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REVIEW ARTICLE

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Cannabis use, abuse, and withdrawal: Cannabinergic mechanisms, clinical, and preclinical findings

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Abstract

Cannabis *sativa* is the most widely used illicit drug in the world. Its main psychoactive component is delta-9-tetrahydrocannabinol (THC), one of over 100 phytocannabinoid compounds produced by the cannabis plant. THC is the primary compound that drives cannabis abuse potential and is also used and prescribed medically for therapeutic qualities. Despite its therapeutic potential, a significant subpopulation of frequent cannabis or THC users will develop a drug use syndrome termed cannabis use disorder. Individuals suffering from cannabis use disorder exhibit many of the hallmarks of classical addictions including cravings, tolerance, and withdrawal symptoms. Currently, there are no efficacious treatments for cannabis use disorder or withdrawal symptoms. This makes both clinical and preclinical research on the neurobiological mechanisms of these syndromes ever more pertinent. Indeed, basic research using animal models has provided valuable evidence of the neural molecular and cellular actions of cannabis that mediate its behavioral effects. One of the main components being central action on the cannabinoid type-one receptor and downstream intracellular signaling related to the endogenous cannabinoid system. Back-translational studies have provided insight linking preclinical basic and behavioral biology research to better understand symptoms observed at the clinical level. This narrative review aims to summarize major research elucidating the molecular, cellular, and behavioral manifestations of cannabis/THC use that play a role in cannabis use disorder and withdrawal.

KEYWORDS
cannabinoids, CB1, CUD, endocannabinoids, marijuana, THC, tolerance

Abbreviations: 2-AG, 2-arachidonoyl glycerol; AC, adenylyl cyclase; AEA, arachidonoyl ethanolamide/anandamide; cAMP, cyclic AMP; CB1, cannabinoid 1 receptor; CB2, cannabinoid 2 receptor; CNS, central nervous system; CRF, corticotrophin releasing factor; CUD, cannabis use disorder; CWS, of cannabis withdrawal symptoms; DA, dopamine; DSE, depolarization-induced synaptic excitation; DSI, depolarization-induced synaptic depression; DSM-5, Diagnostic and Statistical Manual of the American Psychiatric Association – 5th edition.; eCB, endocannabinoids; EPAC, exchange protein directly activated by cAMP; FAAH, fatty acid amide hydrolase; fMRI, functional magnetic resonance imaging; GABA, gamma aminobutyric acid; GPCR, G protein-coupled receptors (GPCRs); GRK, G protein-coupled receptor kinase; GTP, guanosine triphosphate; i.v., intravenous; IP3, inositol 1,4,5-trisphosphate; KC, potassium channel; LTD, Long-term depression; MAPK, mitogen-activated protein kinase; MGL, monoacylglycerol lipase; mGlus, metabotropic glutamate receptors; MOPR, mu opiate receptors; PKA, cAMP-dependent protein kinase; PLC, phospholipase C; SC, Synthetic cannabinoids; STD, Short-lasting eCB-mediated depression; THC, delta-9-tetrahydrocannabinol; VGCC, voltage-gated calcium channel.

1 | INTRODUCTION

Cannabis has been used for millennia for both its recreational and medicinal qualities (Clendinning, 1843; O'Shaughnessy, 1843). Worldwide it is currently the most widely used illicit drug (Smart & Pacula, 2019; Carliner et al., 2017; United Nations Office on Drugs and Crime, 2019). As its name suggests, the cannabis plant is unique in its ability to produce molecular compounds called cannabinoids. Cannabinoids are lipophilic terpenoid molecules that can readily enter all organs upon consumption. When these compounds are plant derived, they are called phytocannabinoids, as opposed to endocannabinoids (eCB) that are endogenously synthesized by animals. In addition are synthetic cannabinoids that act on the same receptors as phytocannabinoids and eCBs. In its whole plant form, cannabis is comprised of over 100 phytocannabinoid compounds (Ahmed et al., 2015; Hanus et al., 2016). The main psychoactive component of cannabis is delta-9-tetrahydrocannabinol (THC), and this compound is primarily responsible for the cognitive and peripheral effects contributing to the "high" achieved by recreational use. It is also one of the major phytocannabinoids used medicinally and the most widely researched in terms of its therapeutic potential. While THC has indeed received considerable focus, synthetic molecules that mimic THC's action on the eCB system are also used in the laboratory to study effects of exogenous cannabinoids on the brain and behavior. These compounds are also used recreationally in illicit drugs such as "spice" or "K2", and while they have effects somewhat similar to cannabis/THC, for example, intoxicating effects and withdrawal symptoms following chronic use (Tai & Fantegrossi, 2014), their pharmacology and metabolism do differ from THC, and can have considerable toxicological and psychiatric effects on users.

While there certainly may be medicinal and therapeutic potential of phyto- and synthetic cannabinoid use, negative effects of using these compounds, both in the short (acute) and long (chronic) term must be carefully considered and understood. A significant subpopulation of regular cannabis users will develop a drug use disorder termed cannabis use disorder (CUD). These individuals experience many of the hallmarks of more well-known substance use disorders including tolerance and withdrawal symptoms. Changes in the societal attitudes about cannabis and its legal status in countries around the world (Carliner et al., 2017; Hasin et al., 2019; Smart & Pacula, 2019) make it increasingly important that we understand the underlying neurobiological substrates of cannabis use and use disorder.

1.1 | Focus of this review

This review will introduce the behavioral, cellular, and molecular substrates of acute cannabis or THC administration in humans and animal models. However, the acute effects of cannabis, THC, and THC-like compounds have been well characterized and reviewed elsewhere. Thus, our primary focus will be on chronic use and molecular substrates of cannabis tolerance, dependence, and withdrawal symptoms (Figure 1), and in particular as they pertain to the eCB system.

2 | BEHAVIORAL COMPONENTS OF CANNABIS USE AND WITHDRAWAL

2.1 | Cannabis use in humans

In the past it had been difficult to perform controlled objective clinical research on the effects of this cannabis on human behavior. This difficulty has eased somewhat because of the recent movement towards reclassification of the legal scheduling of cannabis, yet still much of what is known is derived from subjective reports from recreational consumption or human laboratory setting. Despite this, there appears to be enough evidence to form some consensus on the time frame over which cannabis produces its effects acutely, and how these effects change after prolonged, or chronic, use. Likewise, there is accumulating evidence supporting a relative timeline for withdrawal effects from cannabis use.

2.1.1 | Absorption and pharmacokinetics

The most common route of cannabis administration in humans is smoking; either via inhalation of smoke from burning the plant, or vapors from vaporization of phytocannabinoids in plants or extracts. Other common routes include oral consumption of cannabis infused foods or tablets, sublingual oromucosal absorption of tinctures, and transcutaneous absorption of topical creams or dermal patches. Less common routes typically only found in research or medicinal applications include rectal and intravenous administration. Each of these routes have their own absorption pharmacokinetics with peak plasma THC concentrations occurring most rapidly via intravenous and smoking routes after roughly 10 min, followed by sublingual and rectal administration, and oral and transcutaneous peak THC occurring on the order of 1–5 hr with great variability between formulations (Huestis, 2007).

Upon consumption, THC can readily enter all organs and shows relatively slow pharmacokinetics, particularly in lipid-rich compartments, including the brain (Grotenhermen, 2003; Huestis, 2007), despite rapid first pass hepatic metabolism (Alozie et al., 1980; Matsunaga et al., 1995). Indeed, following acute intake of cannabis drugs, detectable THC metabolite levels have been shown to persist for 1–2 days (Huestis et al., 1995) despite substantial conversion to the inactive metabolite THC-COOH occurring only 1–2 hrs after smoking (Huestis, 2007; Mason & McBay, 1985). In chronic users THC itself can remain detectable in whole-blood samples even 7 days into abstinence (Karschner et al., 2009). This slow removal likely allows the compound to continue acting on molecular targets, at least at a low level, for prolonged periods after drug taking. This pharmacokinetic profile must be borne in mind when considering abstinence/withdrawal following THC and cannabis drug exposure.

