

# Endocannabinoid Signaling in Reward and Addiction: From Homeostasis to Pathology

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**Abstract** The endogenous cannabinoid system is an important regulatory system involved in physiological homeostasis. Endocannabinoid signaling is known to modulate neural development, immune function, metabolism, synaptic plasticity, and emotional state. Accumulating evidence also implicates brain endocannabinoid signaling in the processing of natural and drug-induced reward states and dysregulated endocannabinoid signaling in the etiology of aberrant reward function and drug addiction. In this chapter, we discuss the influence of endocannabinoid signaling on the rewarding and motivational effects of natural rewards such as food, sex, and social interaction, as well as evidence demonstrating an endocannabinoid influence in the rewarding effects of abused drugs. The effects of long-term drug consumption on endocannabinoid signaling are discussed, along with evidence that the resultant dysregulation of endocannabinoid function contributes to various aspects of drug dependence and addiction including physical symptoms of drug withdrawal, increased stress responsivity, negative affective states, dysregulated synaptic plasticity, dysregulated extinction of drug-related memories, relapse to drug taking, and impaired cognitive function. Lastly, consideration is given to the role for dysregulated endocannabinoid signaling in pathological food reward and eating disorders.

Present knowledge of the endogenous cannabinoid system (ECS) derives from decades of research demonstrating that the effects of *Cannabis* are mediated by cannabinoid receptors in the brain and the subsequent identification and characterization of the endogenous ligands for these receptors. Although our understanding of the nature and breadth of endocannabinoid (eCB) influences is constantly expanding, it is now acknowledged that the brain ECS plays a prominent role in modulating brain reward function and the maintenance of emotional homeostasis. This chapter examines the evidence for an eCB influence in the positive reinforcing effects of natural rewards and drugs of abuse, as well as dysregulation of ECS function that may influence or contribute to aberrant synaptic plasticity, negative

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emotional states, and impaired learning and memory processes resulting from long-term drug exposure that sustains compulsive drug consumption characteristic of the addicted state.

## 1 Neurobiology of Reward

The brain reward system plays an important role in our survival as a species. In addition to homeostatic factors that drive behavior, the hedonic or pleasurable effects produced by eating, exercise, and sexual activity provide important motivational effects that increase the likelihood of future engagement in these critical activities (known as positive reinforcement). In a similar manner, though less commonly considered, the reward system participates in negative hedonic responses in which aversive or unpleasant events (sickness, bodily harm) increase the likelihood of behaviors that will relieve or avoid these negative states (negative reinforcement). Accordingly, proper reward system function is critical for the maintenance of behaviors that promote survival.

Our understanding of the neurobiological substrates for reward and reinforcement is derived from studies in the 1950s by Olds and Milner who demonstrated that rodents will work to receive electrical stimulation in various brain regions (Olds and Milner 1954). Although stimulation of many brain sites supports operant behavior, the most sensitive sites involve the trajectory of the medial forebrain bundle that connects the ventral tegmental area (VTA) to the basal forebrain, including the nucleus accumbens (NAc) in the ventral striatum. Substantial subsequent evidence has demonstrated a critical involvement of mesocorticolimbic dopamine (DA) signaling in the mediation of reward and reinforcement, suggesting that activation of this system induces general behavioral activation (Le Moal and Simon 1991), promotes goal-directed behavior (Salamone et al. 2007), and increases incentive salience to environmental stimuli (Robinson and Berridge 1993). Functional neuroimaging studies in humans demonstrate that the mesocorticolimbic system is activated by natural rewards including the sight of appetizing food and orgasm (Komisaruk et al. 2004; Volkow et al. 2011), and rodent studies demonstrate that food consumption, sex, and exercise each increase NAc DA signaling (Bassareo and Di Chiara 1999a; Fiorino et al. 1997; Freed and Yamamoto 1985; Hattori et al. 1994). PET studies in humans have shown that psychostimulants, nicotine, alcohol, and marijuana each increase DA in the dorsal and ventral striatum and that this is associated with the subjective rewarding effects of the drugs (Tomasì and Volkow 2013). Similarly, rodent studies demonstrate that all addictive drugs possess the ability to increase mesocorticolimbic DA and that this contributes to the positive reinforcing effects of these substances (particularly psychostimulants and nicotine) (Di Chiara and Bassareo 2007; Koob and Volkow 2010). Substantial evidence suggests that DA-independent signaling in the mesolimbic system also substantially impacts reward processing, including cholinergic, opioid, glutamatergic, and GABAergic signaling (Koob 1992; Nestler 2005).

The NAc receives input from the amygdala, frontal cortex, and hippocampus that may be converted to motivational actions through its connections with the extra-pyramidal motor system. In particular, the central nucleus of the amygdala (CeA) appears to play a role in mediating/modulating the positive reinforcing effects of abused drugs (Koob and Volkow 2010), and the ventral pallidum/substantia innominata, which receives a major innervation from the NAc, is also critically involved in modulating the positive reinforcing effects of both natural and drug rewards (Koob and Volkow 2010).

In general, NAc DA levels are decreased by many aversive conditions such as unavoidable shock, medial hypothalamic stimulation, chronic pain, and certain patterns of over- or undereating (Umberg and Pothos 2011). Numerous studies have also demonstrated deficiencies in NAc DA during withdrawal from addictive drugs (Umberg and Pothos 2011; Koob and Volkow 2010). Further, dysregulation of key neurochemical elements involved in stress responses mediated by the CeA, bed nucleus of the stria terminalis (BNST), frontal cortex, and medial shell of the NAc plays a major role in the negative reinforcing effects of withdrawal from highly palatable food and drugs of abuse (Koob and Volkow 2010; Koob et al. 2014; Blasio et al. 2013; Iemolo et al. 2013). Signaling systems involved in these processes include dysregulation of both pro-stress (corticotropin-releasing factor (CRF), dynorphin) and anti-stress (NPY, nociceptin) systems.

Thus, reward processing is mediated in large part through an interconnected network of structures that includes the VTA, NAc, ventral pallidum, CeA, BNST, and prefrontal cortex (PFC). In addition to the well-known involvement of mesocorticolimbic DA, reward processing is also heavily influenced by many other systems including glutamate, GABA, opioid peptides, and stress-related signaling systems.

## 2 The Endogenous Cannabinoid System (ECS)

Endocannabinoids are neuroactive lipids that participate in a range of physiological processes including reward, motivation, emotional homeostasis, pain processing, neuroprotection, and synaptic plasticity contributing to learning and memory. For the purposes of this chapter, a superficial overview of the main ECS components is provided below, and readers are referred to more in-depth coverage of this topic provided by several excellent recently published reviews (Lu and Mackie 2015; Hillard 2015; Mechoulam and Parker 2013).

In addition to the endocannabinoid lipid moieties themselves, the ECS is comprised of G protein-coupled receptors and metabolic enzymes for the synthesis and degradation of the ligands. Two major types of cannabinoid receptor have been characterized and cloned: CB<sub>1</sub> and CB<sub>2</sub>. CB<sub>1</sub> receptors (CB<sub>1</sub>Rs) are the most abundant G protein-coupled receptor expressed in the adult brain, with particularly dense expression in each of the interconnected structures involved in reward (Glass et al. 1997; Wang et al. 2003b; Herkenham et al. 1991) where they exert widespread

modulatory influences on excitatory and inhibitory signaling in a manner that influences reward processing (Sidhpura and Parsons 2011; Panagis et al. 2014). In particular, eCBs play a prominent role in fine-tuning the activity of the VTA-NAc DA projection and its influence on approach and avoidance behaviors that govern reward acquisition (Hernandez and Cheer 2015). CB<sub>2</sub> receptors (CB<sub>2</sub>R) are mainly expressed by immune cells with recent evidence also suggesting CB<sub>2</sub>R expression in neurons, glia, and endothelial cells in the brain (Atwood and Mackie 2010). CB<sub>1</sub>R and CB<sub>2</sub>R are coupled to similar transduction systems primarily through G<sub>i</sub> or G<sub>o</sub> proteins. CB<sub>1</sub>R directly inhibit the release of GABA, glutamate, and acetylcholine that produce widespread effects on neural signaling across many neurotransmitter systems.

At present the best characterized endocannabinoid ligands are N-arachidonylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). Due to their lipid nature, AEA and 2-AG are not stored in vesicles but are synthesized on an “on demand” basis by cleavage from membrane precursors and immediate release through Ca<sup>2+</sup>-dependent mechanisms. AEA is derived from the phospholipid precursor N-arachidonoyl phosphatidylethanolamine (NAPE), and while the precise mechanisms for AEA formation are not known, a very likely candidate is through N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD). 2-AG derives primarily from the hydrolytic metabolism of 1,2-diacylglycerol (DAG) by sn-1-selective DAG lipases (DAGL $\alpha$ , DAGL $\beta$ ). AEA is primarily catabolized through fatty acid amide hydrolase 1 (FAAH1), and 2-AG is catabolized through monoacylglycerol lipase (MAGL) and to a lesser extent  $\alpha$ , $\beta$ -hydrolase 6 (ABHD6), cyclooxygenase-2 (COX-2), and FAAH1. The eCB catabolic enzymes have distinct cellular anatomical locations with MAGL localized predominantly in presynaptic terminals and FAAH1 to the postsynaptic domain of neurons. AEA and 2-AG each exert agonist activity at CB<sub>1</sub>R and CB<sub>2</sub>R. AEA binds with slightly higher affinity to CB<sub>1</sub>R vs. CB<sub>2</sub>R, and like  $\Delta$ 9-tetrahydrocannabinol ( $\Delta$ 9-THC, the main psychoactive component of the *Cannabis* plant), AEA exhibits low efficacy as an agonist at both receptors, producing submaximal signaling upon binding. 2-AG binds with essentially equal affinity at CB<sub>1</sub>R and CB<sub>2</sub>R and exhibits greater agonist efficacy than AEA. AEA and 2-AG also exhibit agonist properties at several secondary receptors including peroxisome proliferator-activated receptors (PPARs), GPR55, and GPR119, and AEA exerts potent agonist effects at transient receptor potential ion channels including TRPV1.

