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# Cannabinoid modulation of drug reward and the implications of marijuana legalization

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## Abstract

Marijuana is the most popular illegal drug worldwide. Recent trends indicate that this may soon change; not due to decreased marijuana use, but to an amendment in marijuana's illegal status. The cannabinoid type 1 ($CB_1$) receptor mediates marijuana's psychoactive and reinforcing properties. $CB_1$ receptors are also part of the brain endocannabinoid (eCB) system and support numerous forms of learning and memory, including the conditioned reinforcing properties of cues predicting reward or punishment. This is accomplished via eCB-dependent alterations in mesolimbic dopamine function, which plays an obligatory role in reward learning and motivation. Presynaptic $CB_1$ receptors control midbrain dopamine neuron activity and thereby shape phasic dopamine release in target regions, particularly the nucleus accumbens (NAc). By also regulating synaptic input to the NAc, $CB_1$ receptors modulate NAc output onto downstream neurons of the basal ganglia motor circuit, and thereby support goal-directed behaviors. Abused drugs promote short- and long-term adaptations in eCB-regulation of mesolimbic dopamine function, and thereby hijack neural systems related to the pursuit of rewards to promote drug abuse. By pharmacologically targeting the $CB_1$ receptors, marijuana has preferential access to this neuronal system and can potently alter eCB-dependent processing of reward-related stimuli. As marijuana legalization progresses, greater access to this drug should increase the utility of marijuana as a research tool to better understand the eCB system, which has the potential to advance cannabinoid-based treatments for drug addiction.

### Keywords

endocannabinoids; marijuana; dopamine; ventral tegmental area; nucleus accumbens; mesolimbic

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# Section 1. Introduction

## 1.1. Marijuana: past, present, and future

The marijuana plant – classified as *Cannabis sativa* by Carl Linnaeus in 1753 – has been used by humans for thousands of years in various preparations: as fabric or rope, a source of oil, and as a drug (Abel, 1980; Robson, 2014). Various compounds within the plant have potent biological actions and medical utility, largely due to their anti-inflammatory and analgesic properties. But, humans have most commonly used marijuana for its psychoactive effects. $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) is the primary psychoactive compound in marijuana and is therefore responsible for its extraordinarily high rates of use. Due to concern regarding an unacceptable risk of addiction, the federal United States government declared marijuana illegal in 1937, which remains the case today. Nonetheless, more people currently use marijuana than all other illicit drugs combined (UNODC, 2014). The recent legalization of marijuana as an "over the counter" drug in Colorado, Washington, and Oregon, and as a prescription pharmaceutical in 21 other states, suggests that marijuana may gain an even greater influence on human behavior.

The primary target mediating $\Delta^9$-THC's characteristic psychoactive and reinforcing properties is the cannabinoid type 1 ($CB_1$) receptor (Huestis et al., 2001), which is now recognized as the most abundant G-protein coupled receptor in the brain (Kano et al., 2009). Yet, the $CB_1$ receptor is not simply a neuronal target for $\Delta^9$-THC, but part of a larger endocannabinoid (eCB) system consisting of endogenous cannabinoid ligands (the endocannabinoids; eCBs) and their synthetic, degradative and transport machinery. This neuromodulatory network is involved in numerous brain functions, including: learning, memory, emotion, and motivated behavior (Solinas et al., 2008; Moreira and Lutz, 2008). The eCB system is also particularly important for regulating drug reinforcement. Indeed, $CB_1$ receptors shape synaptic activity in the mesolimbic dopamine system to promote cue-directed reward seeking. Abused drugs exploit this adaptive function by supporting long-term alterations in the synaptic regulation of mesolimbic dopamine function that promote reward seeking. An improved understanding of these mechanisms has the potential to better inform future marijuana policy and the use or development of more effective pharmacological approaches for treating disorders of motivation.

## 1.2. High on cues: eCB regulation of drug seeking

The overvaluation of drug-paired environmental cues (e.g., paraphernalia) motivates drug use and is a critical factor driving relapse following drug abstinence (Childress et al., 1993; Hyman et al., 2006). A general role for the eCB system in conditioned drug-seeking has been proposed (De Vries et al., 2005; Fattore et al., 2007; Lupica and Riegel, 2005). This is supported by the ability of $CB_1$ agonists, including $\Delta^9$-THC, to reinstate extinguished drug-seeking behavior for cannabinoids (Justinova et al., 2008; Spano et al., 2004), opioids (De Vries et al., 2003; Fattore, et al., 2005), ethanol (Lopez-Moreno et al., 2004), nicotine (Biala et al., 2009), and cocaine (De Vries et al., 2001). Additionally, $CB_1$ receptor antagonists potently attenuate cue- or drug-induced reinstatement of drug seeking for $\Delta^9$-THC (Justinova et al., 2008), heroin (De Vries et al., 2003; Fattore et al., 2005), ethanol (Cippitelli et al., 2005; Economidou et al., 2006), nicotine (Cohen et al., 2005; De Vries et

al., 2005), and cocaine (De Vries et al., 2001; Xi et al., 2006). Thus, $CB_1$ receptor signaling supports the conditioned reinforcing properties of drug-paired cues, and pharmacologically increasing or decreasing $CB_1$ receptor activation can increase or decrease drug seeking, respectively. Below, we will briefly describe the unique mechanisms by which eCBs regulate synaptic function and thereby exert such control over specific behaviors (Section 3). We will then describe how eCB regulation of the mesolimbic dopamine system supports cue-directed reward seeking. This occurs via $CB_1$-dependent modulation of phasic dopamine cell firing (Section 4) and the impact of dopamine release on forebrain target neurons (Section 5). This will lead to a description of how this process can be exploited by abused drugs to support drug use (Section 6), and how this process can also be exploited to support better treatments for drug abuse and addiction (Section 7).