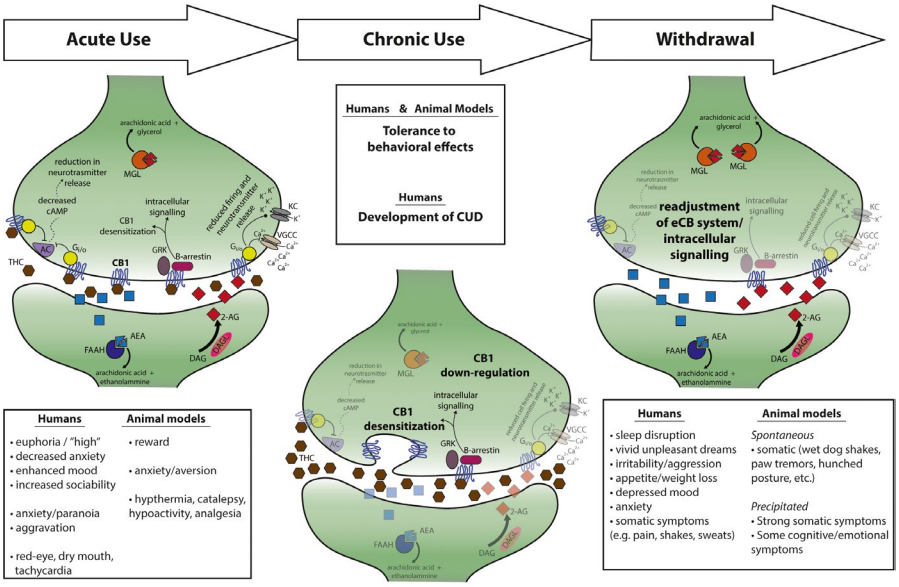

FIGURE 1 Effects of acute cannabis/THC exposure, chronic use, and withdrawal on behavior and synaptic eCB signaling. The stage of cannabis/THC use is listed inside arrows across the top of the figure, with the relevant synaptic cellular/molecular components and behavioral elements beneath. In the synapse cartoons, the left (acute use) includes many of the well-established components, while middle (chronic use) and right (withdrawal) cartoons have bolded the critical changes associated with that stage, while the other components are dimmed. For behavioral elements, the subtitles indicate whether the behavior(s) occur in clinical (human) or preclinical (animal model) settings

2.1.2 | Acute behavioral effects

Regardless of the route of administration, the acute behavioral effects of cannabis use in first-time or inexperienced users have been documented (Gonzalez, 2007; Metrik et al., 2011; Sexton et al., 2019; Solowij et al., 2019; Spindle et al., 2018) and reviewed in several bodies of work (Ashton, 2001; Johns, 2001; Karila et al., 2014). Briefly, behavioral effects of cannabis use occur within minutes of smoking, or obviously longer with other administration routes, and can last for several hours. Behavioral effects include euphoria, or 'high', decreased anxiety and depression, and increased sociability (Ashton, 2001). Conversely, it is not uncommon for new users to experience negative affective processes such as general anxiety and aggravation, and in more extreme cases, panic, paranoia, and other forms of psychosis (Johns, 2001). It is not yet entirely clear why some individuals experience positive and others negative psychological effects early in cannabis use, however, setting and pre-existing expectations or psychiatric conditions can play a role (Cooper & Williams, 2019; Johns, 2001; Karila et al., 2014). In addition to profound behavioral effects in the awake state, acute administration of cannabis produces alterations during sleep (Babson et al., 2017; Kesner & Lovinger, 2020). Non-cognitive effects of acute cannabis use include conjunctival injection ('red-eye'), increased appetite, dry mouth, and tachycardia (American Psychiatric Association, 2013).

2.1.3 | Behavioral effects of prolonged cannabis use

Tolerance. While there is no exact definition for 'chronic' cannabis use, there is a general consensus that it constitutes frequent use ranging from several times a week to several times a day, ultimately resulting in tolerance. Tolerance is characterized by a decrease in the effect of a given amount of the drug, or conversely an increase in amount of the drug needed to produce desired effects. Depending on the regularity of cannabis administration, tolerance can occur quite rapidly. Generally, any regular consumption of cannabis that maintains tissue THC levels between doses over an extended period will produce tolerance, and a study by Jones and colleagues demonstrated significant tolerance to intoxicating effects of cannabis in humans following just four days after administering 10mg/kg doses every four hours (Jones et al., 1981).

We will expound upon the cellular and molecular changes that drive behavioral effects associated with chronic cannabis use in later sections, and several other articles have provided in-depth reviews on chronic use and the development of tolerance in humans (Colizzi & Bhattacharyya, 2018; Cooper & Haney, 2009; D'Souza et al., 2008; Hollister, 1978; Jones et al., 1976, 1981). Interestingly, a double-blind study by D'Souza et. al. compared the acute effects of various doses of THC given to frequent cannabis users and non-users. They found that while psychological, cognitive, and anxiogenic effects of THC are indeed blunted in chronic cannabis users, the euphoric effects remained unaltered. The same study found that cortisol levels were also lower in the frequent users, but heart-rate was similarly elevated in both groups (D'Souza et al., 2008). These findings indicate variability in development of tolerance to different THC actions.

Blunted or not when compared to acute exposure, the psychological and physiological effects of cannabis in experienced users are driven by activity of the cannabinoid 1 receptor (CB1), which is

the major molecular target for THC actions in the brain. Exposure to the CB1 inverse agonist rimonabant (SR141716), significantly reduced subjective levels of intoxication and tachycardia (Huestis et al., 2001).

Dependence. As defined by the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5), prolonged cannabis use can lead to CUD. Many of the hallmarks of CUD are observed in other drug use disorders and addictions—including tolerance resulting in escalation of amounts used, unsuccessful attempts to curb or stop use, craving, using despite adverse consequences, and withdrawal symptoms during early abstinence (American Psychiatric Association, 2013). In a 2020 systematic review and meta-analysis, Lueng and colleagues found that roughly 22% of individuals who use cannabis (lifetime users, recent users, or weekly/daily users) had developed CUD to some degree (Leung et al., 2020).

2.2 | Cannabis withdrawal symptoms in humans

The occurrence of cannabis withdrawal symptoms (CWS) or syndrome in response to cessation of regular cannabis use was contentious during the 1970s through the 1990s (Budney & Hughes, 2006; Rohr et al., 1989), despite reports of withdrawal symptoms as early as the 1940s (Bouquet, 1944; Fraser, 1949; Williams et al., 1946). These early reports were largely ignored, possibly because of contrasting findings in other studies (Gaskill, 1945; Leite & Carlini, 1974), and the relative mildness of the reported withdrawal symptoms when compared to other narcotic drugs (Smith, 2002). Likewise, it is possible that the withdrawal symptoms experienced by cannabis users in the early twentieth century and earlier may have been milder than later in the century and current times because of the much lower THC content, and thereby potency, of the cannabis being consumed earlier in the century (ElSohly et al., 2016; Hart, 1984; Turner, 1983). With publication of methodologically rigorous and well-controlled studies in the late 1990s and 2000s (Budney et al., 1999, 2001, 2003, 2007, 2008; Crowley et al., 1998; Haney et al., 1999a, 1999b; Kouri & Pope, 2000; Kouri et al., 1999; Vandrey et al., ,2005, 2008), the diagnosis of CWS has become far less contentions and indeed is now described in the DSM-5 (American Psychiatric Association, 2013) as a key feature of CUD.

The DSM-5 defines cannabis withdrawal as experiencing at least three of the following symptoms upon cessation of regular cannabis use: (1) Irritability/aggression, (2) nervousness/anxiety, (3) disrupted sleep, (4) hypophagia and weight loss, (5) restlessness, (6) depressed mood, (7) somatic symptoms causing discomfort, for example, abdominal pain, shakes, sweating, fever/chills, and headache (American Psychiatric Association, 2013). Other cannabis withdrawal symptoms have also been reported including vivid unpleasant dreams or nightmares (Budney et al., 2003), feeling tense or unable to achieve goals (Bahji et al., 2020), changes in libido, boredom, and craving cannabis (Copersino et al., 2006). Increased appetite and weight gain have also been observed in individuals abstaining from cannabis, but this is typically reported later in withdrawal (Copersino et al., 2006; Levin et al., 2010), and could potentially be a post-withdrawal symptom (Boggs et al., 2013).