### 3 Rewarding Effects of Altered eCB Signaling

Both exogenous AEA and exogenous 2-AG increase extracellular DA levels in the NAc in a CB<sub>1</sub>-dependent manner (Solinas et al. 2006), and substantial evidence demonstrates a strong eCB influence in fine-tuning the activity of midbrain DA cells (Melis and Pistis 2012). Given this influence, and the rewarding effects produced by natural and synthetic CB<sub>1</sub> agonists, there has been considerable

interest in the influence of eCB signaling in the modulation of brain reward function.

Several preclinical studies have investigated whether enhanced eCB signaling itself produces rewarding effects, and much of this has compared eCB-induced behaviors with those produced by exogenous CB<sub>1</sub> agonists. The metabolically stable AEA analogs (R)-methanandamide, O-1812, and AM1346 each fully generalize to  $\Delta^9$ -THC in drug discrimination tests (Burkey and Nation 1997; Jarbe et al. 2006; Alici and Appel 2004; Solinas et al. 2007), and exogenous AEA itself also produces  $\Delta^9$ -THC-like discriminative effects when administered following FAAH inhibition (Solinas et al. 2007; Vann et al. 2009; Wiley et al. 2014). Because neither AEA nor FAAH inhibition produces  $\Delta^9$ -THC-like responding in their own right (Burkey and Nation 1997; Wiley et al. 1997, 2014; Gobbi et al. 2005; Solinas et al. 2007), these findings suggest that administration of exogenous AEA produces  $\Delta^9$ -THC-like interoceptive effects only under conditions of reduced hydrolytic clearance. In the absence of MAGL inhibition, exogenous 2-AG also does not substitute for  $\Delta^9$ -THC in discrimination tests (Wiley et al. 2014), though interestingly the MAGL inhibitor JZL184 produces partial generalization to  $\Delta^9$ -THC even without exogenously administered 2-AG (Wiley et al. 2014; Long et al. 2009b). However, these effects of JZL184 may result from concurrent MAGL and FAAH inhibition based on evidence that dual inhibition of MAGL and FAAH fully substitutes for  $\Delta^9$ -THC in discrimination tests (Wiley et al. 2014; Long et al. 2009b), and the more selective MAGL inhibitor KML29 does not generalize to  $\Delta^9$ -THC (Ignatowska-Jankowska et al. 2014). The  $\Delta^9$ -THC-like discriminative properties of enhanced eCB signaling are all blocked by CB<sub>1</sub> antagonism. Collectively, these findings indicate that systemic administration of eCBs produces CB<sub>1</sub>-dependent  $\Delta^9$ -THC-like discriminative stimulus effects, though combined enhancement of AEA and 2-AG signaling is most effective for producing  $\Delta^9$ -THC-like effects. Neither exogenously administered AEA nor selective FAAH, MAGL, or dual FAAH/MAGL inhibition produces rewarding effects in the conditioned place preference model (Mallet and Beninger 1998; Gobbi et al. 2005; Gamage et al. 2015), and FAAH inhibitors and putative eCB transport inhibitors do not alter brain stimulation reward thresholds (Vlachou et al. 2006). Drugs that inhibit eCB hydrolysis do not support operant self-administration behavior in rodents, though exogenous AEA, the metabolically stable AEA analog methanandamide, and exogenous 2-AG do support operant self-administration behavior by squirrel monkeys through a CB<sub>1</sub>R-reliant mechanism (Justinova et al. 2005, 2008a, 2011). Moreover, the eCB clearance inhibitors URB597, AM404, and VDM11 support operant self-administration behavior by squirrel monkeys with a prior history of nicotine, cocaine, or AEA self-administration (Justinova et al. 2015; Schindler et al. 2016). However, unlike drugs with prominent abuse liability, these eCB clearance inhibitors do not increase mesolimbic DA release (Solinas et al. 2007; Murillo-Rodriguez et al. 2013; Justinova et al. 2015), and it remains to be determined whether these compounds will be self-administered by drug-naïve monkeys or other species. Collectively, these findings suggest that administration of exogenous eCBs can produce positive reinforcing effects in a variety of paradigms indexing

brain reward, though most evidence suggests that pharmacological compounds that enhance eCB tone (e.g., selective FAAH or MAGL clearance inhibitors) do not produce substantial rewarding effects.

## 4 Endocannabinoid Influence on Natural Rewards

### 4.1 Food Reward

It is well known that palatable foods can lead people to eat, even when satiated. As such, eating can be motivated not only by hunger or homeostatic processes but also by hedonics. The ECS plays a prominent homeostatic role in controlling metabolic functions such as energy balance and food intake (Silvestri and Di Marzo 2013), and growing evidence also demonstrates an important ECS influence in the hedonic or rewarding properties of food intake. Both exogenous and endogenous CB<sub>1</sub> agonists reduce the latency to feed in pre-satiated or free-feeding animals, increase the amount of food consumed, and increase an animal's willingness to work for food reward (Kirkham and Williams 2001; Farrimond et al. 2011; Gallate and McGregor 1999; Kirkham et al. 2002; Williams and Kirkham 1999; Martinez-Gonzalez et al. 2004; Solinas and Goldberg 2005). Manipulations of CB<sub>1</sub> tone appear to preferentially influence the motivation for highly palatable rewards compared with standard isocaloric chow or neutral or mildly aversive rewards (Guegan et al. 2013; Dipatrizio and Simansky 2008; Shinohara et al. 2009). For example, studies on the microstructure of fluid consumption and taste reactivity demonstrate that CB<sub>1</sub> receptor agonists increase the hedonic effects of palatable rewards such as sucrose (Higgs et al. 2003; Jarrett et al. 2005, 2007; Mahler et al. 2007). Conversely, CB<sub>1</sub> receptor antagonism preferentially reduces the consumption of palatable and/or high-fat foods vs. standard chow (Simiand et al. 1998; South et al. 2007; Mathes et al. 2008), reduces the conditioned reinforcing effects produced by palatable substances such as sucrose or chocolate (Chaperon et al. 1998), and reduces the motivation for palatable foods indexed under progressive ratio schedules of reinforcement (Gallate and McGregor 1999; Gallate et al. 1999; Solinas and Goldberg 2005).

The neural pathways contributing to the hedonic aspects of feeding include the mesocorticolimbic system (Kalivas and Volkow 2005; Nestler 2005). Food-related visual or olfactory cues increase mesolimbic DA signaling in both humans (Macht and Mueller 2007) and laboratory animals (Hajnal et al. 2004; Rada et al. 2005; Scalfani et al. 1998) in part through CB<sub>1</sub>-reliant mechanisms (Melis et al. 2007). The mesocorticolimbic system influences feeding behavior through interconnections with hypothalamic nuclei (Berridge et al. 2010), and many of the hypothalamic signaling molecules that modulate homeostatic feeding behavior are also present in mesocorticolimbic structures such as the NAc, VTA, and PFC (Horvath and Diano 2004; Kelley et al. 2005). In fact, an influence of feeding-related

hormones on eCB production (Di Marzo et al. 2001; Bermudez-Silva et al. 2012) and signaling (Edwards and Abizaid 2016) has been described, and this mechanism may play a prominent role in the regulation of consummatory behaviors. Fasting increases AEA and 2-AG levels in the limbic forebrain and hypothalamus of rodents, an effect that is ameliorated following feeding (Kirkham et al. 2002; Hanus et al. 2003). Doses of CB<sub>1</sub> agonists that induce food consumption in satiated rodents activate the corticostriatal-hypothalamic pathway (including the NAc) (Dodd et al. 2009), and food consumption is increased by direct infusion of eCBs or FAAH inhibitors into the hypothalamic nuclei (Anderson-Baker et al. 1979; Jamshidi and Taylor 2001; Verty et al. 2005) or NAc shell (Kirkham et al. 2002; Soria-Gomez et al. 2007). In particular, the NAc shell has been identified as a critical locus for the eCB modulation of the hedonic properties of food (Berridge et al. 2010; Mahler et al. 2007), and intra-NAc eCB infusions increase neural activity in hypothalamic nuclei through a CB<sub>1</sub>-dependent mechanism (Soria-Gomez et al. 2007). Furthermore, transgenic mice overexpressing MAGL in the forebrain (MGL-Tg mice) do not form a conditioned place preference for high-fat foods, indicating that reductions in 2-AG may impede high-fat food reward (Wei et al. 2016). Collectively, these findings demonstrate that eCB signaling in the CNS plays a role in the motivation for and hedonic response to food consumption. Interestingly, there is emerging evidence that in addition to sweet taste receptors (T1R2/T1R3), sweet-sensitive taste cells in the peripheral system also express CB<sub>1</sub> receptors (Jyotaki et al. 2010), and both AEA and 2-AG increase gustatory nerve responses to sweet solutions (Yoshida et al. 2010). Thus, the ECS modulates food palatability via both central and peripheral pathways.