## Section 2. eCB signaling mechanisms: General overview

Insight into the neuronal actions of marijuana began in the early 1990s following the identification of the $CB_1$ receptor (Devane et al., 1988; Herkenham et al., 1991; Matsuda et al., 1990). Its first endogenous ligand was isolated soon after and identified as arachidonyl ethanolamine and named anandamide based on the Sanskrit word *ananda* for “bliss” (Devane et al., 1992). 2-arachidonoylglycerol (2-AG) was later identified as another natural ligand for the $CB_1$ receptor (Sugiura et al., 1995). Both eCBs are synthesized from membrane phospholipids and their release mechanisms differ from that of “classical” neurotransmitters for two main reasons. First, the synthetic enzymes are localized to postsynaptic cell membranes across from $CB_1$ receptors located on presynaptic terminals (Matyas et al., 2008; Uchigashima et al., 2007), indicating a retrograde release mechanism. Second, the lipophilic nature of eCBs precludes vesicular storage, necessitating a mechanism for translating extracellular activity into eCB synthesis and release.

A number of studies now support that eCBs act as retrograde messengers and are synthesized and released “on-demand” in response to synaptic input. The best understood synaptic signals driving eCB mobilization include:, (1) elevated intracellular $[Ca^{2+}]$, (2) $G_{q/11}$-coupled receptor (e.g., group I metabotropic glutamate receptors; mGluR1 and mGluR5) binding, or (3) both $[Ca^{2+}]$ and $G_{q/11}$ receptors acting synergistically (Kano et al., 2009). Additional signals capable of driving eCB synthesis and release include an mGluR1-mediated activation of the adenylyl cyclase-protein kinase A pathway (Azad et al., 2004) and binding of the tyrosine kinase TrkB (Lemtiri-Chlieh, and Levine 2010) or insulin (Labouebe et al., 2013) receptors. eCBs act at presynaptic $G_{i/o}$-coupled $CB_1$ receptors to inhibit presynaptic neurotransmitter release (Wilson and Nicoll, 2001; Ohno-Shosaku et al., 2001; Kreitzer and Regehr, 2001; Maejima et al., 2001). Depending on the nature of the presynaptic signal (i.e., glutamatergic or GABAergic), $CB_1$ binding can suppress or facilitate postsynaptic activity. It should be noted that recent evidence has also identified an important role for the cannabinoid type 2 ($CB_2$) receptor and the transient vanilloid receptor-type 1 (TRPV1) (a ligand-gated ion channel) in regulating behavior – particularly cocaine reinforcement (Grueter et al., 2010; Adamczyk et al., 2012; Xi et al., 2011). However, the majority of work on eCB-regulation of the mesolimbic dopamine system and drug reinforcement has focused on the $CB_1$ receptor, which will be the major focus of this review.

## Section 3. eCB regulation of dopamine signaling and cue-directed reward seeking

Accumulating evidence supports that a prominent function of $CB_1$ receptors in the ventral tegmental area (VTA) is to disinhibit dopamine neurons in reward-related contexts (Figure 1A) (Lupica and Riegel, 2005). Because $CB_1$ receptor antagonists have no effect on baseline rates of dopamine cell firing (Cheer et al., 2003) or release in the NAc (Cheer et al., 2007; Cheer et al., 2004), $CB_1$ receptor-dependent effects emerge only during periods of heightened cellular activity. Indeed, VTA dopamine cell burst firing releases eCBs onto $CB_1$-expressing presynaptic GABA terminals (Szabo et al., 2002; Riegel and Lupica, 2004; Cheer et al., 2000) to initiate a positive feedback loop that enhances dopamine signaling. Because GABA inhibition is sufficient to induce dopamine neuron bursting (Lobb et al., 2010) and reward-oriented behaviors (Stamatakis et al., 2013), $CB_1$ receptor activation on GABA terminals is capable of facilitating these actions. In support of this model, $CB_1$ agonists are sufficient for generating dopamine cell bursting (Cheer et al., 2003; Diana et al., 1998; French et al., 1997) and phasic dopamine release within the nucleus accumbens (NAc) (Cheer et al., 2004; Oleson et al., 2012a), which drives reward seeking.