These symptoms also typically follow a reliable time course (Allsop et al., 2011; Budney et al., 2003; Hesse & Thylstrup, 2013), with sleep disturbances, somatic symptoms, and decreased appetite more prevalent during the initial several days of abstinence, followed by irritability, restlessness, and anxiety. Aggression and anger are more prominent after the first week or so of abstinence (Budney et al., 2003; Hesse & Thylstrup, 2013). Interestingly, while sleep disruption is strongest early in abstinence, vivid/unpleasant dreams can begin at a similar time point but extend for several weeks following cessation (Budney et al., 2003; Vorspan et al., 2010).

There appears to be a common misconception that cannabis withdrawal symptoms are mild, and therefore perhaps clinically irrelevant. In reality, there is strong evidence that cannabis withdrawal symptom severity is similar to that of tobacco/nicotine withdrawal (Budney & Hughes, 2006), and correlates with functional impairment and higher relapse rates (Allsop et al., ,2011, 2012; Chung et al., 2008). As with other drugs of abuse, several factors can contribute to the severity of cannabis withdrawal symptoms, such as psychiatric comorbidities, setting (inpatient or outpatient), duration of use prior to cessation, whether the individual is treatment seeking, and the rate of cessation (HealthQuest (NSW) 2008; Budney & Hughes, 2006; Budney et al., 2004). Regardless of the symptom profile, timeline, or severity, research has shown that 40%–50%, or more, of regular cannabis users will experience withdrawal symptoms (Bahji et al., 2020; Hasin et al., 2008).

2.3 | Sex and gender differences in CUD and CWS

Over the past decade more studies have considered sex as a biological variable pertaining to cannabis use, development of CUD, and strength of CWS (Cooper & Craft, 2018). A 2016 study of 2374 users in Washington State, where cannabis is legal for recreational use, found men are more likely to use cannabis for recreational purposes and consume at higher quantities, while women are more likely to report using for medical reasons and first using cannabis when older than 30 years (Cuttler et al., 2016). A 2020 human laboratory study reported female young-adult regular cannabis users had lower peak concentrations of THC and its metabolites than males, and found little differences in subjective drug effects between sexes using a visual analog scale method (Matheson et al., 2020). Several studies have noted that the duration from first use to onset of CUD is shorter for females than in males (Hernandez-Avila et al., 2004; Khan et al., 2013), a phenomenon termed 'telescoping'. During withdrawal men are more likely than women to report sleep disturbances, while women are more likely to experience nausea and anxiety (Cuttler et al., 2016). In general, women typically report greater withdrawal intensity and negative impact of withdrawal (Copersino et al., 2010; Schlienz et al., 2017; Sherman et al., 2017).

Several biological factors likely contribute to observed sex differences in cannabis use, abuse, and withdrawal. Indeed, there is accumulating evidence at the preclinical level that the eCB system itself is sexually dimorphic (Bradshaw et al., 2006; Craft et al., 2013; Farquhar et al., 2019), and these dimorphisms likely drive differences in effects of endogenous cannabinoids (Craft et al., ,2012, 2013). Likewise, circulating sex hormones certainly contribute to effects of cannabis and cannabinoid administration (Castelli et al., 2014; Marusich et al., 2015; Struik et al., 2018; Winsauer et al., 2012). A 2020 study correlated functional magnetic resonance imaging (fMRI) measurements with cannabis use and responses to cannabis-related cues (Prashad et al., 2020), and while neural response did not differ between males and females, females did have stronger subjective craving relative to males.

In addition to sex-differences, careful consideration should be given to gender differences pertaining to cannabis use. Gender norms are societal based and one's gender identity can play a role in patterns of cannabis use (Brabete et al., 2020; Greaves & Hemsing, 2020). Future studies should consider gender biases when examining subjective effects of cannabis use, as these biases can manifest in questionnaires and may skew data (Altman et al., 2021), masking important outcomes.

2.4 | Synthetic cannabinoids, dependance and withdrawal

Synthetic cannabinoids (SC) were initially developed by research groups to study cannabinoid receptor actions. The SCs are heterogeneous in structure but all act as potent agonists for CB1 and cannabinoid 2 receptor (CB2), that is, they are cannabimimetic (Castaneto et al., 2014). As their initial use was in academic laboratories, the methods for chemically synthesizing these drugs were published and readily available. While governments have scheduled many SCs as illegal, by continuously altering the molecular structure of these compounds, commercial producers of SCs are able to sell them, for the most part legally, in convenience stores or online.

Once consumed, typically via inhalation from smoking or via e-cigarette type products, most of these compounds are potent full CB1 agonists (Fantegrossi et al., 2014) with binding affinities orders of magnitude higher than THC (see Table 1 of van Amsterdam et al., 2015 and Table 4 of Castaneto et al., 2014). Similarly, some SCs can interact with targets outside the eCB system (Baumann et al., 2014; Cooper, 2016) but little is known about how these interactions contribute to their physiological and psychic affects. These differences from THC likely drive adverse effects of these drugs leading to increased hospitalizations in recent years (Karila & Benyamina, 2019). Additionally, the potency and pharmacokinetics of SCs like contribute to the rapid induction of dependance and relative strength of withdrawal symptoms compared to THC (Cooper, 2016).

Acute psychoactive effects of SCs include altered mood, increased heart rate, dry mouth, red-eye (Auwarter et al., 2009), irritability, anxiety, short-term memory and cognitive impairment, and acute psychosis (see Tables 2 and 3 of Castaneto et al., 2014). It is known that both animals (Tai & Fantegrossi, 2014) and humans (Zimmermann et al., 2009) develop tolerance to these drugs. Tolerance is likely induced via mechanisms similar to THC since cross-tolerance occurs between SCs and THC (see Tables 1 of Castaneto et al., 2014). After chronic use and development of tolerance, cessation of SCs also produces withdrawal effects, often times occurring more rapidly and greater in strength than with THC/cannabis (Pehlivan et al., 2020; Sampson et al., 2015; Tai & Fantegrossi, 2014; Zimmermann et al., 2009). A recent study indicates the development of SC dependance and withdrawal symptoms may have genetic components as well (Pehlivan et al., 2020).

Clearly, there are similarities in the effects of SCs and THC/cannabis, and the DSM-5 groups patients experiencing substance use disorder related to abusing SCs together with cannabis. Indeed, the manual indicates that CUD 'refer[s] to all forms of cannabis-like substances, including synthetic cannabinoid compounds' (American Psychiatric Association, 2013). Yet, it is also clear that SCs have considerably more profound negative side-effects, ultimately leading to hospitalization and sever overdose events, which are considerably rarer in relation to phytocannabinoid use.

2.5 | Pre-clinical models of cannabis use, abuse, and withdrawal

Animal models provide valuable information about the underlying physiological mechanisms that govern biological phenomena observed in humans. Often, elucidating these mechanisms is extremely difficult, if not impossible, to do in humans given confounding pre-existing conditions, environmental factors, and ethical considerations. Indeed, animal models have proved invaluable in understanding the biological manifestations of cannabis use and the physiological changes that occur during chronic use and withdrawal.

2.5.1 | Behavioral effects of acute cannabinoid administration in animal models

Cannabis, THC, or SCs are known to produce four classic physiological effects known as the 'tetrad' via their prominent action on CB1—analgesia, hypothermia, hypoactivity, and catalepsy (Metna-Laurent et al., 2017). Despite their frequent use in rodent cannabinoid behavioral research, when compared to the reported behavioral effects of acute cannabis/THC use in humans discussed above, they offer little translational validity beyond determining whether a pharmacological phenomenon is potentially mediated by CB1 activity. A caveat to this statement might be analgesia because of the potential for development of cannabinoid-based pain medications. The tetrad behaviors and other behavioral effects of cannabinoid administration often have clear dose responses, with higher doses being mainly disruptive and inhibitory and low doses potentially stimulatory. For

example, locomotor activity is suppressed at higher doses of THC or synthetics cannabinoids while lower doses can have a stimulatory effect that increases locomotion and behavioral activities (Chaperon & Thiebot, 1999; Stark & Dews, 1980).

