



Published in final edited form as:

Neurobiol Dis. 2022 June 01; 167: 105670. doi:10.1016/j.nbd.2022.105670.

Synaptic changes induced by cannabinoid drugs and cannabis use disorder

Shana M. Augustin^{a,b}, David M. Lovinger^{a,*}

^aLaboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, MD 20852, USA

^bDepartment of Pharmacology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

Abstract

The legalization of cannabis in many countries, as well as the decrease in perceived risks of cannabis, have contributed to the increase in cannabis use medicinally and recreationally. Like many drugs of abuse, cannabis and cannabis-derived drugs are prone to misuse, and long-term usage can lead to drug tolerance and the development of Cannabis Use Disorder (CUD). These drugs signal through cannabinoid receptors, which are expressed in brain regions involved in the neural processing of reward, habit formation, and cognition. Despite the widespread use of cannabis and cannabinoids as therapeutic agents, little is known about the neurobiological mechanisms associated with CUD and cannabinoid drug use. In this article, we discuss the advances in research spanning animal models to humans on cannabis and synthetic cannabinoid actions on synaptic transmission, highlighting the neurobiological mechanisms following acute and chronic drug exposure. This article also highlights the need for more research elucidating the neurobiological mechanisms associated with CUD and cannabinoid drug use.

Keywords

Cannabis sativa; Long-term potentiation; Long-term depression; Synaptic Modulation; Delta-9 tetrahydrocannabinol; Cannabinoid 1 receptor; Endocannabinoid

1. Introduction

Cannabis-derived drugs are among the most widely used illicit substances in the world. According to the 2021 World Drug Report, it is estimated that over 200 million people have used cannabis globally, likely increasing amid the global COVID-19 pandemic (World Drug Report 2021, 2021). However, efforts to decriminalize, legalize, and reclassify the scheduling of these drugs are fast transforming the landscape of cannabis use and research.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

*Corresponding author at: National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 5625 Fishers Lane, Room TS-13A, Rockville, MD 20852, USA. lovindav@mail.nih.gov (D.M. Lovinger).

Declaration of Competing Interest

None.

Despite the UN's reclassification of cannabis and its derivatives, these drugs remain classified as schedule I by the US Drug Enforcement Administration together with other drugs such as heroin, and ecstasy (<https://www.dea.gov/drug-information/drug-scheduling>). Moreover, the perceived decrease in the risks associated with cannabis use has contributed to its popularity and increased usage, already exacerbating a global health problem (Merrill, 2015).

In addition to cannabis, cannabis derivatives are being developed for medicinal purposes, despite the relative paucity of evidence about their safety, efficacy, and benefits. At the same time the evolving recognition of cannabis use disorder (CUD) and cannabis withdrawal syndrome (CWS) DSM-5; (Association, 2013) complicates the situation (Katz et al., 2014). CUD includes not only tolerance to the drug, but dependence on it as well (Branch et al., 1980; Budney et al., 2007; Hollister, 1978; Hollister, 1986; Jones et al., 1976; Patel and Marwaha, 2019; Zehra et al., 2018) and fits within neurobiological models of substance use disorders (Koob and Volkow, 2016). The intoxicating effects of cannabis consist of euphoria, impaired motor coordination, slowed reaction time, anxiety, impaired judgment/memory, and social withdrawal (Crean et al., 2011; Green et al., 2003; Kowal et al., 2015; Pujol et al., 2014; Solowij and Battisti, 2008; Volkow et al., 2016). Some of these effects can last for hours, depending on the method of cannabis administration (Borodovsky et al., 2016; Carlini et al., 2017; Loflin and Earleywine, 2014; Vandrey et al., 2017). In addition, cannabinoids can increase appetite initially, but chronic use may be suppressive (Cluny et al., 2015; Farokhnia et al., 2020; Foltin et al., 1986; Horn et al., 2018; Kirkham, 2009; Le Strat and Le Foll, 2011; Sansone and Sansone, 2014). Notably, cannabis users are less likely to overdose on cannabis when taken alone compared to other substances of abuse (Crocker et al., 2021; Martins et al., 2015). However, the risk of overdose increases with polysubstance use, such as comorbid use of cannabis with alcohol, opioids, or benzodiazepines (Jordan et al., 2018). In some regular cannabis users, CWS occurs after the cessation of cannabis use and it is a clinical indicator of CUD (Association, 2013). The diagnostic criteria for CWS includes, but is not limited to cannabis craving, sleep disruptions, irritability, aggression, suppressed appetite resulting in weight loss, depression, and anxiety (Karila et al., 2014; Katz et al., 2014; Kesner and Lovinger, 2020; Smith, 2002). CWS can also manifest with physiological symptoms, such as sweating, fever, headaches, fatigue, night sweats, and tremors (Katz et al., 2014). These symptoms can appear within days of cannabis cessation (Davis et al., 2016). There are no approved medications for CUD and CWS. However, behavioral treatments including cognitive and motivational enhancement therapies, as well as contingency management are used by CUD individuals to refrain from cannabis use and to remain abstinent (Sherman and McRae-Clark, 2016). While the behavioral effects of cannabis and withdrawal are well characterized, neurobiological research is just beginning to uncover the mechanisms that contribute to these behavioral changes.

2. Cannabinoids and sites of actions

2.1. Exogenous cannabinoids

The molecular constituents of *cannabis*-derived drugs (also known as phytocannabinoids) act on several molecular targets within the nervous system and other organs, but the

most prominent targets are the $G_{i/o}$ protein-coupled cannabinoid receptor types 1 and 2 (CB1 and CB2) (Elsohly and Slade, 2005; Karniol et al., 1975). These receptors inhibit adenylyl cyclase (AC) activity, resulting in decreased levels of cAMP and inhibition of other effector proteins, such as protein kinase activity (PKA) (Ibsen et al., 2017). The predominant psychoactive constituent of cannabis-derived drugs is 9-tetrahydrocannabinol (THC), followed by the second most prominent constituent, cannabidiol (CBD). THC acts as a partial agonist at both CB1 and CB2 receptors (Kano et al., 2009; Pertwee, 2008; Pertwee et al., 2010) and its chemical structure was originally identified by Adams and Gaoni in the 20th century (Adams, 1940; Gaoni and Mechoulam, 1971). Within the brain, THC actions on presynaptic CB1 receptors predominately result in inhibitory actions on synaptic transmission (Felder et al., 1995). CB1 receptors are expressed throughout the brain and signaling through these receptors contributes to the behavioral consequences and possibly the misuse liability of cannabinoids (Augustin and Lovinger, 2018; Hu and Mackie, 2015). CB1 receptor signaling has been implicated in the processing and seeking of drug reward (Parsons and Hurd, 2015; Volkow et al., 2017). Unlike THC, which has a high binding affinity to CB1 receptors, CBD has a low binding affinity and may function as a negative CB1/CB2 receptor allosteric modulator (Kathmann et al., 2006; Laprairie et al., 2015; Ryberg et al., 2007). Another molecular constituent of cannabis is cannabinol (CBN), which is produced from the oxidation and degradation of THC (Merzouki and Mesa, 2002; Upton et al., 2013). CBN is a weak CB1 receptor agonist and mildly psychoactive (Rhee et al., 1997). Like THC, CBN binds to CB1 receptors to mediate its drug effect, although at a significantly lower potency than THC (Rhee et al., 1997). This cannabinoid is known to produce a sedative-like feeling (Musty et al., 1976), which may be beneficial to sleep. There is considerable interest in the development of other cannabis-derived drugs, besides THC, as potential therapeutic agents. However, more research is needed to determine their benefits and/or health risk associated with usage.

Full synthetic CB1 receptor agonists are widely used for therapeutic purposes and more recently for recreational drug use as an alternative to cannabis (Vaughn et al., 2016; Weinstein et al., 2017). As the name implies, “synthetic” cannabinoids are produced in a laboratory and are chemically distinct from THC. As a result, these compounds are difficult to detect with standard drug screening procedures. Some examples of full CB1 receptor agonists are JWH-018, WIN55, 212–2, and CP55,940 (Atwood et al., 2010; Soethoudt et al., 2017). For a more complete list of synthetic cannabinoids and receptor subtype efficiency see (An et al., 2020). These drugs are pharmacologically similar to THC and exhibit a high binding affinity to CB1/CB2 receptors (Potts et al., 2020; Tai and Fantegrossi, 2017; Walsh and Andersen, 2020). Synthetic cannabinoids are generally more potent than phytocannabinoids, including THC (Banister and Connor, 2018), and are now part of widely abused herbal mixtures referred to as “Black Mamba”, “Spice” or “K2”. Furthermore, these compounds are advertised and/or labeled as “legal” or “fake” cannabis as part of “herbal incense” and “potpourri” to be smoked similarly to cannabis (Kelly and Nappe, 2021; Parrott et al., 2017). These compounds are classified as new psychoactive substances (NPS) (Banister and Connor, 2018; Scourfield et al., 2019) and are often sold online or at gas stations and convenience stores. Unlike THC, these cannabinoids are often not regulated by governments and are easily accessible, especially by adolescents (Johnston et al., 2012).

Use of these synthetic compounds can cause drug dependence, tolerance, and withdrawal symptoms, which are all hallmarks of substance misuse (Koob and Volkow, 2016; Nacca et al., 2013; Zimmermann et al., 2009). The neurobiological mechanisms by which these synthetic compounds, such as those in “Spice”, exert their psychoactive effects are not fully understood. Moreover, little is known about the short- and long-term effects of synthetic cannabinoid usage. The use of these compounds raises concerns about escalation of CUD (Alves et al., 2020; Kelly and Nappe, 2021).

2.2. Endogenous cannabinoids

The CB receptors are a key part of the endogenous cannabinoid (endocannabinoid or eCB) juxtacrine signaling system (Ibsen et al., 2017; Lu and Mackie, 2016). The eCBs are naturally produced metabolites of arachidonic acid-containing lipids. These eCBs play important roles in neurodevelopment and synaptic plasticity (Chevalleyre et al., 2006; Lu and Mackie, 2016; Piomelli, 2003). Once released from cells, the eCBs traverse short extracellular distances to activate CB receptors (Mackie, 2005). The two main eCBs are arachidonoyl ethanolamine (AEA) and 2-arachidonoyl glycerol (2-AG). Although both AEA and 2-AG are agonists, 2-AG is a full agonist for CB1/CB2 receptors while AEA is a partial CB1 receptor agonist (Mackie, 2005; Mackie, 2008). These eCBs are synthesized and degraded by distinct enzymatic pathways, which may contribute to differences in physiological and functional roles (Augustin and Lovinger, 2018). In the central nervous system (CNS), eCBs are generated and released mainly from postsynaptic elements such as dendrites, dendritic spines and somata (Alger, 2002; Katona and Freund, 2012; Min et al., 2010). The CB1 receptors are located almost exclusively on presynaptic boutons in CNS where they inhibit neurotransmitter release (Lu and Mackie, 2016).

3. Non-canonical sites of cannabinoid actions

Both exogenous (phyto- and synthetic cannabinoids) and endogenous cannabinoids can bind non-canonical orphan GPCRs, such as G protein-coupled receptor 55 (GPR55) and G protein-coupled receptor 18 (GPR18) (Morales et al., 2017; Morales and Jagerovic, 2016; Pertwee et al., 2010). Additionally, these cannabinoids can bind ligand-gated ion channels and specific transient receptor potential (TRP) channels, as well as nuclear peroxisome proliferator activated receptors (PPARs) (Morales et al., 2017; Muller et al., 2018). For example, the phytocannabinoid CBD interacts with a variety of biomolecules, giving rise to a number of potential physiological actions, albeit although some are indirect (Britch et al., 2021). It is likely that most of the cannabinoid-induced signaling is mediated through the CB1 receptors and these non-canonical GPCRs may play a supporting role in the integration of synaptic signaling to exert their cannabinoid effects. However, more work is needed to determine the functional selectivity of these receptors, especially GPR55 and GPR18 (Morales and Jagerovic, 2016).

4. Synaptic effects of cannabinoid drugs

The eCB system is critical in short- and long-term synaptic modulation mainly via the activation of CB1 receptors in the brain. Given the role of eCBs in synaptic transmission, it is likely that eCBs play a role in the optimization and/or refinement of learning, movement

control, nociception perception, and stress, either directly or indirectly. Moreover, there is mounting evidence that implicates sex differences in the behavioral and physiological effects of cannabinoids (Borgen et al., 1973; Cocchetto et al., 1981; Craft, 2005; Fattore et al., 2007; Mathew et al., 2003; Wiley, 2003). Exogenous cannabinoids, such as THC and synthetic cannabinoids can disrupt and/or alter eCB signaling and function (Cohen et al., 2020; Deadwyler et al., 1990; Schoeler and Bhattacharyya, 2013). Furthermore, these compounds can trigger different CB1 receptor-mediated intracellular signaling pathways, which may contribute to functional specificity (Laprairie et al., 2014). The effects of acute and chronic cannabinoid drug exposure on synaptic transmission are summarized in Table 1, and discussed further later in the review.