## 4.2 Sexual Reward

CB<sub>1</sub> receptors are densely expressed in the neural circuits that regulate sexual behavior, and substantial evidence indicates that both exogenous and endogenous cannabinoids can alter sexual behavior, though the effects are often highly divergent in males and females (Gorzalka et al. 2010; Lopez 2010). With regard to the hedonic aspects of sexual behavior, the majority of studies indicate a facilitatory effect of *Cannabis* on subjective indices of sexual arousal in women including desire, orgasmic function, and pleasure/enjoyment/satisfaction (Koff 1974; Dawley et al. 1979; Halikas et al. 1982; Klein et al. 2012). Similarly, low-dose *Cannabis* exposure increases sexual desire in males though simultaneously hindering erectile functioning. Rodent studies have revealed both facilitatory and inhibitory effects of cannabinoid agonists and eCB clearance inhibition (e.g., FAAH inhibitors) on female sexual receptivity and proceptivity and a general inhibitory effect on male sexual performance (Gorzalka et al. 2010; Lopez 2010; Canseco-Alba and Rodriguez-Manzo 2016), though the relative influence of these manipulations on the motivational vs. performance aspects of sexual behavior is not clear. In the most direct evaluation of an eCB influence on sexual motivation, Klein and colleagues



observed that physiological indices of sexual arousal in women are associated with decreased serum AEA levels, and subjective indices of arousal are associated with decreases in serum levels of both AEA and 2-AG (Klein et al. 2012). However, while these indices reflect an ECS involvement in the anticipatory/motivational effects produced by erotic visual stimuli, it remains unclear whether endocannabinoid signaling is altered by sexual activity itself and, if so, whether this results in a facilitation or attenuation of brain reward processing. Endocannabinoid signaling may also influence sexual reward indirectly through modulation of emotional state and/or sensation perception, though these possibilities have not been explored.

### **4.3 Social Interaction**

Cooperative playing and social interaction are rewarding activities in both humans and rodents (Tabibnia and Lieberman 2007; Douglas et al. 2004). In rodents, social play is enhanced following inhibition of FAAH or putative eCB transporters (with VDM11) but diminished following administration of exogenous CB<sub>1</sub> agonists such as WIN 55,212-2 (Trezza and Vanderschuren 2008a, b, 2009). This highlights the distinct effects produced by selectively enhancing the effects of eCB signaling in selected synapses, wherein eCB formation is evoked (e.g., eCB clearance inhibition) vs. widespread CB<sub>1</sub> activation by exogenous agonists that engage CB<sub>1</sub> signaling in circuits not normally activated by a given behavior (Trezza et al. 2010). The hedonic aspects of social play are mediated through both opioid (mu opioid in particular) and CB<sub>1</sub> mechanisms, and the CB<sub>1</sub> influence appears to involve subsequent increases in DA signaling (Trezza et al. 2010). Interestingly, social reward is influenced by opioid and cannabinoid interactions in a manner similar to drug and food reward (Fattore et al. 2004; Solinas and Goldberg 2005).

## **5 eCB Influence on the Acute Rewarding Effects of Drugs of Abuse**

There is substantial evidence implicating the ECS in the motivational effects produced by several classes of abused drugs including ethanol, nicotine, opiates, and psychostimulants. Much of this is based on the influence of CB<sub>1</sub> receptor signaling on drug-induced behaviors, though some studies have evaluated manipulations of eCB tone on drug reinforcement.

In general, CB<sub>1</sub> receptors exert a facilitatory influence on the rewarding effects of several classes of abused drugs (Table 1). Rodent studies employing the conditioned place preference and operant self-administration paradigms demonstrate that CB<sub>1</sub> agonists increase the motivational and rewarding effects of alcohol (Colombo



**Table 1** Summary of CB<sub>1</sub>R influence on motivation-related effects of abused drugs

Genetic or pharmacological manipulation	Ethanol	Nicotine	Opiates	Psychostimulants
CB <sub>1</sub> R Knockout	↓ CPP <sup>a</sup> ↓ Operant SA ↓ EtOH-induced NAc DA	↓ CPP <sup>b</sup> ↓ Operant SA	↓ CPP <sup>c</sup> ↓ Operant SA	<b>No change</b> in CPP <sup>d</sup> <b>No change</b> in operant SA
CB <sub>1</sub> R Antagonist	↓ Preference <sup>e</sup> ↓ Operant SA ↓ EtOH-induced NAc DA	↓ CPP <sup>f</sup> ↓ Operant SA ↓ Nic-induced NAc DA	↓ CPP <sup>g</sup> ↓ Operant SA	↑↑ Operant SA <sup>h</sup> ↑↑ Cocaine effects on ICSS
CB <sub>1</sub> R Agonist	↑ Operant SA <sup>i</sup> ↑ Motivation for EtOH	↑ CPP <sup>j</sup>	↑ CPP <sup>k</sup> ↑ Motivation for heroin	↓ Operant SA <sup>l</sup> ↓ Cocaine effects on ICSS

<sup>a</sup>Houchi et al. (2005), Thanos et al. (2005), Hungund et al. (2003), Naassila et al. (2004), Wang et al. (2003a)

<sup>b</sup>Cossu et al. (2001)

<sup>c</sup>Martin et al. (2000), Ledent et al. (1999), Cossu et al. (2001)

<sup>d</sup>Martin et al. (2000), Houchi et al. (2005), Cossu et al. (2001), Soria et al. (2005), Li et al. (2009)

<sup>e</sup>Arnone et al. (1997), Freedland et al. (2001), Gallate and McGregor (1999), Colombo et al. (1998), Gessa et al. (2005), Malinen and Hyytia (2008), Alvarez-Jaimes and Parsons (2009), Caille et al. (2007), Wang et al. (2003a), Perra et al. (2005), Cheer et al. (2007)

<sup>f</sup>Cohen et al. (2002), Shoaib (2008), Simonnet et al. (2013), Cheer et al. (2007)

<sup>g</sup>Caille and Parsons (2003, 2006), De Vries et al. (2003), Solinas et al. (2003), Singh et al. (2004), Chaperon et al. (1998), Navarro et al. (2001)

<sup>h</sup>Filip et al. (2006), Caille and Parsons (2006), Xi et al. (2008), Vinklerova et al. (2002), Chaperon et al. (1998), Cheer et al. (2007), Soria et al. (2005), Vlachou et al. (2003), Fattore et al. (1999), Tanda et al. (2000), De Vries et al. (2001), Caille et al. (2007), Lesscher et al. (2005)

<sup>i</sup>Colombo et al. (2002), Wang et al. (2003a), Gallate et al. (1999), Malinen and Hyytia (2008), Getachew et al. (2011)

<sup>j</sup>Valjent et al. (2002), Gamaledin et al. (2012b)

<sup>k</sup>Manzanedo et al. (2004), Solinas et al. (2005)

<sup>l</sup>Vlachou et al. (2003), Fattore et al. (1999)

et al. 2002; Wang et al. 2003a; Gallate et al. 1999; Malinen and Hyytia 2008; Getachew et al. 2011), nicotine (Valjent et al. 2002; Gamaledin et al. 2012b), and opiates (such as morphine and heroin) (Manzanedo et al. 2004; Solinas et al. 2005). In contrast, diminished CB<sub>1</sub> receptor signaling (either genetic receptor deletion or pharmacological inhibition) attenuates the motivational and rewarding effects of alcohol (Houchi et al. 2005; Thanos et al. 2005; Hungund et al. 2003; Naassila et al. 2004; Arnone et al. 1997; Wang et al. 2003a; Freedland et al. 2001; Gallate and McGregor 1999; Colombo et al. 1998; Gessa et al. 2005), nicotine (Cohen et al. 2002; Shoaib 2008; Cossu et al. 2001; Simonnet et al. 2013), and opiates (Chaperon et al. 1998; Navarro et al. 2001; Singh et al. 2004; Martin et al. 2000; Ledent et al. 1999; Cossu et al. 2001; Caille and Parsons 2003; De Vries et al. 2003; Solinas et al. 2003). The CB<sub>1</sub> influence on alcohol and nicotine reward is mediated in part,

through modulation of the mesolimbic DA response to these drugs as CB<sub>1</sub> receptor antagonism blocks the excitation of VTA DA cells produced by alcohol and nicotine, thereby attenuating the effects of these drugs on NAc DA release (Cohen et al. 2002; Hungund et al. 2003; Perra et al. 2005; Cheer et al. 2007). Blockade of CB<sub>1</sub> receptors in the VTA decreases both alcohol and nicotine self-administration (Malinen and Hyytia 2008; Alvarez-Jaimes and Parsons 2009; Caille et al. 2007; Simonnet et al. 2013), and antagonism of NAc CB<sub>1</sub> receptors similarly reduces alcohol consumption (Alvarez-Jaimes and Parsons 2009; Caille et al. 2007). However, while nicotine reward is critically dependent on the mesolimbic DA system (D'Souza and Markou 2011), the motivational and rewarding effects of alcohol and opiates are less DA dependent (Koob 2013; Shippenberg and Elmer 1998; Pettit et al. 1984; Gerrits and Van Ree 1996; Platt et al. 2001) with CB<sub>1</sub>R modulation of the rewarding effects of these drugs likely involving non-dopaminergic mechanisms. Indeed, although CB<sub>1</sub> receptor deletion results in attenuated opiate-induced increases in NAc DA (Mascia et al. 1999), acute CB<sub>1</sub> receptor blockade does not alter opiate-induced increases in NAc DA (Caille and Parsons 2003, 2006; Tanda et al. 1997). Rather, CB<sub>1</sub> receptor antagonism may modulate opiate reward through DA-independent attenuation of opiate-induced reductions in ventral pallidal GABA signaling (Caille and Parsons 2006).