As with many drugs of abuse, THC and THC-like synthetic cannabinoids have a long history of reward, reinforcement, and motivation-related research (Justinova, 2019). Naturally, researchers are interested in studying the neural circuits involved in the addicting characteristics of THC. However, historically this has been difficult to do, as it is difficult to obtain 'rewarding' effects from THC using standard behavioral procedures (Chaperon & Thiebot, 1999; Justinova, 2019). This is clearly different from the case in humans, as many humans obviously readily self-administer cannabis, THC, and THC-like compounds. Acute administration of high doses of THC appears to be aversive as indicated by conditioned place preference and taste aversion studies (Lepore et al., 1995). In these studies, THC is paired with a specific compartment within an arena, or with a novel food, and this will generally cause the animal to avoid that place or food in the future. This is likely because of the initial aversive and anxiogenic potential of THC administration in many animal models (Murray & Bevins, 2010). Indeed, pretreating mice with THC while they are in their home-cage appears to ameliorate the aversive effects of the drug in place preference paradigms (Valjent & Maldonado, 2000) and self-administration (Spencer et al., 2018), presumably by temporally distancing the association of the initial treatment from the conditioning procedure. Interactions between high doses of THC and the endogenous opioid system may mediate these dysphoric effects (Maldonado et al., 2011), as genetic knockdown/knockout of genes involved in endogenous opioid signaling can block dysphoric and facilitate reinforcing effects of cannabinoid administration (Cheng et al., 2004; Mendizabal et al., 2006; Zimmer et al., 2001).

The classic paradigm used in the pre-clinical setting to study drug abuse is the operant self-administration procedure. In this procedure, animals are typically tasked with pressing a lever or poking their nose into a hole to earn drug rewards. Usually, these rewards are brief intravenous (i.v.) infusions of the drug through a chronically implanted jugular catheter. Again, it has been historically quite difficult to obtain i.v. self-administration of THC in animal models, particularly in rodents (Lupica & Hoffman, 2018). That is not to say it is impossible, as there are a few studies reporting i.v. THC self-administration in rats (Spencer et al., 2018; Stringfield & Torregrossa, 2021; Takahashi & Singer, 1979; Wakeford et al., 2017). Most of these studies used smaller doses of THC than typically administered in other behavioral experiments, though Stringfield and Torregrossa found that an escalation procedure potentially allowed adolescent rats to self-administer the drug at relatively higher doses (Stringfield & Torregrossa, 2021). There have been some recent advances in rodent THC/cannabis self-administration procedures that move away from i.v. administration, and instead allow the rodents to earn cannabis-infused dough pellets (Smoker et al., 2019) or brief exposure to cannabis vapor (Freels et al., 2020). These later paradigms are particularly interesting as they better model human administration of these drugs.

While difficult in rodents, THC is readily self-administered by squirrel monkeys (Justinova et al., 2003; Tanda et al., 2000), providing a reliable non-human primate model to study behavioral pharmacology related to specific aspects of cannabis use (Panlilio & Justinova, 2018). The studies using squirrel monkeys and other non-human primates recapitulate most aspects of cannabinoid drug use, including acquisition (Justinova et al., 2003), maintenance (Justinova et al., 2013), relapse/reinstatement (Justinova et al., 2008, 2013), and withdrawal (Fredericks & Benowitz, 1980). These studies can provide valuable insight into pharmacological interventions with translational relevance related to these cannabinoid related drug abuse phenomena. However, it is harder to glean information about the cellular/molecular and systems level neural mechanisms underlying these phenomena because of the lack of transgenic and genetic techniques in non-human primates, as well as the lower availability of subjects and high cost of non-human primate research.

Lupica and Hoffman hypothesize that the difficulty in establishing rodent models of cannabinoid self-administration may stem from their widespread action on CB1 receptors throughout the brain, and in particular in the hippocampus; an effect that can profoundly disrupt coherence of network activity that is critical for learning associations necessary to perform self-administration procedures. They further suggest that differences in experimental conditions between rodent and non-human primate studies might account for differences in the efficacy of self-administration procedures between these types of model organism, though they admit the underlying cause is unclear (Lupica & Hoffman, 2018).

2.5.2 | Preclinical models of cannabinoid tolerance

As in humans, it is well known that animals build tolerance to the effects of exogenous cannabinoid administration (Compton et al., 1990; Gonzalez et al., 2005; Lichtman & Martin, 2005), and animal studies have been valuable in elucidating the potential molecular mechanisms underlying this phenomenon (discussed further below). While conclusions from early preclinical studies were somewhat limited from inconsistent use of dosage and delivery methods (Mcmillan et al., 1971), Bass and Martin rigorously characterized tolerance-inducing THC treatment regimens in mice (Bass & Martin, 2000), which has been used by many with consistent results. In this study, mice were given morning and evening intraperitoneal injections of THC at a dose of 10mg/kg. The authors used two components of the tetrad, antinociception and hypoactivity as behavioral metrics of effects of THC and found tolerance in these behaviors after just 1.5 days of treatment. Tolerance was maximal after 3.5 days and did not increase significantly thereafter. This 3–4 day time frame for developing tolerance to THC appears to be consistent with other species and delivery methods, as a recent study found tolerance to hypothermic and antinociceptive effects of THC after 4 days of chronic THC vapor inhalation in rats (Nguyen et al., 2018).

2.5.3 | Pre-clinical models of cannabis withdrawal

Withdrawal from chronic treatment of cannabinoid drugs can be investigated in two ways: *spontaneous* or *precipitated*. For spontaneous withdrawal, the investigators treat animals to instill tolerance, then abruptly cease treatment and observe the natural behavioral response to no longer receiving the drug. Historically, the presence of cannabis/THC spontaneous withdrawal symptoms in animal models was contentious, with many early studies reporting absence or only mild symptoms. This was often attributed to the lipophilic nature and therefore long half-life of THC prolonging the drug's activity into early abstinence (Lichtman & Martin, 2002). Though research has found that somatic withdrawal symptoms (e.g. wet dog and head shaking, front paw tremor, hunched posture, body tremor, etc.) are reliably measured during spontaneous withdrawal from cannabis, THC, and synthetic cannabinoids (Gonzalez et al., 2005; Lichtman & Martin, 2002; Maldonado & Rodriguez de Fonseca, 2002; Trexler et al., 2018), these do not particularly model human withdrawal symptoms discussed above. That is not to say there is no preclinical evidence of withdrawal symptoms that model human CWS. Chronic treatment with 15mg/kg THC had mild anxiogenic effects on female and anxiolytic effects in male adolescent rats during early THC abstinence (Harte-Hargrove & Dow-Edwards, 2012).

Procedurally, precipitated withdrawal differs from spontaneous withdrawal in that the researcher administers a CB1 antagonist, typically rimonabant, which immediately blocks the effects of the chronically administered cannabinoid drug (Aceto et al., 1995). Precipitated withdrawal reliably induces similar withdrawal symptoms as the spontaneous procedure, though they are typically more profound and intense in nature. In addition, precipitated withdrawal can induce withdrawal symptoms related to cognitive and emotional processes (Marusich et al., 2014), which indeed more closely matches human CWS. An obvious caveat of precipitated withdrawal is that humans ultimately experience spontaneous withdrawal, so the extent to which these symptoms offer translational relevance is unclear.

3 | CELLULAR AND MOLECULAR MECHANISMS ASSOCIATED WITH CHRONIC CANNABIS USE, TOLERANCE, AND DEPENDENCE

3.1 | The endocannabinoid system

The following subsections review the basic cellular and molecular components of the eCB system. These sections are meant to bring readers up to speed on the molecular components of the eCB system to add context to the sections that follow, where we will describe how activity and changes in this system can contribute to behavioral phenomena described in the preceding sections.