4.1. Acute effects of cannabinoid drugs on synaptic transmission

The actions of full CB1 receptor agonists have been examined at synapses throughout the nervous system. As expected from the localization and coupling of CB1 receptors, activation leads to depression of neurotransmitter release and synaptic responses (Table 1). Presynaptic CB1 receptors are generally coupled to Gi/o-type G-proteins, and receptor activation leads to dissociation of the heterotrimeric G protein subunits (Lu and Mackie, 2016). The G β / γ subunits activate the two mechanisms most often implicated in CB1-mediated synaptic depression, inhibition of presynaptic voltage-gated calcium channels (resulting in decreased excitation-secretion coupling) (Fig. 1A), and inhibition of vesicle fusion through actions on the vesicle fusion/release machinery (Fig. 1B) (Chevalleyre et al., 2007; Gerdeman and Lovinger, 2001). The G α subunit liberated by CB1 activation can inhibit adenylyl AC, leading to decreased signaling by cAMP-activated pathways (Lu and Mackie, 2016). Inhibition of this second messenger system is thought to play a role in long-term synaptic depression (LTD) induced by CB1 activation (Fig. 1C) (Augustin et al., 2014; Chevalleyre et al., 2007; Monday et al., 2018).

These synaptic depressant actions occur mainly at GABAergic and glutamatergic synapses, although release of other neurotransmitters is also affected (Kano et al., 2009). The suppression of inhibitory GABAergic transmission leads to increased synaptic and intrinsic excitability of the recipient postsynaptic neurons. In contrast, suppression of glutamate release will have a net inhibitory effect on postsynaptic neurons. Thus, the effect of a CB1 receptor full agonist in a given brain region depends on the balance of these inhibitory and disinhibitory actions. This balance is, in turn, affected by the locations of the different synapses, the timing of CB1 receptor activation relative to the input from the presynaptic neuron, and receptor expression levels. In the basolateral amygdala, cerebral cortex and hippocampus CB1 receptors are abundant on the axon terminals of one type of GABAergic “basket cell” (BC). These BCs make synapses onto the soma and proximal dendrites of glutamatergic projection neurons. Thus, CB1 receptor activation in these regions will reduce a strong source of inhibition of projection neuron firing, resulting in greater neuronal output. In many brain regions CB1 receptor actions and CB1 expression are especially strong on GABAergic synapses (Ademark and Lovinger, 2009; Katona et al., 2001; Katona et al., 1999; Yoshida et al., 2002).

Activation of CB1 receptors by eCBs has often been shown to enhance induction of long-term potentiation (LTP) at glutamatergic synapses in several brain regions (Carlson et al., 2002). In the basolateral amygdala and hippocampal CA1 regions the disinhibitory CB1 effect induced by inhibition of GABA release is implicated in enhancement of LTP induction at synapses onto projection neurons (Chevalleyre and Castillo, 2004). In the hippocampal CA1 region, depression of GABA release at synapses made by basket cells (Chevalleyre and Castillo, 2003), allows for greater glutamatergic synaptic excitation of pyramidal neurons. This enhances activation of NMDA-type glutamate receptors that are crucial for LTP induction. Similar mechanisms occur in the basolateral amygdala, once again likely involving CB1 receptor activation on GABAergic basket cells (Azad et al., 2004). Similar LTP-enhancing effects of CB1 activation have been observed in other brain regions including striatum (Adermark and Lovinger, 2009).

Levels of eCBs can be enhanced in brain by inhibitors of the enzymes that catalyze their degradation. Fatty acid amide hydrolase (FAAH) is the main enzyme involved in AEA catabolism, and a variety of FAAH inhibitors have been developed (Cravatt et al., 2001; Cravatt et al., 1996; Griebel et al., 2018; Lodola et al., 2015). Application of FAAH inhibitors to brain slices generally does not alter synaptic transmission induced by single afferent stimuli (Table 1). However, in striatum, FAAH inhibition by the URB597 compound inhibits dopamine release induced by repetitive afferent activation (Mateo et al., 2017). This is thought to involve activation of CB1 receptors that reduce glutamate release from cortical terminals. Application of FAAH inhibitors has also been shown to enhance LTD mediated by TRPV1 in nucleus accumbens (NAc) brain slices, presumably by increasing AEA activation of this receptor (Grueter et al., 2010). In the hippocampal dentate gyrus, URB597 application has no effect on glutamatergic synaptic transmission, but inhibition is observed when combined with AEA administration (Chavez et al., 2010). This is presumably because the FAAH inhibitor prevents degradation of the applied AEA. Activation of TRPV1 receptors by AEA appears to be the mechanism underlying this synaptic depression. The catabolic enzyme for 2-AG is monoacylglycerol lipase (MAGL). Inhibition of MAGL by the JZL184 compound inhibits repetitive stimulus-driven dopamine release, as previously described for FAAH inhibition (Mateo et al., 2017). Inhibitors of MAGL have little effect on synaptic transmission when applied alone, but prolong eCB-mediated depolarization-induced suppression of inhibitory and excitatory transmission (DSE and DSI respectively) (Hashimoto et al., 2007; Pan et al., 2009; Straiker et al., 2009; Szabo et al., 2006). This is one key piece of evidence indicating that 2-AG mediates the synaptic depression observed in this experimental paradigm. Interestingly, similar effects are seen at some synapses with inhibitors of the COX-2 enzyme that can also contribute to 2-AG degradation (Straiker et al., 2011; Yang et al., 2008).

Impairment of LTP has been observed during application of full CB1 agonists to brain slices (Table 1). The initial characterization of this effect was in brain slices from prefrontal cortex, where application of a full CB1 agonist reduced the incidence of LTP at synapses onto projection neurons, while increasing the incidence of LTD (Auclair et al., 2000). Subsequent studies of LTP in the hippocampal CA1 subregion produced similar findings, in this case during application of highly efficacious CB1 agonists found in spice-like drugs (Basavarajappa and Subbanna, 2014; Hoffman et al., 2017). This finding suggests that

activation of these CB1 receptors at or near maximal efficacy has effects different from partial receptor activation. One possible mechanism underlying LTP disruption by CB1 activation is inhibition of glutamatergic transmission that is needed for LTP induction (Bajo et al., 2009; Slanina et al., 2005).

The synaptic effects of THC have been studied (Table 1), but not to the same extent as full CB1 agonists, mainly due to difficulty in obtaining this highly controlled substance and the very low solubility of this compound (Hoffman and Lupica, 2013). Early studies examined effects of applying THC to brain slices. A biphasic concentration-response was observed in the hippocampal CA1 region, with potentiation of a field potential population spike (PS) and prolongation of the duration of LTP at low-moderate concentrations, changing to inhibition of the PS and shortening of LTP duration at higher concentrations (Foy et al., 1982; Nowicky et al., 1987). However, it was difficult to ascertain the synaptic changes underlying these THC actions, as only extracellular field potential recordings were performed. When GABAergic IPSCs are measured with whole-cell recording in hippocampal CA1 slices, inhibition by THC is comparable to that of full CB1 agonists (Laaris et al., 2010). These findings are consistent with findings indicating that CB1 receptors are most abundant on GABAergic terminals in hippocampal CA1 (Katona et al., 1999). However, it is notable that THC also produces substantial inhibition of glutamatergic synaptic responses at Schaffer collateral-CA1 pyramidal neurons in hippocampal slices (Hoffman et al., 2010). Strong inhibition of glutamatergic transmission by THC has also been observed in hippocampal cultures (Shen and Thayer, 1999), and striatal slices (Brown et al., 2003). However, it should be noted that Straiker and Mackie (2005) did not observe inhibition of glutamatergic transmission in hippocampal autaptic cultures but did find that THC blocked the effect of other CB1 agonists. Thus, despite the fact that THC is a partial CB1 agonist it can have profound effects on both excitatory and inhibitory synaptic transmission. Other synaptic sites of THC action have been suggested, including ionotropic glycine receptors (Hejazi et al., 2006; Xiong et al., 2011).

The acute synaptic effects of CBD have been the subject of increasing research activity in recent years (Table 1). One proposed molecular CBD target is the G protein-coupled lysophosphatidylinositol receptor known as GPR55 (Ryberg et al., 2007). In hippocampal brain slices CBD enhances GABAergic synaptic responses in dentate gyrus (DG) granule neurons (Kaplan et al., 2017). This effect is mimicked and prevented by the GPR55 antagonist DIC 16020046, supporting a role for antagonism of this receptor in the CBD action. Other synaptic receptors implicated in CBD action include the 5-HT_{1A} receptor (Rock et al., 2012; Russo et al., 2005), the ionotropic glycine receptor (Ahrens et al., 2009), and several transient receptor potential (TRP) ionotropic channels (De Petrocellis et al., 2011). Depending on the TRP channel subtypes, CBD can have varying effects on channel activation. For example, TRPV1 and 2, as well as TRPA1 are activated by CBD, whereas CBD acts as an antagonist at TRPM8 (Bisogno et al., 2001; De Petrocellis and Di Marzo, 2010; De Petrocellis et al., 2008; Muller et al., 2018; Qin et al., 2008). The CBD actions involving the 5-HT_{1A} receptor have been suggested to underlie *in vivo* actions of the drug, including potential uses in treatment of Parkinson's Disease symptoms (Patricio et al., 2020). There is also evidence that CBD can inhibit adenosine uptake (Pandolfo et al., 2011). However, there is little data indicating if CBD alters synaptic transmission

mediated by these receptors in *in situ* preparations or the intact brain. The synaptic effects of CBD may contribute to the antiepileptiform and antiseizure effects of the drug (Jones et al., 2010; Rosenberg et al., 2015). The related cannabis constituent cannabidiol has also been shown to activate TRP channels (Iannotti et al., 2014). This compound also inhibits epileptiform activity in hippocampal slices, and this effect in intact tissue appears to involve TRPV1.

4.2. Subacute CB1 agonist actions

The “subacute” effects of THC and other cannabinoid drugs are defined herein as synaptic changes observed within hours of a few days following a single *in vivo* drug exposure. The most commonly used paradigm is a single intraperitoneal drug injection followed some hours later by brain slice preparation and electrophysiological recording (Table 1). For example, Mato and coworkers observed that LTD was impaired at GABAergic synapses in the CA1 hippocampal subregion 15–20 hours after a single THC injection (Mato et al., 2004). These investigators also found a similar impairment of LTD at glutamatergic synapses in the NAc. Impaired LTD persists for up to three days after the drug injection. In slices from the ventral tegmental area (VTA), an increase in synaptic AMPA receptors was observed 24 hours following a single THC injection, perhaps indicative of long-term potentiation at these synapses (Good and Lupica, 2010).

5. Chronic effects of cannabinoid drugs on synaptic transmission

Chronic cannabinoid drug use is associated with increased risk of developing CUD, which is accompanied by neurobiological changes in reward-related and cognitive circuit functions. Cognitive changes following chronic cannabinoid use contribute in part to the maintenance of CUD via increased impulsivity and impaired decision making (Crean et al., 2011; Irimia et al., 2015). Tolerance to the effects of cannabinoid drugs is another notable phenotype that has been widely examined in animal models (Maldonado and Rodriguez de Fonseca, 2002; Martin et al., 2004; Sim-Selley, 2003). The most consistent neurobiological consequence of chronic THC exposure is decreased CB1 receptor numbers, as well as decreased CB1 agonist and eCB-induced presynaptic modulation (reviewed in (Hoffman et al., 2021; Kesner and Lovinger, 2020)) (Table 1). Long-term exposure to THC and synthetic cannabinoids results in region-specific decreases in CB1 receptor expression which likely contribute to differences in receptor radioligand binding and reduced drug sensitivity (Breivogel et al., 1999; Corchero et al., 1999; Oviedo et al., 1993; Rodriguez de Fonseca et al., 1994; Romero et al., 1998; Romero et al., 1997; Zhuang et al., 1998). Furthermore, chronic exposure to cannabinoids impairs synaptic plasticity, and this impairment is accompanied by the desensitization of CB1 receptors (Hoffman et al., 2003; Mato et al., 2005). The desensitization and downregulation of CB1 receptors have been consistently implicated in the development of cannabis tolerance (Maldonado, 2002; Martin et al., 2004; Sim-Selley, 2003) and have been observed in individuals that regularly use cannabis (Villares, 2007). Chronic cannabinoid exposure produces widespread reversible downregulation and desensitization of CB1 receptors (Sim-Selley, 2003). The magnitude of downregulation is generally 25–50% depending on the measurement type (radioligand binding, immunohistochemistry or signaling) and brain region examined. Greater decreases were

reported in the cerebellum and hippocampus compared to somewhat smaller magnitudes in the basal ganglia and midbrain (Breivogel et al., 1999; Cichewicz et al., 2001; Sim-Selley, 2003; Sim-Selley et al., 2006). Given that the magnitude of down-regulation is smaller in the midbrain and basal ganglia, it is not surprising that the rate of reversal is faster in the striatum and midbrain than in other brain regions (Sim-Selley et al., 2006). Together, these mechanisms provide the underlying biological properties by which cannabinoid tolerance can develop (Maldonado et al., 2011; Maldonado and Rodriguez de Fonseca, 2002; Tanda and Goldberg, 2003).