The effects of CB<sub>1</sub> receptor manipulations on psychostimulant reward are less consistent. In contrast to the facilitation of ethanol, nicotine, and opiate reward, CB<sub>1</sub> agonists reduce both cocaine-induced facilitation of brain stimulation reward and cocaine self-administration by rats (Vlachou et al. 2003; Fattore et al. 1999). Further, CB<sub>1</sub> receptor inactivation does not affect psychostimulant-induced place conditioning (Martin et al. 2000; Houchi et al. 2005), psychostimulant self-administration (Cossu et al. 2001; Tanda et al. 2000; Fattore et al. 1999; De Vries et al. 2001; Caille and Parsons 2006; Filip et al. 2006; Caille et al. 2007; Lesscher et al. 2005), cocaine-induced increases in nucleus accumbens dopamine (Caille and Parsons 2003; Soria et al. 2005), or cocaine-induced enhancement of brain stimulation reward (Vlachou et al. 2003; Xi et al. 2008). However, some reports indicate that CB<sub>1</sub> inactivation attenuates cocaine and amphetamine self-administration (Soria et al. 2005; Xi et al. 2008; Vinklerova et al. 2002), blocks cocaine-induced increases in NAc DA signaling (Li et al. 2009; Cheer et al. 2007), and decreases cocaine-induced enhancement of brain stimulation reward sensitivity (Xi et al. 2008). In general, the inconsistent and generally subtle effects reported suggest that CB<sub>1</sub> receptors exert a relatively modest influence over psychostimulant-induced reward.

Recent evidence in mice also implicates CB<sub>2</sub>R in the modulation of drug reward. CB<sub>2</sub>R agonists reduce cocaine-induced CPP and cocaine self-administration in wild-type mice but not CB<sub>2</sub>R knockout mice (Xi et al. 2011; Ignatowska-Jankowska et al. 2013; Zhang et al. 2014a), and cocaine self-administration is also reduced by CB<sub>2</sub>R overexpression in the brain (Aracil-Fernandez et al. 2012). CB<sub>2</sub>R agonists also reduce alcohol-induced CPP and alcohol consumption (Al Mansouri et al. 2014). Mouse VTA DA neurons express CB<sub>2</sub>R mRNA and receptor immunostaining, and CB<sub>2</sub>R agonists decrease the

activity of these neurons in wild-type but not CB<sub>2</sub>R knockout mice (Zhang et al. 2014b). Surprisingly, CB<sub>2</sub>R agonists facilitate nicotine-induced CPP (Ignatowska-Jankowska et al. 2013), and CB<sub>2</sub>R inactivation reduces both nicotine-induced CPP and nicotine self-administration in mice (Navarrete et al. 2013; Ignatowska-Jankowska et al. 2013). In contrast, CB<sub>2</sub>R antagonism does not alter cocaine or nicotine self-administration in rats but attenuates cocaine-induced and conditioned locomotion and reinstatement of cocaine-seeking behavior (without altering nicotine-induced drug seeking) (Blanco-Calvo et al. 2014; Adamczyk et al. 2012b; Gamaledin et al. 2012b). Further, a recent study reported the CB<sub>2</sub>R agonism reduces cocaine consumption by rats, but not mice, and produces opposite effects on the motivation for cocaine in these species (Zhang et al. 2014a). These distinctions may result from species differences in the splicing and expression of CB<sub>2</sub>R genes, possibly conferring distinct CB<sub>2</sub>R structure, function, or pharmacology (Zhang et al. 2014a).

## 6 Evidence that Drugs of Abuse Increase Brain eCB Levels

The inhibitory influence of CB<sub>1</sub> receptor antagonism on drug reward has led to the hypothesis that abused drugs increase brain eCB formation possibly resulting in aberrant eCB signaling following long-term drug exposure. Several observations support these hypotheses.

Early studies reported that chronic alcohol exposure increases 2-AG and AEA formation in human neuroblastoma cells and cultured rodent neurons (Basavarajappa and Hungund 1999; Basavarajappa et al. 2000, 2003). Subsequent evaluations of postmortem brain tissue eCB content clearly demonstrate alcohol-induced alterations in 2-AG and AEA production, though substantial inconsistencies among studies make it difficult to draw clear conclusions on the direction of change and regional nature of the effects (Vinod et al. 2006, 2012; Gonzalez et al. 2002, 2004b; Malinen et al. 2009; Rubio et al. 2007). In vivo microdialysis studies in rats demonstrate that voluntary alcohol consumption robustly increases nucleus accumbens 2-AG but not AEA levels (Caille et al. 2007), while forced alcohol administration decreases AEA levels and induces more modest increases in 2-AG (Ferrer et al. 2007; Alvarez-Jaimes et al. 2009). This provides initial evidence that the volitional nature of drug exposure (e.g., voluntary vs. forced administration) may differentially impact eCB responses. The effects of alcohol on brain eCB production may also be region specific as alcohol-induced disruptions of extracellular eCB levels and mRNA expression of their associated enzymes are consistently observed in striatal regions (Caille et al. 2007; Ceccarini et al. 2013; Ferrer et al. 2007; Alvarez-Jaimes et al. 2009; Henricks et al. 2016) but not frontal cortical areas (Alvarez-Jaimes and Parsons 2009), and ethanol self-administration is reduced by localized antagonism of CB<sub>1</sub> receptors in the VTA and NAc shell but not PFC of outbred rats (Malinen and Hyttia 2008; Alvarez-Jaimes and Parsons 2009; Caille et al. 2007) (though disruptions in eCB processing have been observed in cortical

regions of rats selectively bred for high alcohol consumption (Hansson et al. 2007) and in mice following long-term alcohol exposure (Vinod et al. 2006)).

$\Delta$ 9-THC and synthetic CB<sub>1</sub> agonists also induce region-specific alterations in brain tissue eCB content. For example, chronic  $\Delta$ 9-THC increases AEA (but not 2-AG) in limbic forebrain tissue and increases 2-AG (but not AEA) in the hippocampus, brainstem, and cerebellar tissue (Di Marzo et al. 2000; Gonzalez et al. 2004a; Castelli et al. 2007). In vivo microdialysis studies demonstrate that acute CB<sub>1</sub> agonist exposure increases 2-AG but decreases AEA levels in the rat hypothalamus (Bequet et al. 2007), and preliminary evidence from human clinical research studies also points to cannabinoid-induced increases in 2-AG and decrements in AEA production (Leweke et al. 2007; Morgan et al. 2013).

Chronic nicotine exposure also induces region-specific disruptions in brain tissue eCB content, with increased AEA (but not 2-AG) levels evident in limbic forebrain and caudate but decreased AEA and 2-AG levels in the cortex (Gonzalez et al. 2002). In vivo microdialysis studies demonstrate nicotine-induced increases in both 2-AG and AEA in the VTA and a sensitization of nicotine-induced 2-AG, but not AEA, formation results from chronic nicotine exposure (Buczynski et al. 2013). This enhancement of nicotine-induced VTA 2-AG formation results in diminished inhibitory constraint of VTA cell excitability, thereby enhancing nicotine-induced elevations in mesolimbic DA levels (Buczynski et al. 2016). Interestingly, while VTA 2-AG levels are increased by both voluntary self-administration and response-independent forced nicotine administration, VTA AEA levels are increased only by voluntary self-administration. Together with evidence of distinct eCB responses to self-administered vs. forced alcohol exposure (Caille et al. 2007; Ferrer et al. 2007; Alvarez-Jaimes et al. 2009), these observations suggest that brain eCB production can be influenced by activity of neural systems involved in the motivation for drug consumption, in addition to drug-related pharmacological effects.

Opiates also induce differential effects on brain 2-AG and AEA levels. Chronic morphine dose dependently reduces tissue 2-AG content in the striatum, cortex, hippocampus, hypothalamus, and limbic forebrain, while increased AEA content is observed in these regions (Vigano et al. 2003, 2004). Consistently, in vivo microdialysis studies demonstrate that heroin self-administration significantly increases interstitial AEA levels but decreases interstitial 2-AG levels in the nucleus accumbens (Caille et al. 2007).

In general, psychostimulants induce more subtle alterations in brain eCB levels as compared with the drugs described above (Zlebnik and Cheer 2016). Early studies reported that acute high-dose cocaine administration induces a subtle but significant increase in forebrain 2-AG content in mice (Patel et al. 2003), while chronic cocaine induces comparably subtle decreases in forebrain 2-AG content in rats (Gonzalez et al. 2002), though neither 2-AG nor AEA content is altered in other regions following acute or chronic cocaine exposure (Patel et al. 2003; Gonzalez et al. 2002). Similarly, cocaine self-administration does not alter either 2-AG or AEA content in nucleus accumbens microdialysates (Caille et al. 2007). However, recent studies provide some evidence of psychostimulant-induced alterations in eCB levels and processing. For example, cocaine self-administration is reported to

induce increased cerebellar AEA content; decreased 2-AG content in the frontal cortex, hippocampus, and cerebellum; and an increased ratio of DAGLa/MAGL expression in the hippocampus (Bystrowska et al. 2014; Rivera et al. 2013). Further, sensitization of the motor-activating effects of cocaine is associated with altered eCB metabolic enzyme expression in the cerebellum (Palomino et al. 2014), and detoxified cocaine addicts present significant increases in plasma AEA and decreases in plasma 2-AG content (Pavon et al. 2013).