The ability of VTA $CB_1$ receptors to promote reward seeking was clearly demonstrated by recent work from our laboratory (Oleson et al., 2012a). This study used fast-scan cyclic voltammetry (FSCV) to monitor phasic dopamine release in the NAc of rats lever pressing for brain stimulation reward or food. Systemic or intra-VTA administration of the $CB_1$ receptor antagonist/inverse agonist, SR141716A (rimonabant), dose-dependently decreased cue-evoked phasic dopamine release and cue-directed reward seeking; evidenced by an increase in response latency. Moreover, increasing VTA levels of 2-AG by blocking its enzymatic degradation increased cue-evoked dopamine release and decreased response latency. Interestingly, increasing VTA levels of anandamide antagonized this effect, suggesting that anandamide impedes $CB_1$ receptor binding of 2-AG (Oleson and Cheer, 2012b). Because feeding and locomotion remained unaffected by the pharmacological treatments, this work indicates an important and selective role for the VTA eCB system in regulating cue-evoked NAc dopamine release and reward seeking. We hypothesize a similar role for VTA-$CB_1$ receptors in supporting the ability of drug-paired cues to direct behavior. Indeed, despite marked differences in cellular and pharmacological actions, rimonabant suppresses the ability of cannabinoids, ethanol, nicotine, and cocaine to pharmacologically elicit phasic dopamine release in the NAc (Cheer et al., 2007). This is mediated by rimonabant disrupting VTA $CB_1$ receptor signaling (Covey et al., 2014), which is also hypothesized to support rimonabant's ability to suppress cue-induced drug seeking (Section 1.2).

Collectively, this work suggests that eCBs function in reward-related contexts to enhance dopaminergic signaling by suppressing inhibitory GABAergic, input to VTA dopamine neurons. However, $CB_1$ receptors are also expressed on glutamate terminals synapsing onto VTA dopamine neurons (Matyas et al., 2008), and eCBs released *in vitro* from dopamine neuron depolarization are capable of suppressing excitatory glutamatergic input (Melis et al., 2004). As VTA glutamatergic input is capable of driving phasic dopamine release in the

NAc (Sombers et al., 2009) why $CB_1$ receptor activation in the VTA facilitates dopaminergic output in the NAc (Oleson et al, 2012a) is not readily apparent. One possibility is that what appears to be a selective inhibition of GABAergic input to VTA dopamine neurons arises from the temporal factors driving eCB release. Because eCB synthesis and release occur following cell depolarization, the glutamatergic input driving dopamine cell firing and eCB release will precede $CB_1$-mediated presynaptic inhibition. Thus, glutamate-driven eCB release is able to inhibit presynaptic GABA release and drive dopamine cell bursting (Lobb et al., 2010), thereby supporting the $CB_1$-mediated positive feedback loop described above. Support for this hypothesized model will require a better understanding of the local factors driving dopamine cell firing and how these factors are regulated by eCB signaling. Recent work points to a $CB_1$-mediated inhibition of GABAergic afferents arising from the rostromedial tegmental nucleus (RMTg) as an important site at which eCBs act to facilitate VTA dopamine cell firing (Lecca et al., 2012; Melis et al., 2014).

## Section 4. The duality of the nucleus accumbens

The NAc is a critical region involved in channeling limbic information into motor output (Mogenson et al., 1980). The NAc is composed of largely (>90%) GABAergic medium spiny neurons (MSNs), which project to downstream targets of the basal ganglia; allowing NAc MSNs to regulate motor output and either facilitate or suppress appetitive responding. These cells are largely quiescent and their activity is heavily influenced by converging glutamatergic input arising from the basolateral amygdala, ventral hippocampus and prefrontal cortex (PFC) (Lobo and Nestler, 2011; Sesack and Grace, 2010). The behavioral impact of particular inputs depends on how they influence two functionally distinct, but anatomically overlapping NAc MSN populations (Albin et al., 1989; Gerfen and Surmeier, 2011). ‘Direct’ pathway’ MSNs (dMSNs) project to midbrain regions in the substantia nigra. Stimuli that increase dMSN activity facilitate behavior directed toward that stimulus (i.e., appetitive behavior). In contrast, ‘indirect’ pathway MSNs (iMSNs) project to the ventral pallidum. Stimuli that increase iMSN activity promote behavior directed away from that stimulus (i.e., avoidance behavior). A number of studies using optogenetic or pharmacogenetic approaches to selectively activate or inhibit these individual pathways strongly support this model (Kravitz et al., 2012; Lobo et al., 2010; Hikida et al., 2013; Danjo et al., 2014).

Glutamatergic input to the NAc is modulated by dopamine release from VTA neurons as well as eCBs released from NAc MSNs. Dopamine influences accumbal activity through binding to either excitatory $G_s$-coupled $D_1$-type or inhibitory $G_{i/o}$-coupled $D_2$-type dopamine receptors, which are selectively expressed on dMSNs or iMSNs, respectively. $D_1$ receptors on dMSNs have a low affinity for dopamine and are therefore preferentially activated by large surges in dopamine concentration (Richfield et al., 1989; Dreyer et al., 2010). Thus, phasic dopamine release in response to rewards or their predictive cues (Stuber et al., 2008) is able to promote direct pathway activity and appetitive behavior. In contrast, $D_2$ receptors have a high affinity for dopamine. Consequently, baseline extracellular dopamine concentrations are sufficient to occupy MSN $D_2$ receptors, and thereby inhibit iMSN output and suppress indirect pathway activity. However, decreases in dopamine