The functional significance of AEA and 2-AG in promoting cannabinoid tolerance and dependence have been explored. Repeated administration of AEA or an AEA analog (methanandamide) has yielded inconclusive findings on the reduction of CB1 receptor density and signaling (Aceto et al., 1998; Romero et al., 1999; Romero et al., 1995; Rubino et al., 2000a). Furthermore, pharmacological blockade of FAAH does not alter CB1 receptor expression and function (Schlosburg et al., 2010). In mice lacking FAAH, chronic administration of THC produces similar magnitudes of CB1 receptor desensitization and downregulation in the striatum, hippocampus, and cerebellum compared to controls (Falenski et al., 2010). These findings suggest that AEA signaling doesn't contribute to the receptor downregulation in response to chronic THC exposure. It is worth mentioning that the deletion of FAAH does not alter CB1 receptor expression in brain (Cravatt et al., 2001). On the other hand, chronically elevated levels of 2-AG achieved by genetic deletion or pharmacological blockade of MAGL results in the reduction of CB1 receptor density and function (Chanda et al., 2010; Schlosburg et al., 2010). Thus, increased 2-AG tone can possibly desensitize and down-regulate CB1 receptors (Table 1).

The molecular mechanisms involved in CB1 receptor desensitization and downregulation have been explored, but to date there is little evidence about which mechanisms are involved in loss of presynaptic receptor function. The radioligand binding studies mentioned above, and a few immunochemical studies that indicate decreased receptor numbers are consistent with CB1 receptor internalization or degradation as candidate mechanisms for CB1 receptor desensitization (reviewed in (Hoffman et al., 2021; Kesner and Lovinger, 2020)) (Fig. 2A). Indeed, loss of cell surface receptors consistent with these mechanisms has been observed in heterologous cellular expression systems (Hsieh et al., 1999; Rinaldi-Carmona et al., 1998; Tappe-Theodor et al., 2007) and in primary neuronal cultures (Coutts et al., 2001; Tappe-Theodor et al., 2007). The most direct evidence of decreased CB1 receptor on the plasma membrane of presynaptic terminals induced by chronic THC exposure in adult animals was obtained with super-resolution microscopy imaging of GABAergic terminals in the hippocampal CA1 region (Dudok et al., 2015). Recovery of terminal surface CB1 levels was observed several weeks after cessation of THC treatment. However, reduced CB1 levels are not always apparent under conditions where decreased receptor induced signaling and tolerance to agonist effects on transmission are observed (Romero et al., 1999; Romero et al., 1998; Romero et al., 1997; Rubino et al., 2000b). Thus, other mechanisms of desensitization, such as uncoupling of CB1 receptors from G proteins and other intracellular signaling mechanisms, or changes in the intracellular signaling systems themselves have also been explored (Fig. 2B) (Hutcheson et al., 1998; Martin et al., 2004; Rubino et al., 2000b; Sim-Selley, 2003). As yet, there is insufficient evidence as to which of these

mechanisms underlie the loss of eCB/CB1-mediated plasticity following chronic THC or agonist exposure.

Chronic exposure to THC and CB1 receptor agonists impairs synaptic LTD at glutamatergic synapses in the dorsal and ventral striatum, areas of the brain important for eCB-mediated habitual actions and reward processing, respectively (Augustin and Lovinger, 2018; Chen et al., 1990; Herkenham et al., 1991; Hoffman et al., 2003; Hoffman et al., 2007; Nazzaro et al., 2012; Robbe et al., 2001) (Table 1). The NAc/ventral striatum integrates incoming sensory inputs to modulate cortical activity to influence drug seeking behavior. In fact, drug-induced impairments in LTD have been implicated in compulsive drug seeking and/or taking behavior (Kasanetz et al., 2010). Not surprisingly, operant self-administration of THC and CBD inhibits the induction of LTD at cortical inputs to NAc (Neuhofer et al., 2020), again, bolstering the argument that cannabinoid reward-driven signaling, resulting in voluntary drug seeking/taking behavior is mediated by the inhibition of glutamatergic signaling at these synapses.

Little is known about the effects of CBD alone on long-term changes in synaptic plasticity. However, CBD is hypothesized to reduce the aversive effects of THC (Greydanus et al., 2013; Klein et al., 2011; Russo and Guy, 2006; Vann et al., 2008). It is likely that CBD may exert its long-term effects on plasticity at non-CB1/CB2 receptors, given its low affinity for these receptors (Zou and Kumar, 2018).

The loss of NAc LTD is accompanied by the desensitization of CB1 receptors following chronic THC and cannabinoid exposure (Mato et al., 2005; Neuhofer et al., 2020). Differential changes in the signaling strength of these inputs may contribute to the reinforcing properties of cannabinoid drugs and the regulation of behavior. Alterations in dendritic spine density and morphology in NAc medium spiny neurons occur following chronic exposure to THC (Kolb et al., 2006; Kolb et al., 2018; Spencer et al., 2018). Moreover, loss of LTD is observed at synapses originating from the medial prefrontal cortex (mPFC) and ventral hippocampus (vHipp) (Hwang and Lupica, 2020). Interestingly, chronic THC exposure during adolescence inhibits LTD induction in the mPFC, which is reversed by enhancing AEA levels (Bara et al., 2021; Cuccurazzu et al., 2018). Collectively, these results support the idea that cannabinoids alter CB1 receptor-mediated synaptic modulation to facilitate the reinforcing effects of these drugs and promote tolerance and dependence. Interestingly, chronic THC exposure results in synapse-specific LTD impairments in the NAc, in which LTD at mPFC and vHipp synapses, and not LTD at synapses originating from the basolateral amygdala (BLA) are affected (Hwang and Lupica, 2020). These results suggest that THC-induced synaptic modifications may have very different effects on striatal output, depending on the MSN synapses affected. However, more research is needed to identify whether the induction of LTD at synapses onto different MSN subtypes, indirect- and direct-projecting, are affected. In addition to these presynaptic changes, there is a postsynaptic strengthening of the BLA and vHipp inputs, and the weakening of inputs from mPFC (Hwang and Lupica, 2020). These changes in presynaptic and postsynaptic mechanisms of glutamatergic signaling highlight the importance of the synaptic balance among these brain regions to guide behavior. After prolonged exposure to THC, there is a shift from cortical regions involved in cognitive processes to subcortical regions,

which are involved in memory and emotional processes to promote drug seeking and dependence (Hwang and Lupica, 2020; Lafferty and Britt, 2020). Additionally, it may be this dysregulation in synaptic transmission that contributes to the cannabinoid-induced deficits associated with memory formation.

Loss of LTD in dorsolateral striatum (DLS) following chronic THC exposure appears to contribute to development of habitual instrumental behavior (Nazzaro et al., 2012). The loss of this presynaptic modulation may lead to increased efficacy of inputs from sensorimotor cortical regions that drives DLS and the associated basal ganglia circuitry supporting stimulus/context-driven behavior that overrides goal-direct actions. Synaptic depression mediated by eCBs and CB1 also plays a role in habitual behavior through suppression of orbitofrontal cortical inputs to dorsomedial striatum (Gremel et al., 2016). In this case, the eCB-mediated synaptic modulation suppresses cortical input that drives goal-directed behavior, favoring habitual responding. It has yet to be determined how chronic exposure to THC or other CB1 agonists alters this dorsal striatal eCB role.

Functional cannabinoid tolerance also occurs at excitatory and inhibitory synapses in the hippocampus (Bolla et al., 2002; Hampson and Deadwyler, 1999; Pope Jr et al., 2002). CB1 receptors modulate both glutamatergic and GABAergic hippocampal transmission (Carlson et al., 2002; Chevalleyre and Castillo, 2004). However, these receptors are more abundantly expressed on GABAergic rather than glutamatergic terminals (Katona and Freund, 2008; Marsicano and Lutz, 1999). Modifications at these synapses are likely to contribute to the long-lasting cannabinoid-induced deficits in memory and cognition. Chronic exposure to THC blocks LTP at glutamatergic synapses in the dentate gyrus and CA1 regions of the hippocampus via a CB1 receptor-mediated mechanism (Fan et al., 2010; Hoffman et al., 2007). Similar impairments in hippocampal CA1 LTP are observed *in vivo* with repeated exposure to HU-210, a CB1 receptor full agonist (Hill et al., 2004). Moreover, these impairments are associated with deficits in working memory. It is likely that reduction in glutamate receptor expression and function contributes to the impairments in hippocampal synaptic plasticity (Fan et al., 2010). Chronic exposure to THC reduces cannabinoid CB1 receptor sensitivity and/or efficacy at GABAergic, but not glutamatergic terminals in the CA1 region (Hoffman et al., 2007). This reduced sensitivity is accompanied by a downregulation of CB1 receptors, likely contributing to reduced receptor sensitivity (Dudok et al., 2015). In the hippocampus, eCBs facilitate the induction of LTP through the transient suppression of GABAergic transmission, as mentioned previously (Carlson et al., 2002; Chevalleyre and Castillo, 2004; Monory et al., 2015). However, after chronic THC exposure, the suppression of GABAergic inhibition onto glutamatergic synapses is lost, possibly resulting in LTP impairments. However, this has not been directly tested. Repeated THC exposure also results in the reduction of dendritic spine density in CA1 hippocampal neurons (Chen et al., 2013). These results demonstrate that chronic cannabinoid exposure can induce cellular and synaptic changes that alter plasticity to affect behaviors, such as spatial learning and working memory.

Generally, drugs of abuse often impair the induction of LTP and LTD in reward-related drug seeking and taking circuits (Abrahao et al., 2017; Belmeguenai et al., 2008; Kauer and Malenka, 2007; Martin et al., 2006; Shen and Kalivas, 2013; Wolf et al., 2004). Within the

ventral tegmental area (VTA), chronic THC or CB1 agonist induces LTD at glutamatergic terminals that is dependent on NMDA and AMPA GluA2 receptor endocytosis and CB1 receptor signaling (Liu et al., 2010). The VTA is an integral brain region involved in the reward pathway and sends projections to NAc and mPFC, brain regions involved in regulating the cognitive and motivational aspects of behaviors (Sesack and Grace, 2010).

Chronic drug use can result in long-term changes in synaptic plasticity that persist long after drug cessation. LTD impairments are observed following the self-administration of THC and CBD and a withdrawal period (Neuhofer et al., 2020; Spencer et al., 2018), as well as after chronic exposure (7 days) of THC (Hoffman et al., 2007). It is reported that CB1 receptor downregulation can persist for a short period of time following termination of cannabinoid exposure (Sim-Selley et al., 2006). Some of the neurobiological alterations that occur with prolonged cannabinoid use are reversible. More work is needed to determine which of these changes are reversible or how long this reversal process might take. For example, in human cannabis users, CB1 receptor binding function returns to normal levels after a period of abstinence (D'Souza et al., 2016; Hirvonen et al., 2012). There is also a partial recovery of LTP after the cessation of THC exposure in rodents, suggesting that the cognitive and reward-processing deficits are not permanent (Hoffman et al., 2007). The overall net effects of chronic cannabinoid drug use are the loss of synaptic plasticity that may contribute to tolerance and stabilize drug-oriented behaviors.

6. Cannabis use effects on synaptic plasticity in human brain

Only one study to date has examined synaptic plasticity in the brain of humans diagnosed with CUD (Martin-Rodriguez et al., 2021). In this study, continuous theta burst stimulation (cTBS) delivered via transcranial magnetic stimulation of the motor cortex was used to examine plasticity of motor evoked potentials (MEPs) measured in a contralateral muscle. Decreased MEP persisting for 10s of minutes was induced by cTBS in non-cannabis-users and in cannabis users that did not meet CUD criteria. In contrast this decrease was not observed in individuals with CUD. This finding indicates that high levels of cannabis use can reduce plasticity in the human brain. A reduction in hippocampal volume has been reported in long-term heavy cannabis users compared to non-cannabis users (Demirakca et al., 2011; Yucel et al., 2016; Yucel et al., 2008) (Table 1). This reduction is likely to contribute to alternations in functional connectivity and cognitive impairments associated with chronic cannabis use (Broyd et al., 2016; Harding et al., 2012). Interestingly, prolonged CBD usage has been implicated in restoring hippocampal volume in a region-specific manner and improving cognitive function in chronic cannabis users (Beale et al., 2018; Solowij et al., 2018) (Table 1). More studies examining THC, CB1 agonist effects, and other cannabis derivatives on plasticity, as well as alterations in plasticity and acute drug effects on plasticity in individuals with CUD would help in assessing the translatability of findings in laboratory animals and in back-translating studies from humans to animal models.

