{2A} agonist	Addiction; inflammation	Carrier et al. 2006, Liou et al. 2008, Ferré et al. 2010
Opioid	Mu-opioid ligand	Addiction; pain	Pertwee et al. 2002
	Mu- and delta-opioid positive allosteric modulator	Addiction; pain	Kathmann et al. 2006
Dopamine	D2 allosteric modulator	Addiction	Bloom & Hillard 1985
	Dopamine transporter inhibitor	Addiction; depression	Pandolfo et al. 2011
Other	$GABA_A$ positive allosteric modulator	Addiction	Long et al. 2012
	Alpha-1 and alpha-1-beta glycine receptor positive allosteric modulator	Pain; inflammation	Ahrens et al. 2009
	Regulator of intracellular calcium	Epilepsy; neuroprotection	Drysdale et al. 2006, Ryan et al. 2006
	T-type calcium channel inhibitor	Epilepsy; neuroprotection; pain	Ross 2009
	PPARγ agonist	Vasorelaxation; addiction	O'Sullivan et al. 2009, Enayatfard et al. 2013, Panlilio et al. 2013, de Guglielmo et al. 2014

Abbreviations: 5-HT, 5-hydroxytryptamine; AEA, *N*-arachidonoylethanolamine; CB1 and CB2, cannabinoid receptor type 1 and 2; eCB, endocannabinoid; FAAH, fatty acid amide hydrolase; PPARγ, peroxisome proliferator-activated receptor gamma; THC, Δ^9-tetrahydrocannabinol; TRPA1, transient receptor potential cation channel A1; TRPM8, transient receptor potential cation channel M8; TRPV1 and TRPV2, transient receptor potential cation channel V1 and V2.

Apart from its effects on the eCB system, CBD exhibits promiscuous pharmacological activity across a range of receptor targets (**Table 1**). Several of these receptors may be considered part of an expanded eCB system owing to their affinity for various cannabinoid ligands (McPartland et al. 2015). In particular, the orphan GPCR GPR55 (Ross 2009) and the transient receptor potential (TRP) channels (Di Marzo et al. 2002) have been characterized as potential novel metabotropic and ionotropic cannabinoid receptors, respectively. In addition to actions within the expanded eCB system, CBD inhibits adenosine uptake (**Table 1**) and is both a direct and indirect 5-hydroxytryptamine 1A (5-HT_{1A}) receptor agonist. It is also an allosteric modulator of mu- and delta-opioid, dopamine D2, $GABA_A$, and glycine receptors. To date, most of the work on the molecular targets of CBD has been done only in vitro, and future studies will need to examine their therapeutic relevance in vivo.

TRP: transient receptor potential

5-HT: 5-hydroxytryptamine or serotonin

THERAPEUTIC ACTIONS OF CANNABIDIOL IN DISORDERS OF MOTIVATION

Reward deficits and consequent motivational dysfunction are shared among affective disorders such as depression and anxiety and are an inherent feature of drug addiction (Russo & Nestler 2013). Comorbidity among these disorders is highly prevalent, with as many as 30–40% of individuals suffering from drug addiction also meeting criteria for depression or an anxiety disorder (Conway et al. 2006). This suggests a degree of potential overlap among the neurobiological mechanisms of these disorders, including disruptions of the mesolimbic reward circuitry and its interactions with other brain areas (Nestler & Carlezon 2006, Russo & Nestler 2013). As such, pharmacotherapies targeting these substrates may have beneficial outcomes across these disorders. Here we review the potential applications for CBD in the treatment of drug addiction, anxiety, and depression.

Drug Addiction

Drug addiction is a motivational disorder in which an individual compulsively seeks to use drugs and loses control over drug intake (Koob & Volkow 2009). Relapse to drug use after a period of withdrawal is one of the greatest challenges in the treatment of addiction, and among all the classes of abused drugs, there are currently few effective pharmacotherapies (Potenza et al. 2011). However, in preclinical studies in humans and animals, CBD reduces drug-motivated behavior (Morgan et al. 2013, Ren et al. 2009), attenuates withdrawal effects (Bhargava 1976; Chesher & Jackson 1985; Hine et al. 1975a,b), and limits cravings (Hurd et al. 2015). Consistent with results demonstrating antagonizing effects of CBD on THC-induced pharmacological actions, cannabis containing higher versus lower levels of CBD decreases the incentive salience of cannabis-related stimuli in smokers (Morgan et al. 2013), and a case study reported a reduction in cannabis withdrawal symptoms following CBD administration (Crippa et al. 2013).