3.1.1 | Anandamide and 2-arachidonoyl glycerol

eCBs are fatty acids produced by degradation of arachidonic acid-containing lipids. The two eCBs with prominent effects in the nervous system are arachidonoyl ethanolamide (AEA, also known as anandamide) and 2-arachidonoyl glycerol (2-AG) (Kano et al., 2009). Several enzymatic mechanisms for AEA production have been proposed, and there is ongoing investigation into which pathway predominates in which body and brain region (Lu & Mackie, 2016). In contrast, it is clear that 2-AG is produced via degradation of diacylglycerol catalyzed by diacylglycerol lipase (Bisogno et al., 1997; Prescott & Majerus, 1983; Sugiura et al., 2006). Degradation, and therefore, deactivation of the two eCBs is well characterized, with fatty acid amide hydrolase (FAAH) providing the major catalysis of AEA breakdown, and monoacylglycerol lipase (MGL) primarily catalyzing 2-AG breakdown (Lu & Mackie, 2016). Cyclooxygenase-2 catalyzes oxidation of eCBs (Kozak et al., 2000), and this process can facilitate synaptic signaling through production of prostaglandins that signal through mitogen-activated protein kinase (MAPK) and inositol 1,4,5-trisphosphate (IP3) (Yang & Chen, 2008). The two major eCBs can be produced in cells throughout the body and brain, and evidence indicates that upon production and release they produce juxtracrine actions on nearby cellular elements (Lovinger, 2007).

3.1.2 | eCB-mediated synaptic plasticity

Both AEA and 2-AG activate the G protein-coupled receptors (GPCR) CB1 and CB2, but the efficacy of 2-AG is demonstrably higher than that of AEA (Di Marzo & De Petrocellis, 2012). There is physiological evidence for CB1 activation by both eCBs in the central nervous system (CNS) (Sugiura et al., 1995). Synaptic depression induced by these eCB actions involves decreased neurotransmitter release probability and can persist for different durations. Depolarization of neurons can induce synaptic depression that persists for 10s of seconds. This depolarization-induced synaptic depression has been described at GABAergic synapses (labeled DSI) and glutamatergic synapses (labeled DSE) (Diana & Marty, 2004). The duration of this depression appears to coincide with the duration of extracellular increases in eCBs (Kim & Alger, 2004; Liput et al., 2020; Pan et al., 2009). Pharmacological and genetic knockout experiments indicate that depolarization and activation of postsynaptic voltage-gated calcium channels (VGCCs) produces increased 2-AG production and release and this eCB traverses the synaptic cleft in a retrograde manner to act on presynaptic CB1 and induce depression (Castillo et al., 2012). Short-lasting eCB-mediated depression (STD) induced by synaptic activation or by agonists of Gq-coupled GPCRs involves mechanisms similar to DSI/E. The major difference is that 2-AG production in this case involves metabotropic GPCR/Gq-alpha activation of phospholipase C (PLC) -beta to form diacylglycerol, with diacylglycerol lipase actions necessary for the final eCB synthesis step. A variety of metabotropic GPCRs have been implicated in

STD, most prominently metabotropic glutamate receptors (mGlus) and muscarinic acetylcholine receptors, but also some serotonin receptor subtypes, etc. The short-term forms of eCB-dependent synaptic depression have been observed throughout the CNS and peripheral nervous system (Best & Regehr, 2008; Burattini et al., 2014; Howlett et al., 2002; Parrish & Nichols, 2006; Yuan & Burrell, 2012).

Long-term depression (LTD) dependent on eCBs and CB1 has also been described at a number of CNS synapses. As the name implies, LTD is much longer lasting than DSI/E or STD. Indeed, pharmacological experiments indicate that LTD persists for much longer than the duration of extracellular eCB increases (Chevaleyre et al., 2007; Ronesi et al., 2004; Sjostrom et al., 2003). It appears that CB1 activation by retrograde eCB signaling sets into motion a sequence of molecular signals in the presynaptic terminal leading to decreased neurotransmitter release probability that persists for hours (Yin et al., 2006). These signals include changes in cyclic AMP levels and possibly also altered phosphorylation of vesicle-associated proteins as well as increased protein translation (Castillo et al., 2012; Monday et al., 2018). Like the shorter-lasting forms of synaptic depression, eCB-LTD has been observed at both GABAergic and glutamatergic synapses (Castillo et al., 2012). Activation of group I mGlus is implicated in eCB-LTD induction at a many of these synapses, including at GABAergic synapses (e.g. Chevaleyre and Castillo, 2003). Thus, it is not surprising that Gq and PLC signaling as well as 2-AG are implicated in eCB-LTD induction at many of these synapses. However, there is evidence that eCB-LTD at some synapses, for example, in dorsal striatum and basolateral amygdala, is resistant to alterations in 2-AG production, and may be mediated by AEA (Ade & Lovinger, 2007; Marsicano et al., 2002). Unfortunately, methods to reliably reduce AEA production are not yet available, and thus this hypothesis awaits additional testing.

The different forms of eCB-mediated synaptic depression have been implicated in a variety of in vivo neuronal functions and behaviors. It is thought that eCB-LTD contributes to maturation of synaptic weights in the developing CNS as well as learning and memory in the mature CNS (Augustin & Lovinger, 2018).

3.2 | Central effects of THC following cannabis use

3.2.1 | THC and cannabinoid receptors

Upon entry into the body/brain THC produces its actions via activation CB1 and CB2. These receptors both predominantly activate signaling through the G proteins that contain the alpha$_i$ or alpha$_o$ subunits in addition to the beta/gamma G protein subunit complex. Receptor-induced alpha$_{i/o}$ subunit liberation inhibits AC leading to reduced intracellular cAMP levels (Howlett et al., ,1988, 2002; Rhee et al., 1998). The liberated beta/gamma subunit complex can bind to and alter ion channel function, including inhibition of VGCCs and activation of potassium channels (Betke et al., 2012; Ikeda, 1996). This complex can also activate some subforms of PLC (Camps et al., 1992; Falkenburger et al., 2010; Katz et al., 1992; Smrcka et al., 1991; Taylor et al., 1991). Like many other GPCRs, the CB receptors can also activate signaling through the beta-arrestin protein (Breivogel et al., 2013; Priestley et al., 2017; Tonini et al., 2006). This signaling pathway has been implicated in control of cell surface receptor turnover via mechanisms involving CB1 phosphorylation by a G protein-coupled receptor kinase (GRK) (Jin et al., 1999; Morgan et al., 2014; Nealon et al., 2019; Nguyen et al., 2012). Through these signaling pathways CB receptors can influence a variety of cellular processes, including neurophysiology, membrane protein trafficking and gene expression (Sim-Selley, 2003).

Since THC is a partial agonist at the CB receptors, it is possible that effects on the nervous system and behavior reflect not only receptor activation but also interference in the actions of more efficacious endogenous CB agonists (discussed below). As mentioned previously, more efficacious synthetic CB agonists, that is, SCs, have been developed (D'Ambra et al., 1992) and these compounds generally produce in vivo effects similar to THC but with more pronounced actions on some behaviors and affective measures (e.g. catalepsy in rodents, aversive effects in humans) (Compton et al., 1992; Johnson et al., 2019; Karila & Benyamina, 2019; Richter & Loscher, 1994).

In the nervous system, CB1 is the predominant target of THC (Devane et al., 1988; Shao et al., 2016) and synthetic cannabinoid drugs (D'Ambra et al., 1992; Pacheco et al., 1991). CB1 is expressed predominantly, if not exclusively on presynaptic terminals (Bacci et al., 2004; Ong & Mackie, 1999) where it inhibits neurotransmitter release (Castillo et al., 2012; Lovinger, 2008). The aforementioned inhibition of VGCCs is one mechanism implicated in this inhibition (Betke et al., 2012; Ikeda, 1996). However, $G_{i/o}$-coupled GPCRs, including CB1, also inhibit release via mechanisms downstream of VGCCs, most likely via actions on vesicle-associated proteins (Gerachshenko et al., 2005; Hamid et al., 2014). Glutamatergic (Shen et al., 1996) and GABAergic synapses (Hoffman & Lupica, 2000; Katona et al., 1999) are the major loci of CB1 actions, with the result that CB1 can either reduce or enhance excitatory synaptic drive through direct modulation or indirect disinhibition (Freund et al., 2003). Release of other neurotransmitters and modulators is also modulated by CB1 including acetylcholine (Gifford & Ashby, 1996), and norepinephrine (Schlicker et al., 1997). In addition, there are a few reports of CB1 modulation of neuronal excitability through what appear to be actions on somata or dendrites (Marinelli et al., 2009; Seif et al., 2011), but the subcellular location of the receptors implicated in these actions is not yet clear. Through these modulatory mechanisms CB1Rs shape the input to and output of neurons in circuits throughout the brain. Thus, it is not surprising that CB1 receptor activation by THC or synthetic agonists has such profound effects on behavior, including analgesic, appetitive, cataleptic, hypokinetic, memory altering, sleep promoting, and stress-response regulating actions (Cooper & Williams, 2019).