7. Cannabis use effects on neurotransmitter levels in human brain

There is limited evidence to date of the effects of acute and chronic cannabis use on markers of synaptic function in human brain, but imaging techniques have provided some intriguing

findings. Ligands for positron emission tomography (PET)-based imaging of CB1 receptors have been developed over the last 10–15 years (Hirvonen, 2015). Studies employing these PET ligands in humans have revealed evidence of a small but significant decrease in CB1 receptor availability in several cortical and limbic brain regions (Ceccarini et al., 2015; Hirvonen et al., 2012; Spindle et al., 2021; Weinstein et al., 2016). As mentioned above, the receptor levels return to near baseline values following cessation of cannabis use (Hirvonen et al., 2012).

Many psychoactive drugs, including all drugs that give rise to SUDs, alter brain dopamine (DA) levels (Volkow and Morales, 2015). In general, acute exposure to these drugs increases DA release in the NAc and other brain regions implicated in reward and behavioral actions of these drug (Volkow and Morales, 2015). Cannabis and THC have similar acute DA-increasing actions thought to arise from decreased inhibition of midbrain dopaminergic neurons (Lupica and Riegel, 2005; Peters et al., 2021). Thus, it is important to understand cannabis effects on DA in the human brain. To this end, several recent studies have used brain imaging and spectroscopy approaches to estimate changes in brain DA levels, DA receptor density and other molecules involved in dopaminergic transmission following acute or chronic cannabis use.

A few studies have examined availability of D2 receptors in human striatum using PET or single-photon emission tomography (SPET) imaging to determine if acute THC administration alters binding to striatal D2 dopamine receptors, which is one way to estimate DA release in human brain (Barkus et al., 2011; Bossong et al., 2015; Bossong et al., 2009; Stokes et al., 2009). Bossong and coworkers observed a modest decrease in receptor availability in ventral striatum, consistent with increased DA release, that correlated with THC plasma concentration (Bossong et al., 2015). The other studies found no evidence for altered release despite clear psychoactive effects of the administered THC. These inconclusive results may be due to the relatively low sensitivity of this indirect approach and smaller sample sizes in the (Barkus et al., 2011) and (Stokes et al., 2009) studies.

Using PET imaging to measure DA synthesis capacity with the precursor ^{18}F -DOPA, Bloomfield and coworkers found evidence of reduced DA synthesis in striatum of regular cannabis users (Bloomfield et al., 2014) (Table 1). The whole striatal dopamine synthesis capacity was correlated with the rate of cannabis use as well as the age of onset of first cannabis exposure in this study, with early onset and heavy drug associated with greater synthesis impairment. No correlation between DA synthesis rate and psychotic symptoms was observed. Similar conclusions were drawn in studies examining decreased D2-like dopamine receptor availability following amphetamine and methylphenidate administration in cannabis users determined to be dependent on the drug (van de Giessen et al., 2017; Volkow et al., 2014). Binding availability of the dopamine transporter (DAT) was also reduced in individuals who regularly use both tobacco and cannabis (Leroy et al., 2012). However, it is not clear that use of cannabis, as opposed to tobacco, contributed to this effect. Changes in DA release in response to a stressful task were not altered in regular cannabis users (Mizrahi et al., 2013). Decreased availability of D2-like dopamine receptors has been touted as a biomarker of several substance use disorders (Volkow and Morales, 2015). However, in PET studies of regular cannabis users no change in D2-like availability

was detected (Urban et al., 2012), and similar findings were obtained by (van de Giessen et al., 2017) and (Volkow et al., 2014). Thus, there is no evidence that decreased D2-like receptor levels are associated with regular cannabis use or CUD. Overall, studies of cannabis and the dopamine system in humans indicates that acute drug-induced increases in DA are smaller than those produced by other drugs of abuse. Chronic cannabis use, including use that meets the criteria for CUD, appears to result in decreased dopaminergic function, but there is no decrease in D2 receptor levels, unlike those associated with use disorders for other drugs. It is likely that CUD is associated with relatively mild disruption of brain dopaminergic systems and thus it is not yet clear if DA plays a strong role in this use disorder.

Effects of cannabis on levels of glutamate in human brain have been examined using magnetic resonance spectroscopy (MRS). Administration of THC induced an increase in glutamate levels in the striatum, and the caudate nucleus, in particular (Colizzi et al., 2020; Mason et al., 2019). Lower baseline glutamate levels and larger THC-induced increases were observed in participants in which THC had psychotomimetic effects (Colizzi et al., 2020). Increased striatal glutamate levels were also associated with decreased connectivity of limbic striatum and cortical subregions as measured by functional magnetic resonance imaging (Mason et al., 2019). No effect on GABA concentrations was observed in this study. One study that examined glutamate levels in individuals with CUD found no differences in the levels of the neurotransmitter in hippocampus or striatum compared to the control group (van de Giessen et al., 2017). These findings indicate that THC-induced increases in striatal glutamate may contribute to alterations in brain circuitry associated with cognitive dysfunction and psychosis, but clearly more work is needed on the effects of regular, heavy cannabis use.

Both DA and glutamate are implicated in endocannabinoid-mediated LTD in striatum (Lovinger and Mathur, 2012). Dopamine also plays a key role in LTP at glutamatergic synapses in striatum (Calabresi et al., 2007). Thus, it will be of interest to determine how cannabis use and THC exposure alter striatal synaptic plasticity and associated forms of learning and memory (Augustin and Lovinger, 2018).

8. Conclusions

Agonists for the CB1 receptor, including THC, produce acute intoxication. Long-term CB1 agonist administration at high doses can lead to CUD. The CB1 receptors normally participate in eCB-mediated short- and long-term synaptic plasticity, including both LTD and LTP. Acutely, the CB1 agonists override eCB modulation causing disruption of physiological synaptic plasticity processes. It has long been appreciated that THC is a partial agonist at CB1, while other naturally occurring and synthetic compounds exhibit a range of efficacies. The CB1 partial agonists would be expected to produce smaller effects on intracellular signaling and synaptic transmission than full agonists, and this is evident in studies using GTPgammaS binding (Griffin et al., 1999). The efficacy of AEA for inhibiting voltage-gated calcium channels and activating inwardly-rectifying potassium channels is similar to that of 2-AG and full agonists (Guo and Ikeda, 2004; Mackie et al., 1995; Twitchell et al., 1997), although it should be noted that AEA effects may be partially

mediated by a non-CB1 mechanism (Guo and Ikeda, 2004). However, effects on synaptic transmission are not as clear. The full synthetic agonists and 2-AG generally produce robust synaptic depression, while noladin ether and AEA have smaller effects (Straiker and Mackie, 2005). As discussed above, the actions of THC are inconsistent, with inhibition occurring at some synapses, but not at others (Brown et al., 2003; Hoffman et al., 2010; Shen and Thayer, 1999; Straiker and Mackie, 2005). This differential efficacy could reflect differences in receptor reserve (e.g. due to differential CB1 density) on different presynaptic terminals, with THC efficacy expected to be larger at synapses with greater reserve. It must also be noted that partial agonists can prevent/occlude effects of full agonists by occupying binding sites.

Chronic exposure to THC and other CB1 agonists leads to loss of presynaptic CB1 actions in several brain regions. This loss of receptor function leads, in turn, to deficient eCB-mediated synaptic plasticity that disrupts cognitive functions and contributes to altered reward processing and CUD. Disruption of plasticity and alteration in neurotransmitter levels following CB1 agonist exposure has now been observed in both animal models and human volunteers. In contrast to THC and synthetic high-efficacy CB1 agonists, cannabis constituents such as CBD and CBN have weak actions at CB1 receptors and are not intoxicating or associated with CUD. It remains to be determined how these compounds alter brain function, although several mechanisms have been proposed for CBD. While candidate molecular mechanisms have been identified for loss of CB1 function following chronic agonist exposure, more work is needed to determine if and where these mechanisms occur at presynaptic terminals throughout the brain. Further research is also needed to determine effects of chronic CB1 agonist exposure on brain circuit function, and the contribution of these actions to CUD.

Acknowledgements

The work was funded by AAA000407 to DML and K99AA027740 from the Brain Initiative to SMA.

References

- Abraham KP, et al. , 2017. Alcohol and the brain: neuronal molecular targets, synapses, and circuits. *Neuron* 96, 1223–1238. [PubMed: 29268093]
- Aceto MD, et al. , 1998. Anandamide, an endogenous cannabinoid, has a very low physical dependence potential. *J. Pharmacol. Exp. Ther* 287, 598–605. [PubMed: 9808686]
- Adams R, 1940. Marihuana. *Science* 92, 115–119. [PubMed: 17730206]
- Adermark L, Lovinger DM, 2009. Frequency-dependent inversion of net striatal output by endocannabinoid-dependent plasticity at different synaptic inputs. *J. Neurosci* 29, 1375–1380. [PubMed: 19193884]
- Ahrens J, et al. , 2009. The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-Beta glycine receptor function. *Pharmacology* 83, 217–222. [PubMed: 19204413]
- Alger BE, 2002. Retrograde signaling in the regulation of synaptic transmission: focus on endocannabinoids. *Prog. Neurobiol* 68, 247–286. [PubMed: 12498988]
- Alves VL, et al. , 2020. The synthetic cannabinoids phenomenon: from structure to toxicological properties. A review. *Crit. Rev. Toxicol* 50, 359–382. [PubMed: 32530350]
- An D, et al. , 2020. Targeting cannabinoid receptors: current status and prospects of natural products. *Int. J. Mol. Sci* 21.

- Association., A. P., 2013. Diagnostic and Statistical Manual of Mental Disorders, (5th ed.).
- Atwood BK, et al. , 2010. JWH018, a common constituent of 'Spice' herbal blends, is a potent and efficacious cannabinoid CB receptor agonist. *Br. J. Pharmacol* 160, 585–593. [PubMed: 20100276]
- Auclair N, et al. , 2000. Cannabinoids modulate synaptic strength and plasticity at glutamatergic synapses of rat prefrontal cortex pyramidal neurons. *J. Neurophysiol* 83, 3287–3293. [PubMed: 10848548]
- Augustin SM, Lovinger DM, 2018. Functional relevance of endocannabinoid-dependent synaptic plasticity in the central nervous system. *ACS Chem. Neurosci* 9, 2146–2161. [PubMed: 29400439]
- Augustin SM, et al. , 2014. Cyclic AMP and afferent activity govern bidirectional synaptic plasticity in striatopallidal neurons. *J. Neurosci* 34, 6692–6699. [PubMed: 24806695]
- Azad SC, et al. , 2004. Circuitry for associative plasticity in the amygdala involves endocannabinoid signaling. *J. Neurosci* 24, 9953–9961. [PubMed: 15525780]
- Bajo M, et al. , 2009. Differential alteration of hippocampal excitatory synaptic transmission by cannabinoid ligands. *J. Neurosci. Res* 87, 766–775. [PubMed: 18816788]
- Banister SD, Connor M, 2018. The chemistry and pharmacology of synthetic cannabinoid receptor agonists as new psychoactive substances: origins. *Handb. Exp. Pharmacol* 252, 165–190. [PubMed: 29980914]
- Bara A, et al. , 2021. Cannabis and synaptic reprogramming of the developing brain. *Nat. Rev. Neurosci* 22, 423–438. [PubMed: 34021274]
- Barkus E, et al. , 2011. Does intravenous Delta9-tetrahydrocannabinol increase dopamine release? A SPET study. *J. Psychopharmacol* 25, 1462–1468. [PubMed: 20851843]
- Basavarajappa BS, Subbanna S, 2014. CB1 receptor-mediated signaling underlies the hippocampal synaptic, learning, and memory deficits following treatment with JWH-081, a new component of spice/K2 preparations. *Hippocampus* 24, 178–188. [PubMed: 24123667]
- Beale C, et al. , 2018. Prolonged cannabidiol treatment effects on hippocampal subfield volumes in current cannabis users. *Cannabis. Cannabinoid. Res* 3, 94–107. [PubMed: 29682609]
- Belmeguenai A, et al. , 2008. Alcohol impairs long-term depression at the cerebellar parallel fiber-Purkinje cell synapse. *J. Neurophysiol* 100, 3167–3174. [PubMed: 18922952]
- Bisogno T, et al. , 2001. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br. J. Pharmacol* 134, 845–852. [PubMed: 11606325]
- Bloomfield MA, et al. , 2014. Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. *Biol. Psychiatry* 75, 470–478. [PubMed: 23820822]
- Bolla KI, et al. , 2002. Dose-related neurocognitive effects of marijuana use. *Neurology* 59, 1337–1343. [PubMed: 12427880]
- Borgen LA, et al. , 1973. Cannabis-induced hypothermia: a dose-effect comparison of crude marihuana extract and synthetic 9 -tetrahydrocannabinol in male and female rats. *Res. Commun. Chem. Pathol. Pharmacol* 5, 621–626. [PubMed: 4701259]
- Borodovsky JT, et al. , 2016. Smoking, vaping, eating: is legalization impacting the way people use cannabis? *Int. J. Drug Policy* 36, 141–147. [PubMed: 26992484]
- Bossong MG, et al. , 2009. Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology* 34, 759–766. [PubMed: 18754005]
- Bossong MG, et al. , 2015. Further human evidence for striatal dopamine release induced by administration of 9-tetrahydrocannabinol (THC): selectivity to limbic striatum. *Psychopharmacology* 232, 2723–2729. [PubMed: 25801289]
- Branch MN, et al. , 1980. Acute and chronic effects of delta 9-tetrahydrocannabinol on complex behavior of squirrel monkeys. *Psychopharmacology* 71, 247–256. [PubMed: 6256795]
- Breivogel CS, et al. , 1999. Chronic delta9-tetrahydrocannabinol treatment produces a time-dependent loss of cannabinoid receptors and cannabinoid receptor-activated G proteins in rat brain. *J. Neurochem* 73, 2447–2459. [PubMed: 10582605]
- Britch SC, et al. , 2021. Cannabidiol: pharmacology and therapeutic targets. *Psychopharmacology* 238, 9–28. [PubMed: 33221931]