concentration – as occurs following exposure to aversive stimuli (Oleson et al., 2012c) – relieve $D_2$-mediated suppression of iMSNs, and promote avoidance (Danjo et al., 2014). Further modulation of direct and indirect pathway activity occurs via eCBs released from MSNs, which promote $CB_1$-dependent inhibition of both excitatory and inhibitory presynaptic inputs (Robbe et al., 2001; Hoffman et al., 2003). Based on the influence of direct and indirect pathway activation on behavior and the regulation of these pathways by dopamine and eCBs, long-term adaptations that alter the function of these neuromodulatory signals are hypothesized to shift the balance between dMSN and iMSN control over behavior, thereby resulting in a shift in the strength and direction by which environmental stimuli motivate behavior (e.g., by eliciting approach versus avoidance). Abused drugs are particularly effective at altering these neuromodulatory signals and motivated behavior.

## Section 5. Abused drugs deregulate eCBs

Experience-dependent long-term changes in synaptic strength, i.e., long-term potentiation (LTP) and long-term depression (LTD), serve as the primary cellular mechanisms underlying learning and memory (Malenka and Bear, 2004). LTP and LTD can persist for hours to weeks and are particularly important for long-lasting behavioral adaptations to environmental circumstance. By inhibiting presynaptic signaling, eCBs shape synaptic plasticity throughout the brain, resulting in a depression or potentiation of postsynaptic function by suppressing excitatory glutamatergic (i.e., LTD) or inhibitory GABAergic (i.e., inhibitory LTD; I-LTD) input, respectively. Specifically, eCB-LTD or eCB-I-LTD is defined as a depression of activity that persists after $CB_1$ receptor binding has ceased (Mathur and Lovinger, 2012; Heifets and Castillo, 2009). In this section, we will briefly discuss how eCB signaling supports long-term plasticity in the VTA and NAc. We will then summarize how these forms of plasticity can become altered by chronic drug exposure. A special emphasis will be placed on important differences in plasticity following cannabinoid and non-cannabinoid drug exposure, and how these forms of plasticity may differentially lead to maladaptive reward learning and alter susceptibility to drug abuse and addiction.

### 5.1. eCB regulation of VTA plasticity and its disruption by abused drugs

$CB_1$ receptor signaling regulates drug actions on dopamine neurons via LTD and I-LTD in the VTA. As discussed previously, acute drug exposure promotes phasic dopamine signaling via $CB_1$-mediated inhibition of presynaptic GABAergic input (Section 4). Similarly, chronic cocaine exposure also promotes a long-term disinhibition of VTA dopamine neurons via a $CB_1$-dependent inhibition of $GABA_A$ receptor transduction, a form of I-LTD. This is facilitated by presynaptic $CB_1$ and $D_2$ receptors on GABA terminals and postsynaptic group I mGluRs (Pan et al., 2008a; Pan et al., 2008b). Because $D_2$ and $CB_1$ receptors are both $G_{i/o}$-coupled, elevated extracellular dopamine levels can potentiate eCB-dependent I-LTD by synergistically inhibiting the intracellular cAMP/PKA pathway in presynaptic neurons (Pan et al., 2008a). This would suggest that cocaine-induced dopamine elevations support this form of plasticity. Indeed, subsequent work found eCB-dependent I-LTD in the VTA of brain slices obtained from rats that had exhibited a cocaine conditioned place preference (CPP). Importantly, *in vivo* intra-VTA administration of a $CB_1$ antagonist blocked the acquisition of cocaine CPP and I-LTD (Pan et al., 2008a), indicating this form of plasticity

supports the acquisition of conditioned drug reward. Moreover, I-LTD at VTA dopamine neurons following *in vivo* cocaine exposure primes excitatory glutamatergic synapses for LTP induction (Liu et al., 2005), a form of plasticity also induced by *in vivo* exposure to food reward (Chen et al., 2008; Stuber et al., 2008) and correlated with reward learning (Stuber et al., 2008). LTP of glutamatergic synapses onto VTA dopamine neurons also follows *in vivo* exposure to numerous classes of abused drugs, including nicotine, cocaine, morphine and ethanol, (Saal et al., 2003; Ungless et al., 2001), and currently represents the best characterized form of drug-induced plasticity in the VTA associated with drug reinforcement (Chen et al., 2008; Luscher, 2013). Thus, eCB-mediated I-LTD and glutamatergic LTP could coalesce to augment dopamine cell responsiveness to drugs and drug-paired cues and enhance their ability to reinforce behavior. This scheme, however, may not apply to cannabinoids. For example, rather than promoting a general potentiation of glutamatergic input to VTA dopamine neurons, acute *in vivo* $\Delta^9$-THC exposure potentiates glutamatergic synapses arising selectively from the pedunculopontine nucleus (PPN) without altering alternative glutamatergic synapses (Good and Lupica 2010). Additionally, as will be discussed below, $\Delta^9$-THC is also unique in that chronic exposure appears to promote an overall suppression of dopamine cell excitability.