3.3 | Potential physiological mechanisms underlying cannabis abuse

3.3.1 | Mechanisms of acute and chronic behavioral effects

As described in the previous section on chronic cannabis use in humans, repeated exposure to THC produces tolerance to the acute actions of the drug and can lead to dependence. These persistent effects may start to develop even after the first exposure to the drug. Indeed, acute exposure to THC decreases local glucose utilization in a variety or brain regions, with especially prominent effects in limbic areas (Sim-Selley, 2003; Whitlow et al., 2002). These decreases can persist for up to 24 hr in some regions. It is clear that CB1 receptors mediate THC dependence as the CB1 antagonist rimonabant is generally used to precipitate withdrawal symptoms (Trexler et al., 2018; Wilson et al., 2006). In addition, signs of dependence are lost in mice genetically engineered to lack the CB1 receptor (Ledent et al., 1999; Lichtman et al., 2001). Self-administration of synthetic cannabinoids is also lost in mice treated with CB1 antagonists (Ledent et al., 1999; Martellotta et al., 1998).

Tolerance develops to the inhibitory effect of THC on local glucose utilization in some brain regions following chronic treatment with the drug for 7–21 days (Whitlow, 2003). Notably, tolerance is less prominent in the mesocorticolimbic brain regions. Decreased psychostimulant-induced glucose utilization is also observed in several brain regions in female, but not male, regular cannabis users (Wiers et al., 2016). Studies using functional magnetic resonance imaging have observed decreased activation of the ventral striatum during tasks involving monetary reward in abstinent regular cannabis users (Filbey et al., 2013; Yip et al., 2014). These changes are consistent with observations in rats that chronic THC exposure alters dopamine transmission in the ventral striatum in response to drug reward (Cadoni et al., 2008).

3.3.2 | Tolerance and DSI, STD, LTD

It has been consistently demonstrated that chronic THC exposure reduces the synaptic depressant effect of CB1 activation, and this physiological tolerance has been observed at synapses in several brain regions. Most notably, synaptic tolerance has been observed at synapses in the nucleus accumbency/ventral striatum, dorsal striatum, hippocampal CA1 region, and the ventral tegmental area (Friend et al., 2017; Hoffman et al., 2003, 2007; Mato et al., 2005; Nazzaro et al., 2012). In the typical experimental procedure, effects of a CB1 agonist on GABAergic and glutamatergic transmission are examined in animals given several days of exposure to THC (usually via intraperitoneal injection) compared to vehicle-treated controls. Brain slice recordings are used to assess agonist action and tolerance. However, effects of this chronic THC regimen on eCB-mediated synaptic plasticity induced by afferent stimulation have also been examined (Friend et al., 2017; Nazzaro et al., 2012). The chronic THC regimens used for these experiments are known to produce tolerance to many of the acute effects of the drug, including analgesia (Abood et al., 1993; Mato et al., 2005).

3.4 | Potential molecular mechanisms of cannabis withdrawal symptoms

3.4.1 | CB1 downregulation

Considering the observed loss of CB1-induced synaptic depression following chronic THC exposure, a decrease in receptor expression or cell-surface expression on presynaptic terminals would appear to be a reasonable mechanism for this tolerance. In general, radioligand binding measurements indicate receptor downregulation in several brain regions including cerebellum, globus pallidus and striatum, but this effect was not observed in all studies or brain regions (Breivogel et al., 1999; Martini et al., 2010; Romero et al., 1995, 1997; Tappe-Theodor et al., 2007; Tonini et al., 2006). For example, increased binding was observed in cerebellum and hippocampus following exposure to a low THC dose that might not be sufficient to produce behavioral tolerance (Lee et al., 2003). When decreases were observed they were generally in the maximum specific binding for CB1 ligands, but decreased ligand affinity was also reported in striatum (Oviedo et al., 1993; Romero et al., 1995; Sim-Selley, 2003). Recent studies in humans using positron emission tomography-based CB1 imaging indicate decreased receptor availability during withdrawal in regular cannabis users (D'Souza et al., 2016; Hirvonen et al., 2012). Levels of the receptor appear to return to control values following prolonged abstinence in all brain regions examined except hippocampus (Hirvonen et al., 2012).

Effects of chronic cannabinoid treatment on the CB1 protein measured with immunochemical approaches have also been examined. However, it is admittedly difficult to measure cell surface receptors in small subcellular compartments such as presynaptic terminals, even with confocal microscopy. Reduced cell surface CB1 immunostaining was observed in receptor-expressing cells following chronic exposure to different THC and full agonists (Hsieh et al., 1999; Rinaldi-Carmona et al., 1998). The full agonists produced a stronger response than THC. Using hippocampal neurons in primary culture, Coutts and coworkers (2001) showed that chronic CB1 agonist application decreased cell surface CB1 immunostaining following chronic agonist exposure (Coutts et al., 2001). Newly developed super-resolution imaging techniques should allow for such analysis. Indeed, using the STochastic Optical Reconstruction Microscopy, that is, STORM, approach Katona and coworkers have measured axon terminal-surface and internal receptors at GABAergic synapses in the hippocampus (Dudok et al., 2015). Furthermore, they showed that repeated treatment with THC reduced cell surface CB1 expression at these synapses in a dose-dependent manner. Recovery of receptors on the terminal surface required several weeks following the cessation of THC exposure. This finding indicates that the function of CB1 receptors on

presynaptic terminals will likely be impaired for a considerable time following cessation of cannabis drug use.

Changes in CB1 mRNA are less consistent (Sim-Selley, 2003), perhaps indicating that receptor downregulation does not involve transcriptional changes or changes in mRNA stability. However, decreased CB1 mRNA expression has been observed in striatum during and after chronic THC exposure (Zhuang et al., 1998).

The role of decreased CB1 expression in altered receptor-induced signaling and tolerance to effects of synaptic transmission is not clear. For example, at synapses made by striatal projection neurons in downstream basal ganglia regions there is little to no decrease in receptor binding at time points when tolerance is clearly evident (Romero et al.,. ,1997, 1998, 1999; Rubino et al., 2000). It is also unclear if decreased CB1 expression and function contribute to dependence. Full recovery of receptor binding levels occurs at time points when behavioral measures of antagonist-precipitated withdrawal are already complete (Rubino et al., 1998). Furthermore, receptor function is still downregulated at time points when antagonist exposure no longer elicits withdrawal signs (Rubino et al., 1998; Rubino, Vigano, Massi, & Parolaro, 2000).

Mice expressing a mutant CB1 receptor resistant to receptor-phosphorylating GRKs (Jin et al., 1999) show delayed tolerance to some effects of THC and other agonist treatments (Morgan et al., 2014; Nealon et al., 2019). A similar effect was observed in beta-arrestin knockout mice (Nguyen et al., 2012). These findings indicate that arrestin-associated GRK function may be involved in receptor trafficking/inactivation implicated in tolerance. Interestingly, differential effects on tolerance to different CB1 agonists were observed, and tolerance eventually developed for all agonists after prolonged drug treatment (Nealon et al., 2019). Thus, GRK-mediated phosphorylation appears to be only one mechanism involved in tolerance.

Chronic exposure to full CB1 agonists, such as those which are constituents of "spice" and other SC formulations, also produce neuroadaptations. As observed with THC, the full CB1 agonists such as CP55,940 and WIN 555–212 produce downregulation of CB1, receptor-stimulated guanosine triphosphate (GTP) -gammaS activation, and other consequences of receptor activation in cerebellum, cortex, hippocampus and striatum (Oviedo et al., 1993; Rubino, Vigano, Massi, & Parolaro, 2000; Sim-Selley & Martin, 2002).