- Brown TM, et al. , 2003. Cannabinoids decrease corticostriatal synaptic transmission via an effect on glutamate uptake. *J. Neurosci* 23, 11073–11077. [PubMed: 14657164]
- Broyd SJ, et al. , 2016. Acute and chronic effects of cannabinoids on human cognition-a systematic review. *Biol. Psychiatry* 79, 557–567. [PubMed: 26858214]
- Budney AJ, et al. , 2007. Marijuana dependence and its treatment. *Addict. Sci. Clin. Pract* 4, 4–16. [PubMed: 18292704]
- Calabresi P, et al. , 2007. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends Neurosci.* 30, 211–219. [PubMed: 17367873]
- Carlini BH, et al. , 2017. Beyond joints and brownies: marijuana concentrates in the legal landscape of WA State. *Int. J. Drug Policy* 42, 26–29. [PubMed: 28171805]
- Carlson G, et al. , 2002. Endocannabinoids facilitate the induction of LTP in the hippocampus. *Nat. Neurosci* 5, 723–724. [PubMed: 12080342]
- Ceccarini J, et al. , 2015. [18F]MK-9470 PET measurement of cannabinoid CB1 receptor availability in chronic cannabis users. *Addict. Biol* 20, 357–367. [PubMed: 24373053]
- Chanda PK, et al. , 2010. Monoacylglycerol lipase activity is a critical modulator of the tone and integrity of the endocannabinoid system. *Mol. Pharmacol* 78, 996–1003. [PubMed: 20855465]
- Chavez AE, et al. , 2010. TRPV1 activation by endogenous anandamide triggers postsynaptic long-term depression in dentate gyrus. *Nat. Neurosci* 13, 1511–1518. [PubMed: 21076423]
- Chen JP, et al. , 1990. Delta 9-tetrahydrocannabinol produces naloxone-blockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely-moving rats as measured by intracerebral microdialysis. *Psychopharmacology* 102, 156–162. [PubMed: 2177204]
- Chen R, et al. , 2013. Delta9-THC-caused synaptic and memory impairments are mediated through COX-2 signaling. *Cell* 155, 1154–1165. [PubMed: 24267894]
- Chevalleyre V, Castillo PE, 2003. Heterosynaptic LTD of hippocampal GABAergic synapses: a novel role of endocannabinoids in regulating excitability. *Neuron* 38, 461–472. [PubMed: 12741992]
- Chevalleyre V, Castillo PE, 2004. Endocannabinoid-mediated metaplasticity in the hippocampus. *Neuron* 43, 871–881. [PubMed: 15363397]
- Chevalleyre V, et al. , 2006. Endocannabinoid-mediated synaptic plasticity in the CNS. *Annu. Rev. Neurosci* 29, 37–76. [PubMed: 16776579]
- Chevalleyre V, et al. , 2007. Endocannabinoid-mediated long-term plasticity requires cAMP/PKA signaling and RIM1alpha. *Neuron* 54, 801–812. [PubMed: 17553427]
- Cichewicz DL, et al. , 2001. Changes in opioid and cannabinoid receptor protein following short-term combination treatment with delta(9)-tetrahydrocannabinol and morphine. *J. Pharmacol. Exp. Ther* 297, 121–127. [PubMed: 11259535]
- Cluny NL, et al. , 2015. Prevention of diet-induced obesity effects on body weight and gut microbiota in mice treated chronically with Delta9-tetrahydrocannabinol. *PLoS One* 10, e0144270. [PubMed: 26633823]
- Cocchetto DM, et al. , 1981. Relationship between plasma delta-9-tetrahydrocannabinol concentration and pharmacologic effects in man. *Psychopharmacology* 75, 158–164. [PubMed: 6275440]
- Cohen K, et al. , 2020. Chronic use of synthetic cannabinoids is associated with impairment in working memory and mental flexibility. *Front. Psychiatry* 11, 602. [PubMed: 32695029]
- Colizzi M, et al. , 2020. Delta-9-tetrahydrocannabinol increases striatal glutamate levels in healthy individuals: implications for psychosis. *Mol. Psychiatry* 25, 3231–3240. [PubMed: 30770892]
- Corchero J, et al. , 1999. Time-dependent differences of repeated administration with Delta9-tetrahydrocannabinol in proenkephalin and cannabinoid receptor gene expression and G-protein activation by mu-opioid and CB1-cannabinoid receptors in the caudate-putamen. *Brain Res. Mol. Brain Res* 67, 148–157. [PubMed: 10101241]
- Coutts AA, et al. , 2001. Agonist-induced internalization and trafficking of cannabinoid CB1 receptors in hippocampal neurons. *J. Neurosci* 21, 2425–2433. [PubMed: 11264316]
- Craft RM, 2005. Sex differences in behavioral effects of cannabinoids. *Life Sci.* 77, 2471–2478. [PubMed: 15958268]
- Cravatt BF, et al. , 1996. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. *Nature* 384, 83–87. [PubMed: 8900284]

- Cravatt BF, et al. , 2001. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proc. Natl. Acad. Sci. U. S. A* 98, 9371–9376. [PubMed: 11470906]
- Crean RD, et al. , 2011. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J. Addict. Med* 5, 1–8. [PubMed: 21321675]
- Crocker CE, et al. , 2021. When cannabis use goes wrong: mental health side effects of cannabis use that present to emergency services. *Front. Psychiatry* 12, 640222. [PubMed: 33658953]
- Cuccurazzu B, et al. , 2018. Adult cellular neuroadaptations induced by adolescent THC exposure in female rats are rescued by enhancing anandamide signaling. *Int. J. Neuropsychopharmacol* 21, 1014–1024. [PubMed: 29982505]
- Davis JP, et al. , 2016. Cannabis withdrawal, posttreatment abstinence, and days to first cannabis use among emerging adults in substance use treatment: a prospective study. *J. Drug Issues* 46, 64–83. [PubMed: 26877548]
- De Petrocellis L, Di Marzo V, 2010. Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. *J. NeuroImmune Pharmacol* 5, 103–121. [PubMed: 19847654]
- De Petrocellis L, et al. , 2008. Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. *J. Pharmacol. Exp. Ther* 325, 1007–1015. [PubMed: 18354058]
- De Petrocellis L, et al. , 2011. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br. J. Pharmacol* 163, 1479–1494. [PubMed: 21175579]
- Deadwyler SA, et al. , 1990. The effects of delta-9-THC on mechanisms of learning and memory. *NIDA Res. Monogr* 97, 79–93. [PubMed: 2174124]
- Demirakca T, et al. , 2011. Diminished gray matter in the hippocampus of cannabis users: possible protective effects of cannabidiol. *Drug Alcohol Depend.* 114, 242–245. [PubMed: 21050680]
- D'Souza DC, et al. , 2016. Rapid changes in CB1 receptor availability in cannabis dependent males after abstinence from cannabis. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 1, 60–67.
- Dudok B, et al. , 2015. Cell-specific STORM super-resolution imaging reveals nanoscale organization of cannabinoid signaling. *Nat. Neurosci* 18, 75–86. [PubMed: 25485758]
- Elsohly MA, Slade D, 2005. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. *Life Sci.* 78, 539–548. [PubMed: 16199061]
- Falenski KW, et al. , 2010. FAAH^{-/-} mice display differential tolerance, dependence, and cannabinoid receptor adaptation after delta 9-tetrahydrocannabinol and anandamide administration. *Neuropsychopharmacology* 35, 1775–1787. [PubMed: 20357755]
- Fan N, et al. , 2010. Reduced expression of glutamate receptors and phosphorylation of CREB are responsible for in vivo Delta9-THC exposure-impaired hippocampal synaptic plasticity. *J. Neurochem* 112, 691–702. [PubMed: 19912468]
- Farokhnia M, et al. , 2020. Effects of oral, smoked, and vaporized cannabis on endocrine pathways related to appetite and metabolism: a randomized, double-blind, placebo-controlled, human laboratory study. *Transl. Psychiatry* 10, 71. [PubMed: 32075958]
- Fattore L, et al. , 2007. Cannabinoid self-administration in rats: sex differences and the influence of ovarian function. *Br. J. Pharmacol* 152, 795–804. [PubMed: 17891164]
- Felder CC, et al. , 1995. Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. *Mol. Pharmacol* 48, 443–450. [PubMed: 7565624]
- Foltin RW, et al. , 1986. Behavioral analysis of marijuana effects on food intake in humans. *Pharmacol. Biochem. Behav* 25, 577–582. [PubMed: 3774823]
- Foy MR, et al. , 1982. delta 9-THC and 17-beta-estradiol in hippocampus. *Brain Res. Bull* 8, 341–345. [PubMed: 6284318]
- Gaoni Y, Mechoulam R, 1971. The isolation and structure of delta-1-tetrahydrocannabinol and other neutral cannabinoids from hashish. *J. Am. Chem. Soc* 93, 217–224. [PubMed: 5538858]
- Gerdeman G, Lovinger DM, 2001. CB1 cannabinoid receptor inhibits synaptic release of glutamate in rat dorsolateral striatum. *J. Neurophysiol* 85, 468–471. [PubMed: 11152748]