These collective findings indicate that cannabinoids, ethanol, nicotine, and opiates can alter brain eCB content, consistent with substantial evidence of a CB<sub>1</sub> receptor influence on the behavioral effects produced by these drugs. Although there is relatively less information on psychostimulant-induced alterations in brain eCB content, the modest effects that have been reported are consistent with the subtle disruptions in psychostimulant-induced behaviors observed following CB<sub>1</sub> receptor antagonism.

eCBs are rapidly degraded, and thus strategies that reduce eCB clearance have been employed as a means to further investigate the eCB influence on drug reward. Most investigations have focused on the effects of FAAH inhibition because selective tools for inhibiting MAGL and other eCB clearance enzymes were not available until recently. Such studies have shed light on important species differences that confound the overall conclusions that can be made from existing data. For example, FAAH inhibition in mice increases nicotine reward in the CPP paradigm (Merritt et al. 2008; Muldoon et al. 2013), though in rats, FAAH inhibition prevents nicotine-induced CPP, diminishes nicotine self-administration, and blunts nicotine-induced increases in NAc DA release (Scherma et al. 2008). The potentiation of nicotine reward in mice by FAAH inhibition is CB<sub>1</sub>R mediated, whereas the reduction in nicotine reward in rats results from activation of PPAR- $\alpha$  by non-cannabinoid lipids such as oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) that are hydrolytically cleared by FAAH (Melis and Pistis 2014). FAAH inhibition also produces distinct species-related alterations in alcohol consumption, with increased intake observed in mice but not rats (Blednov et al. 2007; Vinod et al. 2008; Hansson et al. 2007; Cippitelli et al. 2008). The mechanisms underlying these differences are not understood. Brain region-specific disruptions in FAAH activity may be an important factor in regard to alcohol reward as inhibition of FAAH activity specifically in the PFC results in increased alcohol consumption, and rats selectively bred for high alcohol intake and preference are characterized by reduced FAAH activity specifically in the PFC (Hansson et al. 2007; Cippitelli et al. 2008). The effects of FAAH inhibition on opiate and psychostimulant reward have primarily been studied in rats. FAAH inhibition does not alter morphine- or cocaine-induced disruptions in VTA DA cell firing or the self-administration of either drug (Justinova et al. 2008a; Luchicchi et al. 2010). However, FAAH inhibition diminishes cocaine-induced alterations in NAc medium-spiny neuron activity (Luchicchi et al. 2010), and this may contribute to enhanced sensitization of both cocaine-induced motor activity and mesolimbic dopamine responses following repeated cocaine exposure (Mereu et al. 2013). Other studies have investigated the effects of putative eCB transport inhibitors

such as AM404 and VDM11, and the findings thus far suggest that these compounds produce subtle and inconsistent effects on nicotine and cocaine reward (Scherma et al. 2012; Gamaledin et al. 2011, 2013; Vlachou et al. 2008).

While growing evidence implicates ECS influences in the modulation of acute drug reward, additional efforts are needed to further clarify the nature of eCB disruptions caused by different classes of abused drugs and the neural mechanisms through which these eCB influences are mediated. Selective inhibitors of 2-AG clearance have recently been developed, but studies are still in their infancy, so there are presently no published reports on the effects of enhanced 2-AG tone on drug reward and related physiological events. As such there remains a substantial gap of knowledge given the prominent 2-AG influence on neural signaling and plasticity related to both drug and natural rewards. Nevertheless, the role of the CB<sub>1</sub>R in drug reward is unequivocal. Although there is evident complexity related to the effects produced by eCB clearance inhibition (producing discrete modulation of eCB tone in specific synapses/circuits as compared with broad CB<sub>1</sub>R activation by exogenous CB<sub>1</sub>R agonists), the extant evidence strongly supports an eCB influence on the sensitivity to and motivation for several drugs of abuse.

## **7 Overview of Drug Dependence, Addiction, and Withdrawal**

The transition from intermittent and controlled drug use to compulsive forms of drug seeking and drug taking that characterize addiction is influenced by a number of factors. Substantial evidence implicates genetic influences in the development of substance use disorders and pathological forms of eating, sexual behavior, and gambling (Ducci and Goldman 2012). A crucial role for epigenetic mechanisms driving lasting changes in addiction-related gene expression is also increasingly recognized (Nestler 2014). Additionally, long-term drug exposure induces lasting neuroadaptations that alter the motivational mechanisms that propel drug seeking and use. Although initial drug use is motivated by the hedonic effects of drug consumption, prolonged drug exposure results in progressive blunting of reward system function that can motivate consumption of increasingly larger amounts of drug. Evidence suggests this results in part from decreased function of the mesolimbic DA system and its output to the ventral pallidum. Escalated frequency and amount of drug consumption lead to a dependent state wherein negative affective symptoms emerge during drug abstinence (e.g., dysphoria, anxiety, irritability). These negative emotional states arise from the recruitment of stress-signaling systems within the extended amygdala (such as corticotropin-releasing factor and dynorphin) and dysregulation of systems that constrains these responses (such as neuropeptide Y and nociceptin) (Koob and Volkow 2010). Renewed drug consumption alleviates these negative affective states, and this is conceptualized to contribute to compulsive drug use through negative reinforcement mechanisms

(Koob and Volkow 2010). Superimposed on these processes is a dysregulation of corticostriatal mechanisms contributing to stimulus response learning, conditioned reinforcement, and incentive motivation resulting in a narrowed focus on drug seeking at the expense of natural rewards (Kalivas and Volkow 2005; Everitt et al. 2008). eCBs exert prominent modulatory influence in the extended amygdala and corticostriatal circuits implicated in the etiology of addiction, and as described below, increasing evidence suggests that preexisting genetic influences on the ECS and/or drug-induced dysregulation of eCB function may participate in the development and maintenance of addiction. The following sections consider the consequences of chronic drug exposure on eCB signaling within the reward circuitry and related disruptions in synaptic plasticity, affective state, and learning and memory mechanisms related to extinction and relapse.

## 8 Evidence of Altered ECS Function Following Chronic Drug Exposure

It stands to reason that chronic *Cannabis* use induces dysregulation of brain cannabinoid receptors' availability and function. In vivo PET imaging studies in humans have revealed downregulation of brain CB<sub>1</sub>R binding that correlates with the duration of prior *Cannabis* use, with particularly robust decrements observed in the temporal lobe, anterior and posterior cingulate cortex, and nucleus accumbens (Hirvonen et al. 2013; Ceccarini et al. 2015). These decrements in CB<sub>1</sub>R availability appear to progressively recover with prolonged *Cannabis* abstinence. A similar profile of decreased brain CB<sub>1</sub>R function and posttreatment recovery has been consistently reported in rodents given chronic CB<sub>1</sub>R agonist exposure (Breivogel et al. 1999; Sim et al. 1996). Recent experiments employing stochastic optical reconstruction microscopy (STORM) demonstrate that chronic exposure to clinically relevant doses of  $\Delta^9$ -THC results in a startling loss of CB<sub>1</sub>R on terminals of perisomatically projecting GABA interneurons in the mouse hippocampus and internalization of the remaining CB<sub>1</sub>R (Dudok et al. 2015). The resulting deficits in inhibitory CB<sub>1</sub>R control over hippocampal GABA release persisted during several weeks of  $\Delta^9$ -THC abstinence, and this may underlie the enduring loss of hippocampal LTP in rodents and memory deficits in humans evident following chronic cannabinoid exposure (Puighermanal et al. 2012). Surprisingly little is known of the effect of chronic cannabinoid exposure on other facets of ECS function. Chronic cannabinoid exposure increases enzymatic clearance of AEA and reduces brain tissue AEA content in rodents (Di Marzo et al. 2000; Schlosburg et al. 2009), and frequent *Cannabis* smokers present decreased AEA and increased 2-AG levels in the blood (Leweke et al. 2007; Morgan et al. 2013), though increased serum AEA levels are evident following at least 6 months of *Cannabis* abstinence (Muhl et al. 2014). The contribution of these disruptions to *Cannabis* use disorder and related physiological and behavioral disruptions is presently



unexplored. However, as discussed below, eCBs provide important homeostatic constraint over emotional state (Lutz 2009) and sleep function (Murillo-Rodriguez et al. 2011), and it's conceivable that  $\Delta^9$ -THC-induced impairment of eCB signaling contributes to negative emotional states and sleep disturbances present during protracted *Cannabis* abstinence (Budney et al. 2001; Gates et al. 2015).

Chronic exposure to non-cannabinoid drugs also disrupts eCB signaling and processing. Chronic alcohol exposure in rodents alters eCB-related gene expression in a manner sensitive to the intermittent nature of alcohol exposure and post-alcohol abstinence period (Serrano et al. 2012) and downregulates CB<sub>1</sub>R expression and function (Mitrirattanakul et al. 2007; Ceccarini et al. 2013). Postmortem studies of alcohol-dependent humans also demonstrate disrupted CB<sub>1</sub>R expression in the ventral striatum and cortical regions (Vinod et al. 2010), and in vivo imaging studies demonstrate decreased CB<sub>1</sub>R availability in heavy drinking alcoholics that persist for at least 1 month of abstinence (Hirvonen et al. 2013; Ceccarini et al. 2014) (but see Neumeister et al. (2012)). Although a potential contribution of *CNR1* gene variants to these observations cannot be excluded, a common interpretation based on animal studies is that these CB<sub>1</sub>R adaptations in alcoholic humans are a consequence of prolonged alcohol-induced increases in brain eCB levels. This is supported by evidence of transient recovery (and perhaps eventual upregulation) of CB<sub>1</sub>R function in humans during protracted alcohol abstinence (Vinod et al. 2006; Mitrirattanakul et al. 2007). In rodents, chronic nicotine exposure induces distinct age-related disruptions in CB<sub>1</sub>R binding, with increased levels evident in the PFC, VTA, and hippocampus of adolescent but not adult rats (Werling et al. 2009), and increased hippocampal and decreased striatal CB<sub>1</sub>R binding in adult rats during protracted nicotine abstinence (Marco et al. 2007). Few studies have investigated altered CB<sub>1</sub>R binding following chronic opiate or psychostimulant exposure, but findings in rodents implicate impaired CB<sub>1</sub>R function in the development and expression of opiate dependence (Rubino et al. 1997; Cichewicz et al. 2001) and demonstrate that chronic cocaine increases CB<sub>1</sub>R binding in dorsal striatum, NAc, and cortical areas (Adamczyk et al. 2012a). Interestingly, detoxified cocaine addicts present significant increases in plasma AEA and decreases in plasma 2-AG content (Pavon et al. 2013), but the functional consequence of these disturbances is not known. Overall, accruing data suggests that long-term exposure to a variety of drug classes compromises eCB processing and CB<sub>1</sub>R expression and function. As discussed below, these perturbations may contribute to aberrant neural signaling during acute and protracted drug abstinence.