Yet the majority of the treatment effects of CBD have been investigated in the context of opiate drugs. In morphine-dependent rats, CBD reduces withdrawal signs (Bhargava 1976; Chesher & Jackson 1985; Hine et al. 1975a,b) and enhances THC-meditated attenuation of abstinence scores (Hine et al. 1975a,b). Furthermore, although CBD does not reduce heroin self-administration or heroin-primed reinstatement of drug seeking in an animal model of relapse, it nonetheless diminishes heroin cue-primed drug seeking and normalizes heroin-induced impairments in accumbal AMPA and CB1 receptor levels (Ren et al. 2009). In an extension of these findings, a human clinical study demonstrated that CBD does not alter the subjective effects of fentanyl but attenuates heroin cue-induced drug craving and anxiety (Hurd et al. 2015). These results indicate that CBD effectively reduces opioid-paired cue reactivity but has little

BNST: bed nucleus of the stria terminalis

DPAG: dorsal periaqueductal gray

effect on the acute reinforcing properties of opioids. However, additional work shows that the reward-facilitating effects of morphine on intracranial self-stimulation (ICSS) are decreased by systemic CBD administration, and these effects are blocked by injection of the selective 5-HT_{1A} receptor antagonist WAY-100635 into the dorsal raphe (Katsidoni et al. 2013). This finding implicates dorsal raphe 5-HT_{1A} autoreceptors in the mitigating effects of CBD on morphine reward. Importantly, CBD is an agonist of the 5-HT_{1A} receptor (**Table 1**), and evidence suggests that infusion of 5-HT_{1A} agonists directly into the dorsal raphe reduces baseline serotonin and dopamine release in the NAc (Yoshimoto & McBride 1992), suggesting a mechanism whereby CBD may reduce the acute reinforcing effects of morphine. However, the 5-HT_{1A} receptor is also localized postsynaptically in dopamine terminal regions such as the prefrontal cortex, amygdala, and hippocampus as well as the NAc (Pompeiano et al. 1992). Therefore, future investigations concentrating on the actions of CBD on 5-HT_{1A} receptors within the dorsal raphe and elsewhere in the brain reward circuitry may yield promising treatment outcomes for opioid addiction.

In contrast to its effects on opioid-motivated behaviors, CBD has less apparent influence on psychostimulant reward and reinforcement. Administration of CBD fails to alter cocaine-mediated decreases in ICSS thresholds (Katsidoni et al. 2013) or disrupt cocaine- and amphetamine-conditioned place preference (Parker et al. 2004). An exception to this lack of therapeutic effect relates to nicotine reinforcement. Preliminary findings from a pilot study in humans revealed that CBD reduced cigarette smoking significantly compared to placebo in smokers trying to quit (Morgan et al. 2013). Although the mechanism for this effect has not been investigated explicitly, CBD may modulate nicotine reward through its ability to increase eCB tone by FAAH inhibition (**Table 1**). Other work has demonstrated that inhibiting FAAH prevents nicotine seeking (Forget et al. 2009, Scherma et al. 2008), nicotine-induced dopamine release in the NAc (Scherma et al. 2008), and anxiety during nicotine withdrawal (Cippitelli et al. 2011) in animals. These results suggest that, although the therapeutic effects of CBD on nicotine reward are promising, additional work is crucially needed to outline its precise mechanism of action.

Anxiety

Clinical studies have revealed robust anxiolytic effects of CBD. For example, CBD reversed anxiety generated by a high dose of THC (Zuardi et al. 1982) and by a public-speaking simulation in both patients with social phobia (Bergamaschi et al. 2011) and controls (Crippa et al. 2004, Zuardi et al. 1993). Neuroimaging studies also showed that CBD decreased activation of brain regions associated with anxiety, fear, and emotional processing, including the amygdala and the anterior and posterior cingulate cortex (Crippa et al. 2004, Fusar-Poli et al. 2010).