- Good CH, Lupica CR, 2010. Afferent-specific AMPA receptor subunit composition and regulation of synaptic plasticity in midbrain dopamine neurons by abused drugs. *J. Neurosci* 30, 7900–7909. [PubMed: 20534838]
- Green B, et al. , 2003. Being stoned: a review of self-reported cannabis effects. *Drug Alcohol Rev.* 22, 453–460. [PubMed: 14660135]
- Gremel CM, et al. , 2016. Endocannabinoid modulation of orbitostriatal circuits gates habit formation. *Neuron.* 90, 1312–1324. [PubMed: 27238866]
- Greydanus DE, et al. , 2013. Marijuana: current concepts (dagger). *Front. Public Health* 1, 42. [PubMed: 24350211]
- Griebel G, et al. , 2018. The selective reversible FAAH inhibitor, SSR411298, restores the development of maladaptive behaviors to acute and chronic stress in rodents. *Sci. Rep* 8, 2416. [PubMed: 29403000]
- Griffin G, et al. , 1999. An investigation into the structural determinants of cannabinoid receptor ligand efficacy. *Br. J. Pharmacol* 126, 1575–1584. [PubMed: 10323589]
- Grueter BA, et al. , 2010. Postsynaptic TRPV1 triggers cell type-specific long-term depression in the nucleus accumbens. *Nat. Neurosci* 13, 1519–1525. [PubMed: 21076424]
- Guo J, Ikeda SR, 2004. Endocannabinoids modulate N-type calcium channels and G-protein-coupled inwardly rectifying potassium channels via CB1 cannabinoid receptors heterologously expressed in mammalian neurons. *Mol. Pharmacol* 65, 665–674. [PubMed: 14978245]
- Hampson RE, Deadwyler SA, 1999. Cannabinoids, hippocampal function and memory. *Life Sci.* 65, 715–723. [PubMed: 10462072]
- Harding IH, et al. , 2012. Functional connectivity in brain networks underlying cognitive control in chronic cannabis users. *Neuropsychopharmacology* 37, 1923–1933. [PubMed: 22534625]
- Hashimoto-dani Y, et al. , 2007. Presynaptic monoacylglycerol lipase activity determines basal endocannabinoid tone and terminates retrograde endocannabinoid signaling in the hippocampus. *J. Neurosci* 27, 1211–1219. [PubMed: 17267577]
- Hejazi N, et al. , 2006. Delta9-tetrahydrocannabinol and endogenous cannabinoid anandamide directly potentiate the function of glycine receptors. *Mol. Pharmacol* 69, 991–997. [PubMed: 16332990]
- Herkenham M, et al. , 1991. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J. Neurosci* 11, 563–583. [PubMed: 1992016]
- Hill MN, et al. , 2004. Prolonged cannabinoid treatment results in spatial working memory deficits and impaired long-term potentiation in the CA1 region of the hippocampus in vivo. *Eur. J. Neurosci* 20, 859–863. [PubMed: 15255998]
- Hirvonen J, 2015. In vivo imaging of the cannabinoid CB1 receptor with positron emission tomography. *Clin. Pharmacol. Ther* 97, 565–567. [PubMed: 25788235]
- Hirvonen J, et al. , 2012. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Mol. Psychiatry* 17, 642–649. [PubMed: 21747398]
- Hoffman AF, Lupica CR, 2013. Synaptic targets of Delta9-tetrahydrocannabinol in the central nervous system. *Cold Spring Harb. Perspect. Med* 3.
- Hoffman AF, et al. , 2003. Functional tolerance and blockade of long-term depression at synapses in the nucleus accumbens after chronic cannabinoid exposure. *J. Neurosci* 23, 4815–4820. [PubMed: 12832502]
- Hoffman AF, et al. , 2007. Opposing actions of chronic Delta9-tetrahydrocannabinol and cannabinoid antagonists on hippocampal long-term potentiation. *Learn. Mem* 14, 63–74. [PubMed: 17202425]
- Hoffman AF, et al. , 2010. Control of cannabinoid CB1 receptor function on glutamate axon terminals by endogenous adenosine acting at A1 receptors. *J. Neurosci* 30, 545–555. [PubMed: 20071517]
- Hoffman AF, et al. , 2017. Disruption of hippocampal synaptic transmission and long-term potentiation by psychoactive synthetic cannabinoid ‘Spice’ compounds: comparison with Delta(9)-tetrahydrocannabinol. *Addict. Biol* 22, 390–399. [PubMed: 26732435]
- Hoffman AF, et al. , 2021. Impairment of synaptic plasticity by cannabis, Delta(9)-THC, and synthetic cannabinoids. *Cold Spring Harb. Perspect. Med* 11.
- Hollister LE, 1978. Cannabis and the development of tolerance. *Adv. Biosci.* 22–23, 585–589.
- Hollister LE, 1986. Health aspects of cannabis. *Pharmacol. Rev* 38, 1–20. [PubMed: 3520605]

- Horn H, et al. , 2018. Endocannabinoids in body weight control. Pharmaceuticals (Basel) 11.
- Hsieh C, et al. , 1999. Internalization and recycling of the CB1 cannabinoid receptor. J. Neurochem 73, 493–501. [PubMed: 10428044]
- Hu SS, Mackie K, 2015. Distribution of the endocannabinoid system in the central nervous system. Handb. Exp. Pharmacol 231, 59–93. [PubMed: 26408158]
- Hutcheson DM, et al. , 1998. Behavioural and biochemical evidence for signs of abstinence in mice chronically treated with delta-9-tetrahydrocannabinol. Br. J. Pharmacol 125, 1567–1577. [PubMed: 9884086]
- Hwang EK, Lupica CR, 2020. Altered corticolimbic control of the nucleus accumbens by long-term Delta(9)-tetrahydrocannabinol exposure. Biol. Psychiatry 87, 619–631. [PubMed: 31543247]
- Iannotti FA, et al. , 2014. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem. Neurosci 5, 1131–1141. [PubMed: 25029033]
- Ibsen MS, et al. , 2017. Cannabinoid CB1 and CB2 receptor signaling and bias. Cannabis. Cannabinoid. Res 2, 48–60. [PubMed: 28861504]
- Irimia C, et al. , 2015. Persistent effects of chronic Delta9-THC exposure on motor impulsivity in rats. Psychopharmacology 232, 3033–3043. [PubMed: 25925779]
- Johnston LD, Bachman JG, Schulenberg JE, 2012. The Rise in Teen Marijuana Use Stalls, Synthetic Marijuana Use Levels, and Use of ‘Bath Salts’ is Very Low. University of Michigan News Service, Ann Arbor, MI.
- Jones RT, et al. , 1976. Clinical studies of cannabis tolerance and dependence. Ann. N. Y. Acad. Sci 282, 221–239. [PubMed: 798533]
- Jones NA, et al. , 2010. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J. Pharmacol. Exp. Ther 332, 569–577. [PubMed: 19906779]
- Jordan A, et al. , 2018. Exploring the association between initial serum alcohol concentration and polysubstance use: more than a simple “gateway drug” effect? Int. J. Crit. Illn. Inj. Sci 8, 201–206. [PubMed: 30662866]
- Kano M, et al. , 2009. Endocannabinoid-mediated control of synaptic transmission. Physiol. Rev 89, 309–380. [PubMed: 19126760]
- Kaplan JS, et al. , 2017. Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. Proc. Natl. Acad. Sci. U. S. A 114, 11229–11234. [PubMed: 28973916]
- Karila L, et al. , 2014. Acute and long-term effects of cannabis use: a review. Curr. Pharm. Des 20, 4112–4118. [PubMed: 24001294]
- Karniol IG, et al. , 1975. Effects of delta9-tetrahydrocannabinol and cannabinol in man. Pharmacology 13, 502–512. [PubMed: 1221432]
- Kasanetz F, et al. , 2010. Transition to addiction is associated with a persistent impairment in synaptic plasticity. Science 328, 1709–1712. [PubMed: 20576893]
- Kathmann M, et al. , 2006. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. Naunyn Schmiedeberg’s Arch. Pharmacol 372, 354–361. [PubMed: 16489449]
- Katona I, Freund TF, 2008. Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. Nat. Med 14, 923–930. [PubMed: 18776886]
- Katona I, Freund TF, 2012. Multiple functions of endocannabinoid signaling in the brain. Annu. Rev. Neurosci 35, 529–558. [PubMed: 22524785]
- Katona I, et al. , 1999. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J. Neurosci 19, 4544–4558. [PubMed: 10341254]
- Katona I, et al. , 2001. Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. J. Neurosci 21, 9506–9518. [PubMed: 11717385]
- Katz G, et al. , 2014. Cannabis withdrawal - a new diagnostic category in DSM-5. Isr. J. Psychiatry Relat. Sci 51, 270–275. [PubMed: 25841223]
- Kauer JA, Malenka RC, 2007. Synaptic plasticity and addiction. Nat. Rev. Neurosci 8, 844–858. [PubMed: 17948030]

- Kelly BF, Nappe TM, 2021. Cannabinoid Toxicity. StatPearls, Treasure Island (FL).
- Kesner AJ, Lovinger DM, 2020. Cannabinoids, endocannabinoids and sleep. *Front. Mol. Neurosci* 13, 125. [PubMed: 32774241]
- Kirkham TC, 2009. Cannabinoids and appetite: food craving and food pleasure. *Int. Rev. Psychiatry* 21, 163–171. [PubMed: 19367510]
- Klein C, et al. , 2011. Cannabidiol potentiates Delta(9)-tetrahydrocannabinol (THC) behavioural effects and alters THC pharmacokinetics during acute and chronic treatment in adolescent rats. *Psychopharmacology* 218, 443–457. [PubMed: 21667074]
- Kolb B, et al. , 2006. Chronic treatment with Delta-9-tetrahydrocannabinol alters the structure of neurons in the nucleus accumbens shell and medial prefrontal cortex of rats. *Synapse* 60, 429–436. [PubMed: 16881072]
- Kolb B, et al. , 2018. THC alters morphology of neurons in medial prefrontal cortex, orbital prefrontal cortex, and nucleus accumbens and alters the ability of later experience to promote structural plasticity. *Synapse* 72.
- Koob GF, Volkow ND, 2016. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 3, 760–773. [PubMed: 27475769]
- Kowal MA, et al. , 2015. Dose-dependent effects of cannabis on the neural correlates of error monitoring in frequent cannabis users. *Eur. Neuropsychopharmacol* 25, 1943–1953. [PubMed: 26298832]
- Laaris N, et al. , 2010. Delta9-tetrahydrocannabinol is a full agonist at CB1 receptors on GABA neuron axon terminals in the hippocampus. *Neuropharmacology* 59, 121–127. [PubMed: 20417220]
- Lafferty CK, Britt JP, 2020. Cannabis Exposure Enhances Subcortical Control of Nucleus Accumbens Activity. *Biol. Psychiatry* 87, 592–594. [PubMed: 32164914]
- Laprairie RB, et al. , 2014. Type 1 cannabinoid receptor ligands display functional selectivity in a cell culture model of striatal medium spiny projection neurons. *J. Biol. Chem* 289, 24845–24862. [PubMed: 25037227]
- Laprairie RB, et al. , 2015. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *Br. J. Pharmacol* 172, 4790–4805. [PubMed: 26218440]
- Le Strat Y, Le Foll B, 2011. Obesity and cannabis use: results from 2 representative national surveys. *Am. J. Epidemiol* 174, 929–933. [PubMed: 21868374]
- Leroy C, et al. , 2012. Striatal and extrastriatal dopamine transporter in cannabis and tobacco addiction: a high-resolution PET study. *Addict. Biol* 17, 981–990. [PubMed: 21812871]
- Liu Z, et al. , 2010. Synaptic neurotransmission depression in ventral tegmental dopamine neurons and cannabinoid-associated addictive learning. *PLoS One* 5, e15634. [PubMed: 21187978]
- Lodola A, et al. , 2015. Fatty acid amide hydrolase inhibitors: a patent review (2009–2014). *Expert Opin. Ther. Pat* 25, 1247–1266. [PubMed: 26413912]
- Loflin M, Earleywine M, 2014. A new method of cannabis ingestion: the dangers of dabs? *Addict. Behav* 39, 1430–1433. [PubMed: 24930049]
- Lovinger DM, Mathur BN, 2012. Endocannabinoids in striatal plasticity. *Parkinsonism Relat. Disord* 18 (Suppl. 1), S132–S134. [PubMed: 22166411]
- Lu HC, Mackie K, 2016. An introduction to the endogenous cannabinoid system. *Biol. Psychiatry* 79, 516–525. [PubMed: 26698193]
- Lupica CR, Riegel AC, 2005. Endocannabinoid release from midbrain dopamine neurons: a potential substrate for cannabinoid receptor antagonist treatment of addiction. *Neuropharmacology* 48, 1105–1116. [PubMed: 15878779]
- Mackie K, 2005. Distribution of cannabinoid receptors in the central and peripheral nervous system. *Handb. Exp. Pharmacol* 299–325. [PubMed: 16596779]
- Mackie K, 2008. Cannabinoid receptors: where they are and what they do. *J. Neuroendocrinol* 20 (Suppl. 1), 10–14. [PubMed: 18426493]
- Mackie K, et al. , 1995. Cannabinoids activate an inwardly rectifying potassium conductance and inhibit Q-type calcium currents in AtT20 cells transfected with rat brain cannabinoid receptor. *J. Neurosci* 15, 6552–6561. [PubMed: 7472417]