## 9 eCB Influence on Physical Withdrawal Symptoms

In dependent individuals, drug abstinence is associated with transient physical or somatic symptoms that can persist for several days. The intensity of these symptoms varies between drug classes, with severe somatic withdrawal signs evident during abstinence from opiates and alcohol and substantially less severe symptoms

during abstinence from nicotine, cocaine, and cannabinoids (West and Gossop 1994). Early conceptualizations of addiction are focused on the relief from somatic withdrawal symptoms as the motivational basis for drug use by dependent individuals (Wikler 1948; Dole 1965; Dole et al. 1966), though more recent evidence suggests that alleviation of somatic withdrawal is not a major factor contributing to relapse (Heilig et al. 2010; Hershon 1977). In fact the greatest susceptibility to drug relapse typically occurs well after the abatement of somatic withdrawal symptoms. Nonetheless, there is value in understanding the mechanisms contributing to somatic withdrawal symptoms for the development of palliative therapies for dependent individuals and avoidance of medically serious conditions associated with acute drug detoxification.

Chronic alcohol exposure results in significant downregulation of CB<sub>1</sub> receptor expression and function in many brain regions (Basavarajappa et al. 1998; Basavarajappa and Hungund 1999; Vinod et al. 2006, 2010; Moranta et al. 2006; Mitrirattanakul et al. 2007; Ceccarini et al. 2013, 2014; Hirvonen et al. 2013; Neumeister et al. 2012) and leads to disruptions in brain tissue AEA and 2-AG content (Vinod et al. 2006, 2012; Gonzalez et al. 2002, 2004b; Malinen et al. 2009; Rubio et al. 2007). Clinical research has revealed a correlation between the severity of alcohol withdrawal symptoms and polymorphisms in the gene encoding CB<sub>1</sub> receptors (Schmidt et al. 2002), and alcohol withdrawal severity is increased in CB<sub>1</sub> receptor knockout mice (Naassila et al. 2004). Accordingly, it is possible that impaired CB<sub>1</sub> signaling contributes to the intensity of physical symptoms of alcohol withdrawal. In this regard, it is notable that FAAH knockout mice exhibit significantly diminished alcohol withdrawal-related seizures relative to wild-type mice (Vinod et al. 2008; Blednov et al. 2007). The somatic symptoms of alcohol withdrawal, including seizure activity, result primarily from excessive excitatory glutamate signaling (De Witte et al. 2003). Interestingly, AEA modulates NMDA receptor function (Hampson et al. 1998) and reduces NMDA- and electroshock-induced seizures (Hayase et al. 2001; Wallace et al. 2002). Therefore, enhancement of AEA tone may provide protection against alcohol withdrawal-related seizures, though more research is necessary to support this possibility.

Chronic nicotine exposure does not appear to alter brain CB<sub>1</sub> receptor expression (Gonzalez et al. 2002), and precipitated somatic withdrawal signs in nicotine-dependent mice are not altered by CB<sub>1</sub> receptor deletion or moderate doses of the CB<sub>1</sub> receptor antagonist SR141716A (Castane et al. 2002, 2005; Cossu et al. 2001; Balerio et al. 2004; Merritt et al. 2008). In contrast, the Manzanares group observed that somatic indices of nicotine withdrawal are absent in CB<sub>2</sub> knockout mice and are attenuated in WT mice by treatment with the CB<sub>2</sub> antagonist AM630 (Navarrete et al. 2013), though no genotypic differences in somatic withdrawal were evident following a shorter duration of nicotine exposure (7 days vs. 14 days) (Ignatowska-Jankowska et al. 2013). This suggests a potential CB<sub>2</sub> influence in the somatic symptoms of withdrawal following long-term nicotine exposure. Acute  $\Delta^9$ -THC administration decreases somatic symptoms of nicotine withdrawal (Balerio et al. 2004, 2006). Moreover, nicotine-dependent MAGL knockout mice exhibit diminished precipitated withdrawal signs, and the MAGL inhibitor JZL184

dose-dependently reduces somatic and aversive signs of precipitated nicotine withdrawal in dependent mice through a CB<sub>1</sub> receptor-dependent mechanism (Muldoon et al. 2015). This same study also points to an association between MAGL gene polymorphisms and the severity of nicotine withdrawal symptoms in humans. In contrast, acute FAAH inhibition does not diminish somatic nicotine withdrawal symptoms in rats (Cippitelli et al. 2011), while somatic symptoms of withdrawal are worsened in mice by FAAH inhibition, though this may occur through non-CB<sub>1</sub> mechanisms (Merritt et al. 2008). Collectively these findings suggest that enhanced CB<sub>1</sub> receptor signaling resulting from MAGL inhibition may provide therapeutic benefit for the somatic symptoms of nicotine withdrawal.

Chronic opiate exposure alters CB<sub>1</sub> receptor expression and function (Rubino et al. 1997; Cichewicz et al. 2001; Smith et al. 2007), and this appears to play a role in the development and expression of opiate dependence. For example, the somatic symptoms of opiate withdrawal are significantly reduced in CB<sub>1</sub> knockout mice or WT mice receiving chronic CB<sub>1</sub> antagonist treatment concurrent with chronic morphine administration (Ledent et al. 1999; Lichtman et al. 2001; Mas-Nieto et al. 2001; Rubino et al. 2000), and it has long been recognized that  $\Delta^9$ -THC effectively reduces the intensity of somatic symptoms of opiate withdrawal (Bhargava 1976; Hine et al. 1975). These findings suggest that chronic opiate exposure dysregulates CB<sub>1</sub> receptor or eCB function in a manner that contributes to elicitation of somatic symptoms during drug withdrawal. Consistent with this hypothesis, administration of  $\Delta^9$ -THC, exogenous AEA, or exogenous 2-AG attenuates the intensity of somatic withdrawal symptoms (Vela et al. 1995; Yamaguchi et al. 2001; Gamage et al. 2015), and high doses of the selective MAGL inhibitor JZL184 significantly reduce all indices of somatic withdrawal in opiate-dependent mice, while the selective FAAH inhibitor PF-3845 reduces only a subset of withdrawal responses (Ramesh et al. 2011, 2013; Gamage et al. 2015). Perhaps more importantly, a novel dual inhibitor exhibiting >100-fold greater potency at FAAH vs. MAGL (SA-57) (Niphakis et al. 2012) significantly reduces somatic indices of precipitated withdrawal (Gamage et al. 2015). This is an important observation given that high-dose JZL184 exposure elicits some cannabimimetic effects (Long et al. 2009a), and repeated high-dose JZL184 administration induces functional CB<sub>1</sub> receptor tolerance and results in cannabinoid dependence (Schlosburg et al. 2010); these effects may limit the clinical viability of selective MAGL inhibition for treatment of opiate withdrawal. In contrast, SA-57 doses that efficaciously reduce opiate withdrawal do not produce cannabimimetic effects (Ramesh et al. 2013), and the moderate MAGL inhibition induced by this compound is not likely to induce CB<sub>1</sub> receptor downregulation or cannabinoid dependence (Kinsey et al. 2013; Ghosh et al. 2013). However, a caveat to these findings is that while SA-57 attenuates somatic aspects of withdrawal, its administration does not prevent the aversive aspects of withdrawal as measured by the conditioned place aversion assay in mice (Gamage et al. 2015). Nonetheless, these collective findings suggest that modest pharmacological enhancement of eCB signaling may provide palliative effects for the physical symptoms of opiate withdrawal.

## 10 Stress Responsivity

Substantial clinical and preclinical data indicate that various forms of stress are involved in the etiology and maintenance of addiction. High levels of stress often precede the development of substance use disorders (Jose et al. 2000; Richman et al. 1996; Rospenda et al. 2000), and stress-related increases in glucocorticoid signaling increases the acquisition of drug self-administration by rodents (Goeders 2002; Goeders and Guerin 1996; Koob and Kreek 2007; Vengeliene et al. 2003). Consistently, evidence suggests that both stress- and drug-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis sensitizes the function of reward pathways through glucocorticoid mechanisms (Piazza and Le Moal 1998; Rouge-Pont et al. 1995, 1998; Tidey and Miczek 1997). However, long-term drug use results in a blunting of reward system function, increased influence of CNS stress systems, and dysregulation of the HPA axis that is theorized to induce an allostatic shift in motivational influence that propels an escalation of drug consumption (Koob and Kreek 2007; Le Moal 2009; Koob and Le Moal 1997).

It is now well established that eCB signaling serves a homeostatic role in the constraint of HPA axis activation (Cota 2008; Gorzalka et al. 2008; Morena et al. 2016; also see chapter “Endocannabinoids, Stress, and Negative Affect” that details this function in greater depth). Stress-induced glucocorticoid secretion increases eCB production in several regions implicated in drug dependence and addiction including the amygdala, hippocampus, PFC, hypothalamic nuclei, and periaqueductal gray (Di et al. 2003, 2005, 2009; Hill et al. 2010a; Hohmann et al. 2005; Patel et al. 2004, 2005). Strong evidence demonstrates that eCB-mediated CB<sub>1</sub> activation in these and other regions constrains stress-induced HPA axis activation and resultant increases in glucocorticoid secretion (Barna et al. 2004; Cota et al. 2007; Di et al. 2003; Manzanares et al. 1999; Patel et al. 2004; Uriguen et al. 2004; Wade et al. 2006). In contrast, stress-induced reductions in AEA content are consistently observed in the amygdala, PFC, and hippocampus (Hill et al. 2008, 2009; Patel et al. 2005; Rademacher and Hillard 2007), and this is theorized to contribute to stress responsivity through a release of tonic HPA axis inhibition (Patel et al. 2004). Regardless of the specific mechanism that prevails, it is clear that eCB signaling participates in the constraint of HPA axis activation and may contribute to the termination of stress responses.