### 5.2. Cannabinoid exposure promotes tolerance and LTD of VTA dopamine neurons

A well-characterized consequence of chronic marijuana exposure is tolerance to its behavioral effects (Maldonado and Rodriguez de, 2002). Repeated exposure to cannabinoids, including $\Delta^9$-THC, also promotes rapid tolerance to the neurophysiological effects of these drugs. For example, rats exposed to $\Delta^9$-THC for 14 consecutive days exhibit less $\Delta^9$-THC-induced hypothermia, catalepsy, and hypolocomotion, and this behavioral desensitization is associated with a reduced ability of $\Delta^9$-THC to increase dopamine cell firing rate (Wu and French, 2000). Interestingly, *in vitro* work demonstrates tolerance to $\Delta^9$-THC at dopamine neurons in the SNc, but not the VTA (Wu and French, 2000; Cheer et al., 2000). However, subsequent work shows that animals treated with the $CB_1$ agonist WIN 55,212-2 (WIN) for 3 days develop robust tolerance to WIN-induced increases in VTA dopamine cell firing (Pistis et al., 2004). One of the few studies to associate the rewarding effects of cannabinoids with cannabinoid-induced VTA plasticity found that development of a $\Delta^9$-THC CPP was associated with $CB_1$-dependent LTD of glutamatergic synapses onto VTA dopamine neurons (Liu et al., 2010). As discussed above, *in vivo* exposure to virtually all other addictive drug classes promotes LTP at these synapses. Drug-dependent differences in this form of plasticity (i.e., LTD versus LTP of glutamate synapses) may potentially support different motivational states that drive cannabinoid versus non-cannabinoid drug use (Section 6.4). The mechanisms underlying cannabinoid-induced depression of VTA dopamine cell excitability and its influence on drug-taking behavior, however, require further investigation.

### 5.3. eCB regulation of cortico-accumbens synaptic plasticity and its disruption by abused drugs

eCB-dependent plasticity within the NAc is generally measured as an LTD of evoked postsynaptic currents following prolonged (5–10 min), moderate frequency (10–13 Hz) electrical stimulation of afferent inputs, generally presumed to arise from the PFC (Robbe et

al., 2002). Acute and chronic *in vivo* exposure to abused drugs (both cannabinoid and non-cannabinoid) is capable of abolishing eCB-LTD in the NAc. For example, Fourgeaud et al., (2004) observed a loss of eCB-LTD following a single *in vivo* injection of cocaine. This was not mediated by altered presynaptic $CB_1$ receptor function, but was due to reduced postsynaptic mGluR5 expression and function, indicating suppressed receptor-mediated eCB mobilization (Section 3). Interestingly, one of the few studies to measure drug-induced changes in eCB-dependent plasticity in distinct NAc pathways found that eCB-LTD only occurred at iMSN inputs, and, similar to previous work (Fourgeaud et al., 2004), is dependent on postsynaptic mGluR5 signaling and abolished by *in vivo* cocaine exposure (Grueter et al., 2010; Loweth et al., 2014). Nevertheless, this effect is only partially dependent on $CB_1$ receptors, but is still eCB-dependent as pharmacological blockade or genetic deletion of the eCB-sensitive TRPV1 receptor abolished eCB-LTD. Interestingly, in contrast to $CB_1$-mediated actions, the TRPV1-dependent mechanism was of postsynaptic origin, further adding to the complexity of eCB actions in the NAc. The diminished eCB-mediated LTD at excitatory cortico-accumbal synapses may increase susceptibility to drug relapse. Indeed, reinstatement of previously extinguished cocaine seeking behavior following non-contingent drug administration in rodents is reliant on intact PFC-NAc signaling and is associated with cocaine-induced increases in PFC-evoked NAc glutamate concentrations (Xi et al., 2006; McFarland et al., 2003).

But, if eCB-LTD only occurs at iMSNs (Grueter et al., 2010), then its loss should increase iMSN output, which has repeatedly been shown to decrease cocaine reward and reinforcement (Lobo et al., 2010; Lobo and Nestler, 2011). However, $D_1$ dMSN receptors preferentially respond to large, phasic surges in extracellular dopamine release (Dreyer et al., 2010), which only occurs in response to particularly salient stimuli. Thus, loss of eCB-LTD at iMSN synapses may promote avoidance, except in circumstances that drive dMSN signaling, such as drug-related cues. Coupled with LTP of glutamate-VTA dopamine cell synapses, which may increase the magnitude and frequency of these phasic release events (Jones and Bonci, 2005), drug-induced alterations in eCB-dependent mesolimbic plasticity could support the narrowing of behavioral repertoires (i.e, increased avoidance) and enhanced incentive-motivational properties of drug-related stimuli that support addiction (Hyman et al., 2006; Childress et al., 1993).