- Maldonado R, 2002. Study of cannabinoid dependence in animals. *Pharmacol. Ther* 95, 153–164. [PubMed: 12182962]
- Maldonado R, Rodriguez de Fonseca F, 2002. Cannabinoid addiction: behavioral models and neural correlates. *J. Neurosci* 22, 3326–3331. [PubMed: 11978807]
- Maldonado R, et al. , 2011. Neurochemical basis of cannabis addiction. *Neuroscience* 181, 1–17. [PubMed: 21334423]
- Marsicano G, Lutz B, 1999. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. *Eur. J. Neurosci* 11, 4213–4225. [PubMed: 10594647]
- Martin BR, et al. , 2004. Signaling pathways involved in the development of cannabinoid tolerance. *Trends Pharmacol. Sci* 25, 325–330. [PubMed: 15165748]
- Martin M, et al. , 2006. Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens. *Nat. Neurosci* 9, 868–869. [PubMed: 16732275]
- Martin-Rodriguez JF, et al. , 2021. Impaired motor cortical plasticity associated with cannabis use disorder in young adults. *Addict. Biol* 26, e12912. [PubMed: 32323450]
- Martins SS, et al. , 2015. Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. *Am. J. Public Health* 105, e29–e49.
- Mason NL, et al. , 2019. Cannabis induced increase in striatal glutamate associated with loss of functional corticostriatal connectivity. *Eur. Neuropsychopharmacol* 29, 247–256. [PubMed: 30553697]
- Mateo Y, et al. , 2017. Endocannabinoid actions on cortical terminals orchestrate local modulation of dopamine release in the nucleus accumbens. *Neuron* 96, 1112–1126 (e5). [PubMed: 29216450]
- Mathew RJ, et al. , 2003. Postural syncope after marijuana: a transcranial Doppler study of the hemodynamics. *Pharmacol. Biochem. Behav* 75, 309–318. [PubMed: 12873621]
- Mato S, et al. , 2004. A single in-vivo exposure to delta 9THC blocks endocannabinoid-mediated synaptic plasticity. *Nat. Neurosci* 7, 585–586. [PubMed: 15146190]
- Mato S, et al. , 2005. Presynaptic homeostatic plasticity rescues long-term depression after chronic Delta 9-tetrahydrocannabinol exposure. *J. Neurosci* 25, 11619–11627. [PubMed: 16354920]
- Merrill RM, 2015. Use of marijuana and changing risk perceptions. *Am. J. Health Behav* 39, 308–317. [PubMed: 25741676]
- Merzouki A, Mesa JM, 2002. Concerning kif, a *Cannabis sativa* L. preparation smoked in the Rif mountains of northern Morocco. *J. Ethnopharmacol* 81, 403–406. [PubMed: 12127244]
- Min R, et al. , 2010. DAG lipase involvement in depolarization-induced suppression of inhibition: does endocannabinoid biosynthesis always meet the demand? *Neuroscientist* 16, 608–613. [PubMed: 20837870]
- Mizrahi R, et al. , 2013. Dopamine response to psychosocial stress in chronic cannabis users: a PET study with [¹¹C]-+PHNO. *Neuropsychopharmacology* 38, 673–682. [PubMed: 23212454]
- Monday HR, et al. , 2018. Long-term plasticity of neurotransmitter release: emerging mechanisms and contributions to brain function and disease. *Annu. Rev. Neurosci* 41, 299–322. [PubMed: 29709205]
- Monory K, et al. , 2015. Cannabinoid CB1 receptor calibrates excitatory synaptic balance in the mouse hippocampus. *J. Neurosci* 35, 3842–3850. [PubMed: 25740514]
- Morales P, Jagerovic N, 2016. Advances towards the discovery of GPR55 ligands. *Curr. Med. Chem* 23, 2087–2100. [PubMed: 27109575]
- Morales P, et al. , 2017. Molecular targets of the phytocannabinoids: a complex picture. *Prog. Chem. Org. Nat. Prod* 103, 103–131. [PubMed: 28120232]
- Muller C, et al. , 2018. Cannabinoid ligands targeting TRP channels. *Front. Mol. Neurosci* 11, 487. [PubMed: 30697147]
- Musty RE, Shirikawa I, Takahashi RN, Knobel E, 1976. Interactions of delta-9-tetrahydrocannabinol and cannabiniol in man. In: *The Pharmacology of Marihuana*. Raven Press, New York.
- Nacca N, et al. , 2013. The synthetic cannabinoid withdrawal syndrome. *J. Addict. Med* 7, 296–298. [PubMed: 23609214]

- Nazzaro C, et al. , 2012. SK channel modulation rescues striatal plasticity and control over habit in cannabinoid tolerance. *Nat. Neurosci* 15, 284–293. [PubMed: 22231426]
- Neuhof D, et al. , 2020. The loss of NMDAR-dependent LTD following cannabinoid self-administration is restored by positive allosteric modulation of CB1 receptors. *Addict. Biol* 25, e12843. [PubMed: 31733097]
- Nowicky AV, et al. , 1987. The modulation of long-term potentiation by delta-9-tetrahydrocannabinol in the rat hippocampus, in vitro. *Brain Res. Bull* 19, 663–672. [PubMed: 2830949]
- Oviedo A, et al. , 1993. Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study. *Brain Res.* 616, 293–302. [PubMed: 8395305]
- Pan B, et al. , 2009. Blockade of 2-arachidonoylglycerol hydrolysis by selective monoacylglycerol lipase inhibitor 4-nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl (hydroxy)methyl)piperidine-1-carboxylate (JZL184) Enhances retrograde endocannabinoid signaling. *J. Pharmacol. Exp. Ther* 331, 591–597. [PubMed: 19666749]
- Pandolfo P, et al. , 2011. Cannabinoids inhibit the synaptic uptake of adenosine and dopamine in the rat and mouse striatum. *Eur. J. Pharmacol* 655, 38–45. [PubMed: 21266173]
- Parrott AC, et al. , 2017. Recreational stimulants, herbal, and spice cannabis: the core psychobiological processes that underlie their damaging effects. *Hum. Psychopharmacol* 32.
- Parsons LH, Hurd YL, 2015. Endocannabinoid signalling in reward and addiction. *Nat. Rev. Neurosci* 16, 579–594. [PubMed: 26373473]
- Patel J, Marwaha R, 2019. Cannabis Use Disorder. StatPearls Publishing, Treasure Island, FL.
- Patricio F, et al. , 2020. Cannabidiol as a therapeutic target: evidence of its neuroprotective and neuromodulatory function in Parkinson's disease. *Front. Pharmacol* 11, 595635. [PubMed: 33384602]
- Pertwee RG, 2008. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br. J. Pharmacol* 153, 199–215. [PubMed: 17828291]
- Pertwee RG, et al. , 2010. International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacol. Rev* 62, 588–631. [PubMed: 21079038]
- Peters KZ, et al. , 2021. A brain on cannabinoids: the role of dopamine release in reward seeking and addiction. *Cold Spring Harb. Perspect. Med* 11.
- Piomelli D, 2003. The molecular logic of endocannabinoid signalling. *Nat. Rev. Neurosci* 4, 873–884. [PubMed: 14595399]
- Pope HG Jr., et al. , 2002. Cognitive measures in long-term cannabis users. *J. Clin. Pharmacol* 42, 41S–47S. [PubMed: 12412835]
- Potts AJ, et al. , 2020. Synthetic cannabinoid receptor agonists: classification and nomenclature. *Clin. Toxicol. (Phila.)* 58, 82–98. [PubMed: 31524007]
- Pujol J, et al. , 2014. Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users. *J. Psychiatr. Res* 51, 68–78. [PubMed: 24411594]
- Qin N, et al. , 2008. TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. *J. Neurosci* 28, 6231–6238. [PubMed: 18550765]
- Rhee MH, et al. , 1997. Cannabinol derivatives: binding to cannabinoid receptors and inhibition of adenylylcyclase. *J. Med. Chem* 40, 3228–3233. [PubMed: 9379442]
- Rinaldi-Carmona M, et al. , 1998. Modulation of CB1 cannabinoid receptor functions after a long-term exposure to agonist or inverse agonist in the Chinese hamster ovary cell expression system. *J. Pharmacol. Exp. Ther* 287, 1038–1047. [PubMed: 9864290]
- Robbe D, et al. , 2001. Localization and mechanisms of action of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens. *J. Neurosci* 21, 109–116. [PubMed: 11150326]
- Rock EM, et al. , 2012. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus. *Br. J. Pharmacol* 165, 2620–2634. [PubMed: 21827451]

- Rodriguez de Fonseca F, et al. , 1994. Downregulation of rat brain cannabinoid binding sites after chronic delta 9-tetrahydrocannabinol treatment. *Pharmacol. Biochem. Behav* 47, 33–40. [PubMed: 8115426]
- Romero J, et al. , 1995. Changes in rat brain cannabinoid binding sites after acute or chronic exposure to their endogenous agonist, anandamide, or to delta 9-tetrahydrocannabinol. *Pharmacol. Biochem. Behav* 51, 731–737. [PubMed: 7675852]
- Romero J, et al. , 1997. Effects of chronic exposure to delta9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Brain Res. Mol. Brain Res* 46, 100–108. [PubMed: 9191083]
- Romero J, et al. , 1998. Time-course of the cannabinoid receptor down-regulation in the adult rat brain caused by repeated exposure to delta9-tetrahydrocannabinol. *Synapse* 30, 298–308. [PubMed: 9776133]
- Romero J, et al. , 1999. Cannabinoid receptor and WIN-55,212–2-stimulated [35S] GTPgammaS binding and cannabinoid receptor mRNA levels in several brain structures of adult male rats chronically exposed to R-methanandamide. *Neurochem. Int* 34, 473–482. [PubMed: 10402222]
- Rosenberg EC, et al. , 2015. Cannabinoids and epilepsy. *Neurotherapeutics* 12, 747–768. [PubMed: 26282273]
- Rubino T, et al. , 2000a. Loss of cannabinoid-stimulated guanosine 5'-O-(3-[(35)S] Thiotriphosphate) binding without receptor down-regulation in brain regions of anandamide-tolerant rats. *J. Neurochem* 75, 2478–2484. [PubMed: 11080200]
- Rubino T, et al. , 2000b. Changes in the cannabinoid receptor binding, G protein coupling, and cyclic AMP cascade in the CNS of rats tolerant to and dependent on the synthetic cannabinoid compound CP55,940. *J. Neurochem* 75, 2080–2086. [PubMed: 11032897]
- Russo E, Guy GW, 2006. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med. Hypotheses* 66, 234–246. [PubMed: 16209908]
- Russo EB, et al. , 2005. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem. Res* 30, 1037–1043. [PubMed: 16258853]
- Ryberg E, et al. , 2007. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br. J. Pharmacol* 152, 1092–1101. [PubMed: 17876302]
- Sansone RA, Sansone LA, 2014. Marijuana and body weight. *Innov. Clin. Neurosci* 11, 50–54. [PubMed: 25337447]
- Schlosburg JE, et al. , 2010. Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system. *Nat. Neurosci* 13, 1113–1119. [PubMed: 20729846]
- Schoeler T, Bhattacharyya S, 2013. The effect of cannabis use on memory function: an update. *Subst. Abus. Rehabil* 4, 11–27.
- Scourfield A, Ross J, Wood DM, Thurtle N, Stellmach D, Dargan PI, 2019. Synthetic cannabinoid availability on darknet drug markets – changes during 2016–2017. *Toxicol. Commun* 3, 7–15.
- Sesack SR, Grace AA, 2010. Cortico-Basal Ganglia reward network: microcircuitry. *Neuropsychopharmacology* 35, 27–47. [PubMed: 19675534]
- Shen H, Kalivas PW, 2013. Reduced LTP and LTD in prefrontal cortex synapses in the nucleus accumbens after heroin self-administration. *Int. J. Neuropsychopharmacol* 16, 1165–1167. [PubMed: 23110855]
- Shen M, Thayer SA, 1999. Delta9-tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. *Mol. Pharmacol* 55, 8–13. [PubMed: 9882692]
- Sherman BJ, McRae-Clark AL, 2016. Treatment of cannabis use disorder: current science and future outlook. *Pharmacotherapy* 36, 511–535. [PubMed: 27027272]
- Sim-Selley LJ, 2003. Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. *Crit. Rev. Neurobiol* 15, 91–119. [PubMed: 14977366]
- Sim-Selley LJ, et al. , 2006. Prolonged recovery rate of CB1 receptor adaptation after cessation of long-term cannabinoid administration. *Mol. Pharmacol* 70, 986–996. [PubMed: 16760363]
- Slanina KA, et al. , 2005. Endocannabinoids restrict hippocampal long-term potentiation via CB1. *Neuropharmacology* 49, 660–668. [PubMed: 15950248]