In this regard, it is conceivable that disrupted eCB-mediated plasticity induced by long-term drug exposure contributes to a persistent dysregulation of HPA axis function and increases stress sensitivity associated with addiction (Koob and Kreek 2007; Le Moal 2009; Koob and Le Moal 1997). Because stress exposure is implicated in the development of addiction (Goeders 2002; Goeders and Guerin 1996; Jose et al. 2000; Koob and Kreek 2007; Richman et al. 1996; Rospenda et al. 2000; Vengeliene et al. 2003), it is notable that stress can alter eCB-mediated plasticity in addiction-related brain regions (Natividad et al. 2017). For example, prolonged stress exposure impairs eCB-mediated DSI, LTD, and fEPSPs in the NAc (Wang et al. 2010), attenuates eCB-mediated DSE and DSI in the PVN

(Wamstecker et al. 2010), and enhances 2-AG-mediated DSI in the basolateral amygdala (Patel et al. 2009). Similarly, establishment of conditioned fear increases the efficacy of DSE and DSI in the central nucleus of the amygdala (Kamprath et al. 2011).

## 11 Affective Disruptions

In addition to transient somatic symptoms (West and Gossop 1994), withdrawal from most drugs of abuse is associated with increased negative affective symptoms such as anxiety and depression (Alling et al. 1982; Coffey et al. 2000; Janiri et al. 2005; Nunes and Levin 2004; Nunes et al. 2004). Withdrawal-related negative affective states can persist for months and in some cases years during protracted abstinence, and the severity of these symptoms is closely associated with susceptibility to relapse (Annis et al. 1998; Miller and Harris 2000). Moreover, there is a prevalent comorbidity between affective disorders and substance use disorders, and affective disruption may be an antecedent to addiction (Bruijnzeel et al. 2004; Castle 2008; Conway et al. 2006; Pani et al. 2010; Schuckit 2006). As discussed in detail in chapter “Lipid Mediators in the Regulation of Emotions, Memory and Cognitive Functions” of this book, substantial evidence implicates the ECS in the regulation of affective state, and dysfunctional eCB signaling is associated with increased anxiety and depression. In light of the evidence for drug-induced changes in brain eCB levels and eCB-mediated synaptic regulation, it is conceivable that dysregulated eCB function contributes to affective disturbances associated with drug dependence and protracted withdrawal. Several studies have begun to investigate an involvement of eCB signaling in withdrawal-related affective disruptions (or the efficacy of eCB manipulations as treatments for these disruptions), and as described below, these studies have predominantly focused on anxiety-like behavior that accompanies withdrawal from chronic exposure to drugs of abuse and highly palatable food.

In tobacco-dependent individuals, smoking cessation leads to withdrawal symptoms that persist for several months (Hughes 2007; Hughes et al. 1991; Markou 2008). Symptoms such as dysphoria/aversion, anxiety, and irritability contribute to negative reinforcement mechanisms that perpetuate nicotine addiction (Hughes et al. 1991; Koob and Volkow 2010; Piper et al. 2011; Allen et al. 2008; Rose et al. 2010), and the severity of these symptoms is a predictor of increased relapse risk (Piasecki et al. 2003a, b, c; al’Absi et al. 2004). Because eCB signaling is implicated in the initiation and maintenance of nicotine self-administration, it is possible that persistent disruptions in eCB signaling contribute to the negative affective states of nicotine withdrawal. However, few studies have investigated this possibility.

The Maldonado group reported that CB<sub>1</sub> knockout mice exhibit more robust anxiety-like behavior during nicotine withdrawal than similarly treated wild-type mice do (Bura et al. 2010). However, nicotine-naïve CB<sub>1</sub> knockout mice also

exhibit greater anxiety-like behavior than wild types (Bura et al. 2010; Haller et al. 2002; Martin et al. 2002; Uriguen et al. 2004), and this innate phenotype clouds the determination as to whether or not withdrawal-related anxiety-like behavior is exacerbated by CB<sub>1</sub> receptor deletion. In rats, significant increases in anxiety-like behavior are evident after 36 h of spontaneous nicotine withdrawal, and this is dose-dependently reversed by treatment with the FAAH inhibitor URB597 at doses that do not alter anxiety-like behavior in nicotine-naïve rats (Cippitelli et al. 2011). This is temporally correlated with significant increases in AEA content in the amygdala, hypothalamus, and prefrontal cortical tissue, though no significant alterations in tissue 2-AG content are evident regardless of region analyzed (Cippitelli et al. 2011). It is somewhat surprising that FAAH inhibition ameliorates anxiety-like behavior at a time when AEA levels appear to be increased in brain regions known to modulate anxiety-like behaviors. However, while increased AEA content in these regions may reflect a compensatory response to withdrawal, it is possible the effect magnitude is insufficient to fully constrain withdrawal-related disturbances underlying increased anxiety. Thus, the bolstering of this response through FAAH inhibition provides more efficacious reversal of withdrawal-related neural dysfunction (Cippitelli et al. 2011). It is worth noting, however, that disruptions in postmortem tissue AEA content may not provide a precise index of signaling-competent AEA levels *in vivo* (Buczynski and Parsons 2010), and a more clear *in vivo* view of withdrawal-related disruptions in regional eCBs may require further study. Nonetheless, these findings provide compelling evidence that acute FAAH inhibition ameliorates increased anxiety-like states during protracted nicotine withdrawal.

The putative eCB uptake inhibitor AM404 has been found to attenuate nicotine withdrawal-related increases in immobility in the Porsolt forced swim test (Mannucci et al. 2011). Increased immobility in this test is often interpreted as a form of despair or hopelessness, and this paradigm is commonly used as a screen for antidepressant efficacy. Accordingly, withdrawal-related increases in immobility in the Porsolt test may reflect a form of depressive-like behavior, and the effects of AM404 may thus reflect a beneficial effect of enhanced eCB signaling on withdrawal-related depressive-like states (Mannucci et al. 2011). However, AM404 also dose-dependently reduced immobility in nicotine-naïve mice in this study, and as such a preferential influence of this eCB clearance inhibitor on withdrawal-related behaviors is unclear. Moreover, modeling depressive-like behavior in rodents is best accomplished through the use of several paradigms (Abelaira et al. 2013; Yan et al. 2010), and further work is clearly needed to evaluate possible eCB influences on nicotine withdrawal-related depression-like behavior.

Post-traumatic stress disorder (PTSD) is an anxiety disorder with particularly high prevalence among individuals with alcohol use disorders (Kessler et al. 1995). The fear-potentiated startle (FPS) paradigm is often used to model PTSD-like behaviors (Grillon 2002; Hijzen et al. 1995). Rodent lines selectively bred for high alcohol consumption exhibit significantly greater FPS than corollary lines bred for low alcohol consumption (McKinzie et al. 2000; Barrenha and Chester

2007), and these rodent lines may thus provide models for characterizing mechanisms contributing to the anxiety, alcohol use disorders, and intersection of these pathologies. In this regard, the nonselective FAAH inhibitor LY2183240 selectively reduces FPS in high alcohol-preferring mice but not low alcohol-preferring mice (Powers et al. 2010). However, LY2183240 effects on FPS were evident only following repeated FPS testing and not upon first exposure to the FPS paradigm, suggesting that FAAH inhibition facilitates the extinction of learned fear responses in high alcohol-preferring mice, consistent with substantial evidence that FAAH inhibition generally accelerates extinction of aversive memories (Gunduz-Cinar et al. 2013). LY2183240 also enhanced the expression of alcohol-induced conditioned place preference without altering alcohol consumption itself. This suggests that FAAH inhibition influences memory-related processes regulating the expression of conditioned fear and conditioned alcohol reward in animals genetically predisposed toward high alcohol consumption. Recent evidence also points to the efficacy of the more selective FAAH inhibitor URB597 for attenuating anxiety-like behavior evident in rats following acute, high-dose alcohol administration (Cippitelli et al. 2008). In this study, URB597 did not alter alcohol self-administration, cue-induced alcohol-seeking, or stress-induced alcohol-seeking behavior. Collectively, these findings suggest that FAAH inhibition may be beneficial for reducing alcohol-related anxiety-like behavior, though further investigation is warranted, particularly evaluations of persistent anxiety-like behavior associated with protracted withdrawal in alcohol-dependent subjects.

In humans, the chronic use of the NMDA glutamate receptor antagonist phencyclidine (PCP) evokes both positive and negative symptoms of schizophrenia and many of the characteristic cognitive deficits associated with the disease (Murray 2002). In rats, withdrawal from sub-chronic PCP exposure is associated with reduced social interaction (Lee et al. 2005; Seillier and Giuffrida 2009; Seillier et al. 2013), a phenotype often interpreted as an anxiety-like behavior (Lapiz-Bluhm et al. 2008) and reminiscent of negative symptoms of schizophrenia. PCP withdrawal is associated with reduced AEA content in the amygdala and prefrontal cortex (Seillier and Giuffrida 2009; Seillier et al. 2013), and withdrawal-related reductions in social interaction are reversed by the FAAH inhibitor URB597 through a CB<sub>1</sub>-reliant mechanism (Seillier and Giuffrida 2009; Seillier et al. 2013).