Similar to cocaine, *in vivo* $\Delta^9$-THC exposure can block eCB-LTD of glutamatergic synapses in the NAc. This was demonstrated following single low dose (3 mg/kg) (Mato et al., 2004) or chronic (7 day) high dose (10 mg/kg) (Hoffman et al., 2003) $\Delta^9$-THC injections. However, unlike cocaine, which did not alter $CB_1$ receptor function, $\Delta^9$-THC-induced loss of eCB-LTD was associated with $CB_1$ receptor desensitization. Subsequent work using a chronic (7 day) low dose (3 mg/kg) $\Delta^9$-THC regimen also found $CB_1$ receptor desensitization, but that eCB-LTD remained unaffected. This was due to a recruitment of the inhibitory mGluR2/3 receptors that compensated for reduced $CB_1$ receptor function (Mato et al., 2005). Based on measures of CPP in rodents, the dose administered by Mato et al., (2005) is rewarding, while the dose administered by Hoffman et al., (2003) is aversive (Murray and Bevins, 2010), suggesting divergent neuromodulatory actions in brain regions implicated in reward (e.g. the mesolimbic system) and aversion (e.g. the extended

amygdala) which may explain the observed differences in eCB-LTD following chronic administration. It will be interesting to see if this loss of homeostatic plasticity following the high dose of $\Delta^9$-THC (Hoffman et al., 2003) has important long-term implications for $\Delta^9$-THC concentration-dependent effects of marijuana. This is particularly important as the $\Delta^9$-THC content in marijuana has nearly tripled since 1995 (see Volkow et al., (2014a) for discussion). Moreover, because the $CB_1$ receptor is critically involved in normal NAc signaling, such as in the mediation of food and drug reward (Oleson and Cheer, 2012a), its functional disruption by $\Delta^9$-THC exposure is likely to have widespread behavioral implications beyond an altered sensitivity to $\Delta^9$-THC.

### 5.4. Does THC promote a hypofunctioning dopamine system?

While cannabinoid administration to naïve subjects acutely elevates VTA dopamine cell firing and NAc dopamine release (Cheer et al., 2003; Cheer et al., 2004), excessive cannabinoid exposure depresses dopamine neuron function (Figure 1B). For example, rats chronically (6.5 d) treated with high dose (15 mg/kg) $\Delta^9$-THC exhibit decreased baseline rates of VTA dopamine cell firing and suppressed bursting activity (Diana et al., 1998), which is in line with an eCB-dependent LTD of VTA glutamatergic input following chronic $\Delta^9$-THC exposure (Section 6.2). Indeed, PET measurements suggest a blunted dopamine signal in the ventral striatum (i.e., NAc) of chronic marijuana abusers (Volkow et al., 2014b). This decreased dopamine signal correlates with the duration and severity of marijuana abuse, and is associated with greater measures of negative affect. In chronic, heavy marijuana users, negative affect is accompanied by a greater propensity to take non-cannabinoid drugs, and the alleviation or avoidance of a negative emotional state is the primary motivation for marijuana use in this population (Hyman and Sinha, 2009). Loss of eCB-LTD at iMSNs (Hoffman et al., 2003) and the induction of eCB-dependent LTD at VTA dopamine neurons following chronic, high dose $\Delta^9$-THC (Liu et al., 2010) should collectively support augmented indirect pathway function and avoidance behavior. While augmented indirect pathway activity may not be causing the negative affect, it could be a consequence of it.

## Section 6. Adolescent marijuana use can promote lasting changes in brain structure and function

A growing body of evidence suggests that marijuana use during adolescence results in enduring alterations in mesolimbic structure and function that can support future drug use and abuse. While a full discussion on the detrimental effects of adolescent marijuana use is beyond the scope of this review (see reviews by (Volkow et al., 2014a; Batalla et al., 2013)), given the high incidence of marijuana use in adolescent populations this topic merits recognition. Indeed, similar to adults, marijuana is the most commonly abused illicit drug among adolescents in the United States, with 34–45% of high school students reporting having used marijuana at least once and an astonishing 6.5% of $12^{th}$ grade students reporting daily use (Terry-McElrath et al., 2013). These numbers are particularly disturbing given the increased likelihood of deleterious consequences in this vulnerable population. For example, regular marijuana use in adolescence is associated with the development of psychiatric disease (Chadwick et al., 2013; Fernandez-Espejo et al., 2009), including drug abuse,

addiction, and anxiety (Kandel, 1975; Hadland and Harris, 2014). Behavioral disturbances are mirrored by alterations in addiction-related brain regions, including the frontal cortex (Battistella et al., 2014; Batalla et al., 2013) and the NAc (Gilman et al., 2014). Human research, however, can only provide correlations between adolescent cannabis use, subsequent development of addiction-related behaviors, and underlying neurobiology, highlighting a need for animal research to investigate how adolescent cannabinoid exposure alters the adult brain and behavior.

In rodents, adolescent cannabinoid exposure promotes changes in neuronal development that can alter future neurobehavioral responses to abused drugs. Cannabinoid-induced changes in mesolimbic dopamine system function are likely to be particularly important in altering future drug-taking behavior, as this system is exceedingly plastic during adolescence (Benes et al., 2000) and critical to reward and motivation. Indeed, CB1 receptor number as well as CB1 binding is reduced in the accumbens and VTA of adult animals exposed to cannabinoids during adolescence (Marco et al., 2009; Rubino et al., 2008). Additionally, sub-chronic adolescent, but not adult, cannabinoid exposure promotes cross tolerance to the ability of non-cannabinoid drugs, including amphetamine, cocaine and morphine, to alter VTA dopamine cell firing (Pistis et al., 2004). $\Delta^9$-THC administration during adolescence also promotes a permanent suppression of cortical oscillations in adult mice within the medial prefrontal cortex that is associated with impaired working memory (Raver and Keller, 2014). Loss of oscillatory activity is accompanied by a decrease in GABAergic transmission in the prefrontal cortex (Zamberletti et al., 2014; Cass et al., 2014), which – according to measures in adult rodents (Section 5.3) – may increase PFC-NAc glutamatergic signaling and support reinstatement of drug seeking. While cannabinoid exposure at an early age is clearly capable of altering mesolimbic dopamine system function, the current animal literature presents a largely incomplete picture of how this may alter future drug seeking behavior.