3.4.2 | AC, cAMP and PKA

Chronic THC exposure has been shown to alter several intracellular signaling processes that could contribute to physiological and behavioral changes during withdrawal. Receptor-stimulated GTPgammaS binding is decreased following chronic exposure to THC (Martin et al., 2004; Sim-Selley, 2003). This supports the idea that the first step in CB1-stimulated intracellular signaling, namely G-protein dissolution, shows tolerance following lasting receptor activation.

The inhibition of AC following CB1 activation of $G_{i/o}$-coupled G proteins occurs predominantly in presynaptic terminals given the localization of CB1 in this subcellular compartment. Decreased AC activity will lower cAMP levels and decrease activation of downstream enzymes such as the cAMP-dependent protein kinase (PKA) and exchange protein directly activated by cAMP (EPAC). Changes in AC, cAMP and PKA activity have been observed following chronic THC exposure and withdrawal in both rat and mouse brains (Hutcheson et al., 1998; Rubino, Vigano, Massi, Spinello, et al., 2000). Enhanced function of AC isoforms that are inhibited upon acute CB1 activation may contribute to these effects (Rhee et al., 1998). However, in the case of antagonist-precipitated withdrawal in mouse, the increase in cAMP appears to be confined to the cerebellum. Indeed, inhibition of PKA in cerebellum can block precipitated withdrawal signs in mouse, while PKA activation mimics precipitated withdrawal (Tzavara et al., 2000). Phosphorylation of CB1 mediated by the c-Jun terminal kinase has also been implicated in THC-induced tolerance (Henderson-Redmond et al., 2020).

3.4.3 | Endocannabinoids

Very few studies to date have examined changes in eCBs following chronic THC or cannabinoid drug use. Chronic exposure to THC at a dose that produces behavioral tolerance in rat resulted in decreased tissue levels of AEA and 2-AG in striatum as measured by liquid chromatograph-mass spectrometry (Di Marzo et al., 2000). In contrast, AEA levels were increased in limbic forebrain (Di Marzo et al., 2000; Gonzalez et al., 2004). Enhanced expression of mRNA for MGL was observed in the hypothalamus following chronic THC exposure (DeVuono et al., 2018). There was no effect on FAAH, but this study only examined RS/1 Huntington's disease model mice (Dowie et al., 2010). Treatment with inhibitors of FAAH and MGL reduced precipitated withdrawal signs following chronic THC exposure but is it unclear if this effect involved increases in AEA or 2-AG and if changes in the function of these enzymes contribute to withdrawal effects (Schlosburg et al., 2009). Also of note are the profound effects on sleep of FAAH and MGL inhibitors (Pava et al., 2016), especially given the hypnogenic properties of cannabis/THC and disrupted sleep during withdrawal.

3.5 | Other neurotransmitters implicated in cannabinoid actions

3.5.1 | Dopamine

Dopamine (DA) is a neuromodulator intimately involved in movement control (Panigrahi et al., 2015), reward and reinforcement (Ilango et al., 2014; Ilango, Kesner, Keller, et al., 2014; Wise, 2004) and effects of drugs of abuse (Volkow & Morales, 2015). There is considerable evidence that exogenous cannabinoids indirectly modulate DA activity which has ramifications for development of CUD and CWS (for systematic review of this extensive literature see Rubino, et al., 2000; also see Bloomfield et al., 2016,

Covey et al., 2017, and El Khoury et al., 2012). Exposure to the SC HU-210 for fourteen days enhances the locomotor effect of a peripherally injected D2 dopamine receptor antagonist (Moreno et al., 2005). It is unclear how prolonged and efficacious activation of CB1 would produce such an effect, but this may involve changes in eCB actions on midbrain dopaminergic neurons or changes in striatal neuron excitability or synaptic transmission. Indeed, chronic THC increases ligand binding to D2 and 3-type DA receptors and enhances the psychomotor effect of intra-striatal and midbrain administration of quinpirole, an agonist of these receptors (Tournier et al., 2016). Acute exposure to THC has been shown to increase extracellular DA levels in the striatum of rodents (Tanda et al., 1999; Lecca et al., 2006; Tanda et al., 1997; Ng Cheong Ton et al., 1988) and humans (Bloomfield et al., 2014; Bossong et al., 2015; Stokes et al., 2010). There is emerging evidence for changes in dopaminergic function during withdrawal following chronic THC exposure, including changes in dopaminergic neuronal activity and evidence of altered dopamine levels and reduced psychostimulant-induced DA release in human striatum (Diana et al., 1998; Volkow et al., 2014).

3.5.2 | Endogenous opioid roles in THC dependence and tolerance

There is abundant evidence that endogenous opiates affect cannabinoid dependence. Indeed, mice genetically engineered to lack the opiate peptide precursor proenkephalin show reduced antagonist-precipitated withdrawal following chronic THC exposure (Lichtman et al., 2001). Similar results were obtained in mice lacking mu opiate receptors (MOPR), implicating this receptor in opiate peptide roles in cannabis withdrawal (Valverde et al., 2000). Ventral tegmental area microinjections of beta-endorphin, an endogenous opioid with effects mirroring abused opiate drugs, increases the ability of rats to discriminate effects of THC (Solinas et al., 2004), also implicating the opiate system in CUD and the abuse liability of THC.

Bidirectional cross-tolerance between morphine and THC has been observed in rodent studies (Robledo et al., 2008; Thorat & Bhargava, 1994; Vigano et al., 2005). Chronic treatment with THC at doses that induce tolerance to the analgesic, hypothermic, locomotor and heart rate-altering drug actions in mice also reduces these responses to a subsequent morphine injection (Bloom & Dewey, 1978; Hine, 1985; Robledo et al., 2008; Tulunay et al., 1982). Similar reductions in THC effects on some of these measures were also observed following chronic morphine administration. The rewarding effect of morphine, assessed with conditioned place preference, is also diminished during withdrawal following chronic exposure to THC (Jardinaud et al., 2006). Genetic components likely contribute to interaction between eCB and opiate systems related to THC reward, as the effects of adolescent cannabis exposure on heroin reinforcement in rats is strain dependent (Cadoni et al., 2015; Lecca et al., 2020). Moreover in addition to cross-talk between eCB and opiate systems related to THC reward, there appears to be important interactions between these systems and the DA system (Cadoni et al.,. ,,,,,2008, 2015).

However, in contrast to the rodent studies just discussed, chronic administration of a long-acting CB1 agonist to non-human primates did not alter opiate self-administration (Desai et al., 2013). Chronic exposure to a dose of THC that produced tolerance (as measured by a diminished analgesic effect) did not alter expression of delta opiate receptors, kappa opiate receptors, or MOPRs in mouse midbrain (Cichewicz et al., 2001; Thorat & Bhargava, 1994). Yet this THC treatment regimen was able to prevent receptor down-regulation when given in conjunction with a chronic morphine treatment that normally downregulates the receptors, and other studies have found altered MOPR function and levels in reward-related regions in rats treated with THC (Ellgren et al., 2007) or cannabinoid receptor agonist WIN 55,212–2 (Fattore et al., 2007).

Unlike the cross-tolerance seen with some opiate responses, enhanced locomotion produced by heroin appears to show cross-sensitization (i.e. is increased) following chronic THC (Cadoni et al., 2001; Lamarque et al., 2001; Pontieri et al., 2001a, 2001b; Singh et al., 2005). Levels of opiate peptides in hypothalamus are also increased following chronic THC exposure (Kumar et al., 1984).

3.5.3 | Corticotrophin releasing factor

Corticotrophin releasing factor (CRF), a neuropeptide known to be regulated by several drugs of abuse, is increased in central amygdala during antagonist-precipitated withdrawal following chronic exposure to HU-210 (Rodriguez de Fonseca et al., 1997). This stress-related neuropeptide may contribute to negative affect during withdrawal. Increased mRNA for CRF has also been noted in hypothalamus following chronic exposure to THC and other CB1 agonists (Corchero et al., 1999; Corchero et al., 1999).