In rodents, the anxiolytic effects of CBD are also well established across numerous different behavioral paradigms. Results have indicated a clear inverted U-shaped dose-response curve for the effects of CBD on anxiety measures, with lower doses more efficacious than higher doses (Guimarães et al. 1990). Anxiolytic properties of systemic CBD have been confirmed in the elevated plus maze (Campos & Guimarães 2008, Gomes et al. 2010, Guimarães et al. 1990, Onaivi et al. 1990), elevated T maze (de Paula Soares et al. 2010), Vogel conflict test (Campos & Guimarães 2008, Gomes et al. 2010, Moreira et al. 2006), and contextual fear conditioning model (Resstel et al. 2006). Moreover, direct microinjection of CBD into several brain regions identified sites involved in its antianxiety effects. CBD administration into the central nucleus of the amygdala (Hsiao et al. 2012), bed nucleus of the stria terminalis (BNST) (Gomes et al. 2010, 2012), and dorsal periaqueductal gray (DPAG) (Campos & Guimarães 2008, de Paula Soares et al. 2010) promotes anxiolytic-like effects in behavioral anxiety procedures; within the BNST (Gomes et al. 2010, 2012) and DPAG (Campos & Guimarães 2008, de Paula Soares et al. 2010), these effects are

blocked by preadministration of a 5-HT_{1A} receptor antagonist. Together, these findings strongly implicate 5-HT-mediated transmission in key brain areas as a potential mechanism underlying the effects of CBD on anxiety.

Depression

Stress is a predisposing factor for anxiety and depression (Kessler 1997), and many preclinical tests of depression involve acute or chronic stress and inescapable aversive stimuli and often induce both depression- and anxiety-like symptoms (Campos et al. 2012, Russo & Nestler 2013). In such tests, CBD reduces autonomic indices of stress (Resstel et al. 2009) and behavioral manifestations of depression and anxiety (El-Alfy et al. 2010, Granjeiro et al. 2011, Resstel et al. 2009, Zanelati et al. 2010). For example, increases in heart rate and blood pressure during restraint stress as well as anxiety-like performance on an elevated plus maze following restraint stress are mitigated by systemically (Resstel et al. 2009) and centrally (Granjeiro et al. 2011) administered CBD. Additionally, although CBD does not modify the tail suspension test (El-Alfy et al. 2010), it significantly reduces immobility in the forced swim test (El-Alfy et al. 2010, Zanelati et al. 2010). On these tasks, the antidepressant and anxiolytic effects of CBD are likely 5-HT_{1A}-mediated, as they are blocked by the 5-HT_{1A} receptor antagonist WAY-100635 (Resstel et al. 2009, Zanelati et al. 2010).

However, similar to classical antidepressants, CBD may also reduce depressive symptoms by stimulating hippocampal neurogenesis (Campos et al. 2013, David et al. 2010). This is supported by recent work demonstrating that repeated administration of CBD in mice exposed to chronic unpredictable stress reduced depressive- and anxiety-like behaviors and stimulated hippocampal progenitor proliferation and neurogenesis. Moreover, these beneficial actions of CBD are prevented by genetic ablation of proliferating progenitor cells (Campos et al. 2013). The mechanism whereby CBD stimulates neurogenesis is hypothesized to depend on elevation of hippocampal AEA levels, as overexpression of FAAH inhibits CBD-induced cell proliferation. Interestingly, a clinical study found that whereas serum levels of AEA were negatively correlated with anxiety in patients with major depression, they were not associated with major depressive symptoms (Hill et al. 2008). However, in patients with minor depression, AEA levels were increased compared to control levels, suggesting a neuroprotective or compensatory mechanism in patients with less severe depressive symptoms. The significance of AEA levels and eCB tone and their moderation by CBD in depression warrants further research. Nevertheless, present results signify an important therapeutic role for CBD in the treatment of depression and anxiety.

CONCLUSIONS AND FUTURE DIRECTIONS

Results from a growing number of preclinical and clinical studies identify a novel treatment application for CBD in disorders of motivation, including drug addiction, anxiety, and depression (**Table 1**). A review of the findings suggests that CBD may attenuate motivational dysfunction through activation of the 5-HT_{1A} receptor and elevations in eCB tone. Given the multitude of molecular targets for CBD, there is substantial potential for additional beneficial effects through actions at other receptors. Further in vivo exploration of these targets will be fundamental for developing a thorough understanding of the therapeutic efficacy of CBD for drug addiction and affective disorders. Critically, isolating the mechanisms of CBD may pinpoint selective targets for rational drug development. Yet the greatest treatment value of CBD may lie in its multitarget actions or polypharmacology (Hopkins 2008). Pharmacotherapies that target numerous receptors across neural networks may be more efficacious than those that are maximally selective for a

single target (Hopkins 2008, Mencher & Wang 2005). Evidence for this comes from the use of antidepressants and antipsychotics, which derive their therapeutic effects via interactions across various GPCRs (Anighoro et al. 2014). Therefore, in motivational disorders with complex etiology and underlying neural substrates, the multitarget effects of CBD may make it a highly efficacious treatment option.

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