Indeed, while adolescent cannabinoid exposure has been associated with a greater susceptibility to seek drugs as adults, it remains unclear what produces this change in behavior. For example, adolescent exposure to $\Delta^9$-THC reliably enhances heroin self-administration in adult rodents in an FR1 schedule (Ellgren et al., 2007; Tomasiewicz et al., 2012). This may be explained by the ability of adolescent $\Delta^9$-THC exposure to enhance heroin-induced dopamine release in the NAc (Cadoni et al., 2013). However, adolescent exposure to $\Delta^9$-THC does not increase breakpoints for obtaining heroin in a progressive ratio schedule, indicating that heroin self-administration is not driven by an increase in the motivational value of heroin (Solinas et al., 2004). Alternatively, adolescent THC exposure can increase measures of heroin reward in a CPP task, but this differs by rat strain (Cadoni et al., 2013). Thus, the long-term effects of cannabis exposure on addiction susceptibility may be genetically biased. Another possibility is that cannabinoid exposure may motivate future drug use through negative reinforcement mechanisms, such as that seen in human marijuana users (Hyman and Sinha, 2009). Indeed, chronic treatment with the $CB_1$ agonist WIN or $\Delta^9$-THC during adolescence results in increased anxiety levels (Stopponi et al., 2014; Rubino and Parolaro, 2008) and this is associated with greater levels of stress-induced heroin seeking in adulthood (Stopponi et al., 2014). Unfortunately, a strong connection between adolescent cannabinoid exposure and abuse of psychostimulants in adulthood is

lacking, which is surprising given the positive correlation between these occurrences in humans (Swift et al., 2012; SAMHSA, 2013). Taken together, future research is drastically needed to determine how adolescent cannabinoid exposure affects different aspects of drug abuse, including drug motivation, reward and aversion.

## Section 7. Implications of marijuana legalization

Marijuana, like other abused drugs, is addictive, can lead to a number of adverse health effects, and is particularly harmful for adolescent users (Volkow et al., 2014a; DuPont and Lieberman, 2014). Accordingly, as shifting social tides lead to more widespread legalization of marijuana, apprehension has been raised regarding the dangers of a potential increase in marijuana use. However, the high rates of marijuana use indicate access to this drug has not been substantially reduced by threat of legal ramifications. Thus, whether marijuana legalization will actually increase the number of people using marijuana is not clear. Another potential consequence of marijuana legalization is a dramatic increase in our understanding of how this drug affects behavior and, in turn, its therapeutic utility. Because marijuana is mostly illegal, its rates and patterns of use are not well-documented and are largely based on self-reports. Marijuana legalization should lead to much better documentation of its patterns of use and abuse. Additionally, laboratory research on marijuana, not simply $\Delta^9$-THC, is sparse. Furthermore, stringent regulations have made investigations into the precise neurobiological actions of the nearly 100 cannabinoids in marijuana (i.e., phytocannabinoids) difficult. Such work, however, is likely to yield important insight into eCB system function. We would argue that due to its anatomically ubiquitous expression, functionally diverse actions, and relatively recent discovery, research into the eCB system should not be hindered, but highly encouraged.

The unimpeded study of marijuana's effects is particularly important based on the established and potential medical utility of eCB-targeted treatments. For example, marijuana and synthetic cannabinoids are effective for treating certain types of pain (Robson, 2014). As the current primary medical treatment for pain, prescription opioids, contribute to more overdose deaths per year in the United States than any other drug class – more than heroin and cocaine combined (Okie, 2010; CDC, 2011) – cannabinoid-based treatments may offer a better option. Indeed, a recent report shows a nearly 35% decrease in rates of opioid overdose deaths in states with medical cannabis laws (Bachhuber et al., 2014). While a causal link is difficult to demonstrate, this is nonetheless a promising trend.

The potent ability of $CB_1$ receptor antagonists to suppress cue-induced drug relapse (Section 1.2) also indicates potentially powerful cannabinoid-based addiction treatments. However, $CB_1$ receptor antagonists, while effective, are associated with significant negative side effects in humans, such as depression and suicidal tendencies (Hill and Gorzalka, 2009). Alternatively, because eCB mobilization occurs only in response to heightened activity, disrupting endogenous activity (e.g., by blocking enzymatic degradation) may more selectively target those synapses that are active during a specific event, such as re-exposure to drug cues (Oleson et al., 2014; Loewinger et al., 2013; Katona and Freund, 2008). This final point highlights that, while cannabinoids have had a pervasive influence on human culture for millennia, the recent discovery of the eCB system has permitted an

unprecedented understanding (yet far from incomplete) of how these drugs affect the brain and behavior. Thus, as marijuana legalization permits greater and easier access to this drug, we are in a unique position to use this opportunity to exploit marijuana for its medical and scientific utility.