- Smith NT, 2002. A review of the published literature into cannabis withdrawal symptoms in human users. *Addiction* 97, 621–632. [PubMed: 12084124]
- Soethoudt M, et al. , 2017. Cannabinoid CB2 receptor ligand profiling reveals biased signalling and off-target activity. *Nat. Commun* 8, 13958. [PubMed: 28045021]
- Solowij N, Battisti R, 2008. The chronic effects of cannabis on memory in humans: a review. *Curr. Drug Abuse Rev* 1, 81–98. [PubMed: 19630708]
- Solowij N, et al. , 2018. Therapeutic effects of prolonged cannabidiol treatment on psychological symptoms and cognitive function in regular cannabis users: a pragmatic open-label clinical trial. *Cannabis. Cannabinoid. Res* 3, 21–34. [PubMed: 29607408]
- Spencer S, et al. , 2018. A model of Delta(9)-tetrahydrocannabinol self-administration and reinstatement that alters synaptic plasticity in nucleus accumbens. *Biol. Psychiatry* 84, 601–610. [PubMed: 29861097]
- Spindle TR, et al. , 2021. Brain imaging of cannabinoid type I (CB1) receptors in women with cannabis use disorder and male and female healthy controls. *Addict. Biol* 26 (6), 1–12. 10.1111/adb.13061.
- Stokes PR, et al. , 2009. Can recreational doses of THC produce significant dopamine release in the human striatum? *Neuroimage* 48, 186–190. [PubMed: 19539765]
- Straiker A, Mackie K, 2005. Depolarization-induced suppression of excitation in murine autaptic hippocampal neurones. *J. Physiol* 569, 501–517. [PubMed: 16179366]
- Straiker A, et al. , 2009. Monoacylglycerol lipase limits the duration of endocannabinoid-mediated depolarization-induced suppression of excitation in autaptic hippocampal neurons. *Mol. Pharmacol* 76, 1220–1227. [PubMed: 19767452]
- Straiker A, et al. , 2011. COX-2 and fatty acid amide hydrolase can regulate the time course of depolarization-induced suppression of excitation. *Br. J. Pharmacol* 164, 1672–1683. [PubMed: 21564090]
- Szabo B, et al. , 2006. Depolarization-induced retrograde synaptic inhibition in the mouse cerebellar cortex is mediated by 2-arachidonoylglycerol. *J. Physiol* 577, 263–280. [PubMed: 16973696]
- Tai S, Fantegrossi WE, 2017. Pharmacological and toxicological effects of synthetic cannabinoids and their metabolites. *Curr. Top. Behav. Neurosci* 32, 249–262. [PubMed: 28012093]
- Tanda G, Goldberg SR, 2003. Cannabinoids: reward, dependence, and underlying neurochemical mechanisms—a review of recent preclinical data. *Psychopharmacology* 169, 115–134. [PubMed: 12827346]
- Tappe-Theodor A, et al. , 2007. A molecular basis of analgesic tolerance to cannabinoids. *J. Neurosci* 27, 4165–4177. [PubMed: 17428994]
- Twitchell W, et al. , 1997. Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons. *J. Neurophysiol* 78, 43–50. [PubMed: 9242259]
- Upton R, Craker L, El Sohly M, Romm A, Russo E, et al. (Eds.), 2013. *Cannabis Inflorescence (Cannabis spp.) Standards of Identity, Analysis, and Quality Control American Herbal Pharmacopeia*, Scotts Valley, CA.
- Urban NB, et al. , 2012. Dopamine release in chronic cannabis users: a [¹¹C]raclopride positron emission tomography study. *Biol. Psychiatry* 71, 677–683. [PubMed: 22290115]
- van de Giessen E, et al. , 2017. Deficits in striatal dopamine release in cannabis dependence. *Mol. Psychiatry* 22, 68–75. [PubMed: 27001613]
- Vandrey R, et al. , 2017. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. *J. Anal. Toxicol* 41, 83–99. [PubMed: 28158482]
- Vann RE, et al. , 2008. Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of Delta(9)-tetrahydrocannabinol. *Drug Alcohol Depend.* 94, 191–198. [PubMed: 18206320]
- Villares J, 2007. Chronic use of marijuana decreases cannabinoid receptor binding and mRNA expression in the human brain. *Neuroscience* 145, 323–334. [PubMed: 17222515]
- Volkow ND, Morales M, 2015. The brain on drugs: from reward to addiction. *Cell* 162, 712–725. [PubMed: 26276628]

- Volkow ND, et al. , 2014. Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. *Proc. Natl. Acad. Sci. U. S. A* 111, E3149–E3156. [PubMed: 25024177]
- Volkow ND, et al. , 2016. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA Psychiatry* 73, 292–297. [PubMed: 26842658]
- Volkow ND, et al. , 2017. Don't worry, be happy: endocannabinoids and cannabis at the intersection of stress and reward. *Annu. Rev. Pharmacol. Toxicol* 57, 285–308. [PubMed: 27618739]
- Walsh KB, Andersen HK, 2020. Molecular pharmacology of synthetic cannabinoids: delineating CB1 receptor-mediated cell signaling. *Int. J. Mol. Sci* 21.
- Waugh J, et al. , 2016. Epidemiology and clinical features of toxicity following recreational use of synthetic cannabinoid receptor agonists: a report from the United Kingdom National Poisons Information Service. *Clin. Toxicol. (Phila.)* 54, 512–518. [PubMed: 27091041]
- Weinstein A, et al. , 2016. Brain imaging studies on the cognitive, pharmacological and neurobiological effects of cannabis in humans: evidence from studies of adult users. *Curr. Pharm. Des* 22, 6366–6379. [PubMed: 27549374]
- Weinstein AM, et al. , 2017. Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health. *Front. Psychiatry* 8, 156. [PubMed: 28878698]
- Wiley JL, 2003. Sex-dependent effects of delta 9-tetrahydrocannabinol on locomotor activity in mice. *Neurosci. Lett* 352, 77–80. [PubMed: 14625027]
- Wolf ME, et al. , 2004. Psychomotor stimulants and neuronal plasticity. *Neuropharmacology* 47 (Suppl. 1), 61–79. [PubMed: 15464126]
- World Drug Report 2021 2021, (United Nations publication, Sales No. E.21.XI.8).
- Xiong W, et al. , 2011. Cannabinoid potentiation of glycine receptors contributes to cannabis-induced analgesia. *Nat. Chem. Biol* 7, 296–303. [PubMed: 21460829]
- Yang H, et al. , 2008. COX-2 oxidative metabolism of endocannabinoids augments hippocampal synaptic plasticity. *Mol. Cell. Neurosci* 37, 682–695. [PubMed: 18295507]
- Yoshida T, et al. , 2002. The cannabinoid CB1 receptor mediates retrograde signals for depolarization-induced suppression of inhibition in cerebellar Purkinje cells. *J. Neurosci* 22, 1690–1697. [PubMed: 11880498]
- Yucel M, et al. , 2008. Regional brain abnormalities associated with long-term heavy cannabis use. *Arch. Gen. Psychiatry* 65, 694–701. [PubMed: 18519827]
- Yucel M, et al. , 2016. Hippocampal harms, protection and recovery following regular cannabis use. *Transl. Psychiatry* 6, e710. [PubMed: 26756903]
- Zehra A, et al. , 2018. Cannabis addiction and the brain: a review. *J. NeuroImmune Pharmacol* 13, 438–452. [PubMed: 29556883]
- Zhuang S, et al. , 1998. Effects of long-term exposure to delta9-THC on expression of cannabinoid receptor (CB1) mRNA in different rat brain regions. *Brain Res. Mol. Brain Res* 62, 141–149. [PubMed: 9813289]
- Zimmermann US, et al. , 2009. Withdrawal phenomena and dependence syndrome after the consumption of “spice gold”. *Dtsch. Arztebl. Int* 106, 464–467. [PubMed: 19652769]
- Zou S, Kumar U, 2018. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. *Int. J. Mol. Sci* 19.

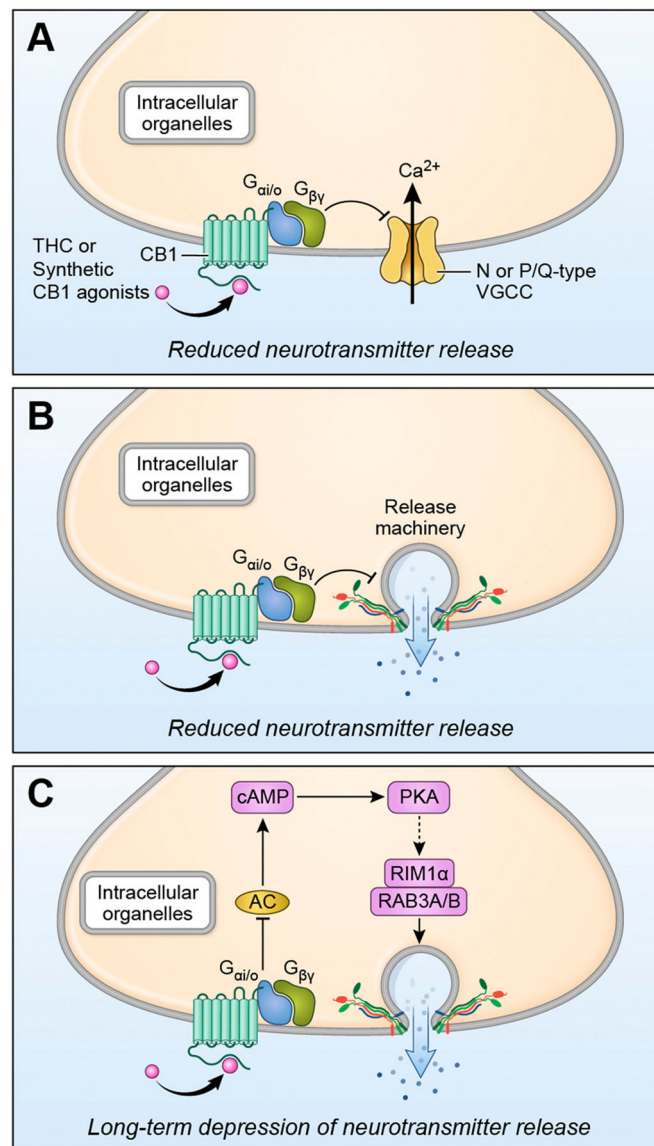


Fig. 1. Mechanisms involved in presynaptic depression induced by acute CB1 agonist exposure. A) Receptor activation inhibits presynaptic VGCCs implicated in excitation-secretion coupling through actions of the $G_{\beta\gamma}$ G protein subunit. B) Receptor activation inhibits vesicle fusion directly, presumably via $G_{\beta\gamma}$ subunit interactions with proteins that are part of the fusion/release machinery. C) Receptor activation inhibits release via G_{α} G protein subunit inhibition of Adenylyl cyclase (AC) leading to decreased protein kinase A (PKA)-mediated phosphorylation of proteins that regulate vesicle fusion. This mechanism is implicated in LTD.

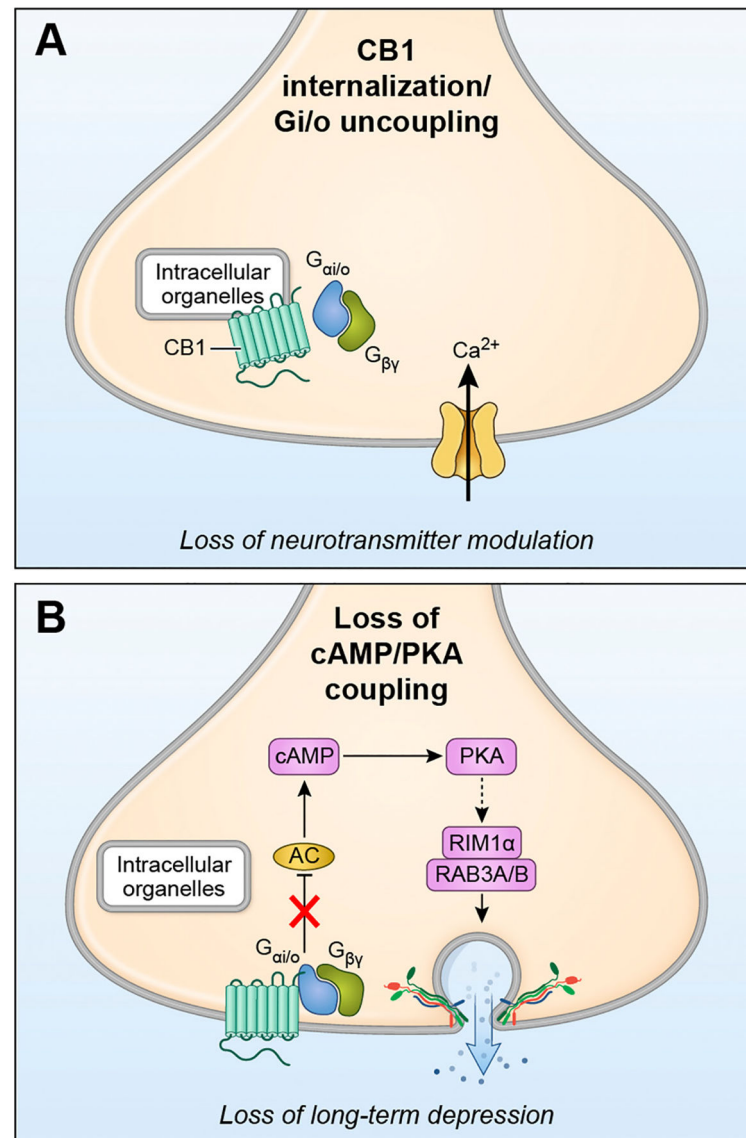


Fig. 2. Presynaptic alterations in CB1 desensitization. A) Following prolonged CB1 agonist exposure receptors are internalized and uncoupled from $G_{\beta/\gamma}$ G protein subunit. B) Receptor/G-protein signaling may also be uncoupled from AC inhibition, leading to loss of LTD-inducing mechanisms. Increased cyclic AMP levels and PKA activity might also occur under this condition.