It should be clear from the foregoing subsections that chronic THC and CB1 agonist exposure alters the function of a variety of neurotransmitters and neuromodulators. However, interactions with the hundreds of other signaling molecules in the brain remain unexplored. Clearly, this is an area ripe for future investigation.

4 | TREATMENTS FOR CUD AND CWS

Clearly CUD and CWS are clinically relevant pathologies and over the past two decades there has been growing interest in therapeutic research towards symptom alleviation (Danovitch & Gorelick, 2012). Progress thus far in development of pharmacotherapies has been relatively modest (Kondo et al., 2020; Sherman & McRae-Clark, 2016, 2019; Vandrey & Haney, 2009).

Cannabinoid agonist replacement was one of the first CUD/CWS pharmacotherapies tested in the clinical setting, because of the past success of nicotine and opioid agonists in treating cigarette and opioid addictions, respectively (Brezing & Levin, 2019). Indeed, this class of pharmacotherapy remains the most widely studied for treating

CUD/CWS. Drugs like the synthetic THC, dronabinol, and nabilone, a CB1-agonist with THC-like properties, appear to be effective at diminishing the abuse-potential-related acute effects of cannabinoids and reducing withdrawal symptoms (Budney et al., 2007; Haney et al.,. ,2004, 2013; Vandrey et al., 2013). In addition, combining THC with cannabidiol, another phytocannabinoid that is gaining significant clinical interest, in formulations such as Nabiximols (also known as Sativex) has been shown to be effective in treating CWS (Allsop et al., 2014). While effective at reducing abuse and CWS, the overall efficacy of cannabinoid agonist replacement as a treatment for CUD is still controversial because of the relative ineffectiveness of these treatments at prolonging abstinence or increasing treatment retention (Kondo et al., 2020; however, see Brezing & Levin, 2020).

Also of note are clinical trials using the CB1 antagonist/inverse-agonist, rimonabant, to treat CUD and CWS. While this compound showed initial promise in curbing CUD and CWS (Huestis et al., 2001, 2007), all clinical trials using this drug were halted because of adverse psychiatric effects such as anxiety, depression, and suicide (Roberfroid et al., 2010; Topol et al., 2010). However, others have speculated that rimonabant's inverse-agonist properties may be related to its adverse side effects, leading to the possibility that compounds with a more purely antagonist-like pharmacology may be as therapeutically efficacious without the troubling adverse side-effects (Balter et al., 2014; Brezing & Levin, 2020). Negative allosteric modulators of CB1 may also be considered for similar reasons.

Briefly, other therapies include: drugs targeting other neurotransmitter or neuropeptides including serotonergic, noradrenergic, dopaminergic, and oxytocin systems (Sherman & McRae-Clark, 2019); anticonvulsants (Mason, 2019); prodrug compounds such as N-acetylcysteine (Gray, 2019); antipsychotics and antidepressants (Arout et al., 2019); and non-pharmacological treatments such as cognitive behavioral and other psychosocial therapies (Aklin & Bedard-Gilligan, 2019; Kiselica & Duhig, 2019; Shurtleff, 2019). In addition, the α-2A-adrenergic receptor agonist, guanfacine, was shown to ameliorate CWS (Haney et al., 2019), as did the fatty acid amide hydrolase inhibitor, PF-04457845 (D'Souza et al., 2019). Interestingly, a small study examining the efficacy of the hormone progesterone in female heavy cannabis users indicated that the treatment may reduce craving and relapse (Sherman et al., 2019).

Sleep disturbance is one of the most commonly reported CWS symptoms and is often cited as a main driver of relapse to cannabis use during attempted abstinence (Babson et al., 2013; Bonn-Miller et al., 2014, 2019). As such, targeting this symptom to treat CWS and prevent relapse has become an attractive area of study. Indeed, it appears sleep disturbance is a common symptom in many, if not all substance use disorders (Brower & Perron, 2010; Roehrs & Roth, 2015). Two studies have assessed the effects of Zolpidem, a common prescription medication used to treat insomnia, on CWS when given during early abstinence. While both studies reported positive effects in treating sleep disturbances during abstinence, neither found significant effects in ameliorating other CWS symptoms (Herrmann et al., 2016; Vandrey et al., 2011). Another study similarly tested the efficacy of lithium and the benzodiazepine, nitrazepam, on treating sleep disturbances during cannabis withdrawal, and found that lithium in conjunction with nitrazepam showed positive effects on sleep disturbances, and that increases in sleep efficacy resulted in modest improvement in treatment retention (Allsop et al., 2015).

It is important to note that treatment of CUD and CWS remains an emerging and dynamic field and the long-term efficacy of many treatments remains unknown (Bonnet & Preuss, 2017).

5 | CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

Much progress has been made at the clinical level in terms of characterizing and understanding CUD and CWS since being brought to light roughly 30 years ago. Connections to earlier preclinical studies and back-translational studies have also provided considerable understanding of the neurophysiological substrates of cannabinoid-related biological phenomena that may ultimately manifest as CUD and CWS. Still there clearly remains much to be learned.

One burgeoning area for further research is that of genetic and epigenetic components of CUD. The fact that only a subpopulation of chronic cannabis users develop CUD or express CWS strongly suggests genetic predispositions might be at play (Agrawal & Lynskey, 2006; Blecha et al., 2019; Bogdan et al., 2016) / There are relatively few human genetics studies aiming to identify heritable genetic factors linked to CUD, including familial transmission analysis (Gfroerer, 1987), twin studies (Vink et al., 2010), whole genome sequencing (Gizer et al., 2018; Sherva et al., 2016), and genome-wide association studies (Bogdan et al., 2016; Sherva et al., 2016). Clearly, there will be polygenic contributions to CUD and CWS, as is the case for all substance abuse disorders. In a recent review, Thorpe and coworkers discussed several genes associated with different cannabis use phenotypes/stages of use (Thorpe et al., 2021). Among the most prominent genes associated with these phenotypes were FAAH, the CB1, the alpha2 nicotinic acetylcholine receptor subunit, and neuronal adhesion molecules such as Cell Adhesion Molecule 2. Further studies are needed to refine the endophenotypes related to polymorphisms in these genes, and to determine if altering expression of the gene products alters CUD or CWS. Additional work examining genetic influences on components of the eCB signaling system and differences in responses to cannabinoid drugs in non-human animal models is also needed. The density of CB1 in the lateral globus pallidus and the ratio of N-acyl phosphatidylethanolamine-specific phospholipase D/FAAH mRNA expression in several brain regions is higher in Fisher 344 rats than in the Lewis rat strain (Coria et al., 2014). These two strains show differences in self-administration of a variety of drugs, as well as THC effects on brain stimulation reward and thus genetic differences in the eCB signaling system between the two strains may contribute to abuse liability. As with genetic

studies, there have been only a few studies investigating epigenetic aspects of cannabis use and more work is clearly needed in this area (for review see Szutorisz & Hurd, 2016).

At the preclinical level, advances in neurotransmitter sensor technologies will likely provide valuable insight into the underlying systems neuroscience factors mediating behavioral symptoms of CUD and CWS. In these types of studies researchers use optical techniques, such as fiber photometry, to record changes in light intensity from neurons that express fluorescent proteins whose fluorescence is modulated by neurotransmitter action. Indeed there appears to be an ever expanding palette of sensors specific to different neurotransmitters and neuromodulators (O'Banion & Yasuda, 2020), including eCBs (Dong et al., 2020; Liput et al., 2020), which will allow for unprecedented analysis of how different neural circuits respond to various cannabis treatment procedures.

Finally, there is a clear inconsistency in terms of cannabinoid compounds (particularly at the preclinical level), doses, routes of administration, and behavioral task conditions used in the studies discussed in this review. These inconsistencies are likely to explain the disparate conclusions obtained in many studies addressing CUD and CWS. It will be important for further research to address this, potentially using more translationally relevant paradigms (e.g. vapor self-administration in rodent models, or full spectrum cannabis/cannabis extracts in both clinical and preclinical settings). This would obviously be facilitated by government rescheduling of cannabis and phytocannabinoid compounds so both clinical and preclinical studies can be conducted to further our understanding and develop treatments for CWS and CUD.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

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