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- Endocannabinoid signaling modulates mesolimbic dopamine function and conditioned reward seeking.
- Abused drugs disrupt endocannabinoid system function, which promotes synaptic adaptations that support drug abuse.
- Long-term alterations in endocannabinoid regulation of dopamine signaling facilitate cue-directed drug seeking.
- Marijuana legalization may support the advent of cannabinoid-based drugs that target compromised endocannabinoid signaling.

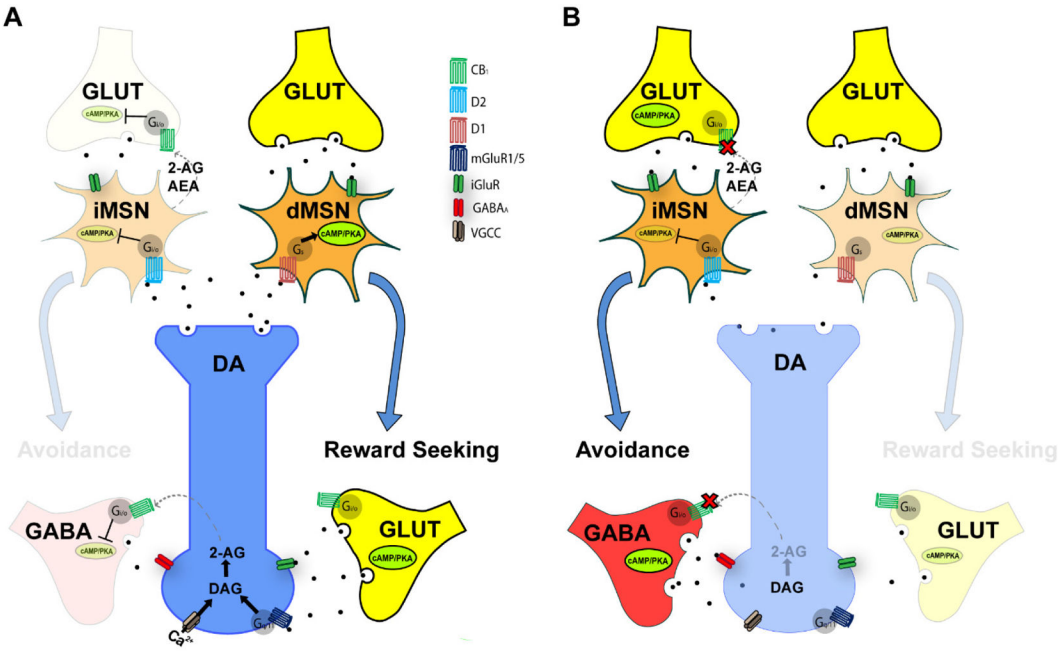


**Figure 1.**

Mesolimbic dopamine signaling during reward seeking and following chronic cannabinoid exposure. (A) Exposure to reward-related stimuli promotes (1) burst firing of dopamine neurons driven by ionotropic glutamate receptor (iGluR) binding. $Ca^{2+}$ influx via voltage-gated calcium channels (VGCCs) and group 1 metabotropic glutamate receptor (mGluR1/5) binding promotes the enzymatic synthesis of 2-AG from diacylglycerol (DAG). Retrograde 2-AG release disinhibits dopamine neurons via $CB_1$ receptor binding to presynaptic $GABA_A$ receptors. (2) Burst firing elicits phasic dopamine release in the NAc onto indirect pathway medium spiny neurons (iMSNs) and direct pathway MSNs (dMSNs). $D_2$ receptor binding inhibits iMSNs via $G_{i/o}$ inhibition of cAMP/PKA pathway. (3) 2-AG and anandamide (AEA) mobilization in the NAc is also mediated by mGluR1/5 and VGCCs (not shown). $D_2$ receptor binding supports eCB mobilization by inhibiting adenosine A2A receptor inhibition of eCB release (not shown; Lerner et al., 2010). $CB_1$ receptor binding on presynaptic glutamate terminals suppresses iMSN excitatory drive to further inhibit indirect pathway function and avoidance behavior. (3) Phasic dopamine release binds $G_s$-coupled $D_1$ receptors to activate the cAMP/PKA pathway and depolarize dMSNs. Work showing eCB-LTD is preferential to iMSNs (Grueter et al., 2010) permits excitatory drive onto dMSNs to support direct pathway function and reward seeking. (B) Following chronic, high dose cannabinoid exposure, (1) dopamine neurons become inhibited due to $CB_1$ receptor desensitization on presynaptic GABA terminals, and LTD at glutamate synapses. (2) Reduced dopamine release decreases $D_1$-mediated activation of dMSNs and reduces direct pathway activation of reward seeking. (3) $CB_1$ desensitization reduces eCB-LTD and enhances excitatory drive onto iMSNs, increasing indirect pathway function and avoidance behavior.