Similar to drug addiction, eating disorders and pathological obesity are conceptualized as chronic relapsing conditions with alternating periods of abstinence (e.g., dieting) and relapse (compulsive overeating) (Corwin and Grigson 2009; Cottone et al. 2009a; Epstein and Shaham 2010; Johnson and Kenny 2010; Parylak et al. 2011). Rats given scheduled intermittent access to highly palatable sucrose food exhibit a withdrawal state upon forced abstinence from the palatable food, including increased anxiety-like behavior and decreased motivation for standard lab food (Cottone et al. 2008, 2009a, b). These effects are most evident during early abstinence and abate within 2–3 days. Moreover, these animals exhibit robust excessive food consumption of the palatable food when given renewed access. The negative affective state during abstinence and the excessive consumption upon renewed access to palatable food are each mediated by increased CRF1 signaling in



the amygdala (Iemolo et al. 2013), similar to withdrawal-related negative affective states and compulsive drug consumption evident in drug-dependent subjects (Koob et al. 2014; Koob 2010). This suggests that dysregulation of amygdalar signaling is a common factor contributing to pathological motivation for and consumption of food and drugs. Interestingly, 2-AG content is significantly increased in the CeA following 4 days' abstinence from palatable food, and this occurs in conjunction with increased CeA CB<sub>1</sub> mRNA and CB<sub>1</sub> protein expression (Blasio et al. 2013). Moreover, either systemic or intra-CeA administration of the CB<sub>1</sub> antagonist rimonabant precipitates an anxiogenic-like state in animals with a history of palatable food consumption but not in rats given only with standard lab chow. This suggests that increased 2-AG-mediated CB<sub>1</sub> signaling in CeA counteracts a withdrawal-like state in rats during abstinence from palatable food (Blasio et al. 2013).

## 12 Synaptic Plasticity

Substantial evidence demonstrates that exposure to most drugs of abuse dysregulates synaptic plasticity mechanisms in a variety of brain regions involved in the evolution of addiction (Hyman et al. 2006; Luscher and Malenka 2011). Acute exposure to alcohol, nicotine, morphine, or cocaine induces transient loss of LTP at inhibitory GABAergic synapses in the VTA (Niehaus et al. 2010; Liu et al. 2005; Melis et al. 2002; Nugent et al. 2007) and enhanced excitatory strength onto VTA DA neurons (Borgland et al. 2004; Faleiro et al. 2004; Saal et al. 2003). This tandem potentiation of excitatory transmission and loss of inhibitory LTP at VTA synapses serves to heighten midbrain DA cell excitability, increasing dopaminergic signaling throughout the mesocorticolimbic system.

As described in detail in the chapter titled "Endocannabinoid-Dependent Synaptic Plasticity in Striatum", eCBs and CB<sub>1</sub> receptors are implicated in several forms of synaptic plasticity involving presynaptic expression mechanisms (Lovinger 2008; Heifets and Castillo 2009). Both short- and long-term forms of eCB-mediated synaptic plasticity occur in many brain regions critically involved in various stages of the addiction cycle including the NAc, VTA, amygdala, prefrontal cortex, hippocampus, and dorsal striatum. Accordingly, drug-induced disruption of these mechanisms may contribute to aberrations in learning, memory, and affective state that propel addiction. Although a full description of these processes is provided in "Endocannabinoid-Dependent Synaptic Plasticity in Striatum", it is worth noting here that exposure to several classes of abused drugs dysregulates eCB-mediated forms of synaptic plasticity. For example, eCB-mediated LTD of excitatory and inhibitory signaling in the rodent NAc and hippocampus is abolished following a 7-day treatment with either  $\Delta^9$ -THC or the synthetic CB<sub>1</sub> agonist WIN 55,212-2 (Hoffman et al. 2003; Mato et al. 2004), correlating with decreased sensitivity to CB<sub>1</sub> inhibition of both excitatory and inhibitory signaling.

Both acute and chronic alcohol exposure substantially reduces a CB<sub>1</sub>-dependent form of plasticity that results in long-lasting disinhibition of striatal output neurons (Clarke and Adermark 2010; Adermark et al. 2011) and reduces eCB-mediated LTD at inhibitory striatal synapses (though alcohol-induced disruption of eCB-LTD at excitatory synapses has not been observed) (Clarke and Adermark 2010). Because the dorsal striatum is involved in reward-guided learning and habitual behavior (Volkow et al. 2007; Yin et al. 2008), it is possible that these alcohol-induced disruptions in eCB-LTD contribute to maladaptive habitual behavior that contributes to addiction. Consistent with this hypothesis, recent work by the Lovinger lab demonstrates that chronic and intermittent alcohol exposure increases 2-AG levels in the dorsolateral striatum (DLS), leading to a compensatory downregulation of CB<sub>1</sub> receptor signaling and loss of CB<sub>1</sub>-mediated LTD at excitatory synapses (DePoy et al. 2013). This was associated with enhancement of DLS-mediated learning processes that may contribute to habitual behaviors.

Cocaine exposure results in the loss of eCB-LTD of evoked excitatory transmission in the NAc (Fourgeaud et al. 2004) and facilitated eCB-LTD of GABAergic signaling at VTA DA synapses (Pan et al. 2008; Fourgeaud et al. 2004; Liu et al. 2005). Collectively, these cocaine-induced disruptions in eCB-LTD result in imbalanced mesolimbic DA function characterized by diminished inhibitory control over VTA DA cell bodies and heightened excitatory signaling in the NAc. Chronic cocaine exposure also results in disruption of eCB-LTD of excitatory transmission in the bed nucleus of the stria terminalis (BNST) (Grueter et al. 2006), a stress-responsive structure wherein excitatory transmission is critically involved in mediating stress-reward interactions and anxiety-like behavior (Delfs et al. 2000; McElligott and Winder 2009). The BNST sends substantial projections to the VTA, and accordingly disruption of BNST plasticity likely influences motivational responses to stress.

Little is known regarding the potential influence of opiate or nicotine exposure on eCB-mediated forms of synaptic plasticity. However, a recent report demonstrated that a history of nicotine self-administration induces CB<sub>1</sub>-dependent LTP at synapses of infralimbic cortex afferents to the BNST (Reisiger et al. 2014). This perturbation may have relevance to many consequences of chronic nicotine exposure, and clear evidence is provided that this neuroplastic change contributes to cue-induced reinstatement of nicotine-seeking behavior (in an animal model of relapse).

As noted above, stress is implicated in the development of addiction (Koob and Kreek 2007), and it is therefore notable that stress can alter eCB-mediated plasticity in addiction-related brain regions. Prolonged exposure to unpredictable stress impairs eCB-mediated DSI, LTD, and fEPSPs in the NAc (Wang et al. 2010), while repeated restraint stress reduces eCB-mediated DSE and DSI in the rat PVN (Wamsteeker et al. 2010) and increases 2-AG-mediated DSI in the mouse basolateral amygdala (Patel et al. 2009). Similarly, establishment of conditioned fear increases the efficacy of eCB-mediated DSE and DSI in the central nucleus of the amygdala (Kamprath et al. 2011). Further, it has recently been shown that acute restraint stress induces a switch from eCB-mediated LTD to eCB-mediated LTP at

synapses of mPFC afferents to the BNST (Glangetas et al. 2013). As previously discussed, the ECS participates in a negative feedback system that limits the expression of anxiety under stressful circumstances and contributes to the suppression of aversive memories. These processes are mediated in part through eCB-mediated synaptic plasticity in the amygdalar nuclei (Kamprath et al. 2011; Lafenetre et al. 2007; Viveros et al. 2007), and disruptions of this eCB-mediated plasticity may contribute to its dysregulated affect (including increased anxiety) associated with protracted drug abstinence.

## 13 Extinction and Relapse

The ECS plays a prominent role in learning and memory processes (Hashimoto et al. 2007; Heifets and Castillo 2009; Marsicano and Lafenetre 2009), and because eCB signaling is disrupted by most drugs of abuse (see above sections), a role for the ECS in learning and memory components of addiction may be hypothesized. As previously reviewed, CB<sub>1</sub> receptors play an important role in the conditioned rewarding effects of alcohol (Houchi et al. 2005; Hungund et al. 2003; Thanos et al. 2005), opiates (Chaperon et al. 1998; Martin et al. 2000; Navarro et al. 2001; Singh et al. 2004), and nicotine (Castane et al. 2002; Forget et al. 2005, 2006; Le Foll and Goldberg 2004; Merritt et al. 2008), with a lesser CB<sub>1</sub> influence reported for the conditioning effects of psychostimulants (Houchi et al. 2005; Martin et al. 2000). Although these behaviors are generally interpreted in the context of drug reward, a CB<sub>1</sub> receptor influence on the associative learning aspects of drug exposure is also likely, which as discussed below may have relevance to the persistent reactivity to drug-related memories that characterize addiction.

### 13.1 Drug Seeking (Relapse)

Drug exposure produces powerful interoceptive effects, and memory of these effects increases the likelihood of continued drug use. With continued drug use, these interoceptive effects become associated with environmental cues to the extent where these drug-associated cues alone can induce craving and thereby propel drug use. This form of drug-related memory is also causal in relapse to drug use following periods of abstinence (Carter and Tiffany 1999; McLellan et al. 2000). Several factors are believed to be causal in drug relapse including craving induced by environments or situations previously associated with drug use (e.g., conditioning factors), acute exposure to the drug itself or a pharmacologically related agent during abstinence (e.g., drug priming), and stressful events.

Recently developed animal models of drug seeking demonstrate an important influence of cannabinoid signaling in the reinstatement of extinguished drug-seeking and drug-taking behaviors. For example,  $\Delta^9$ -THC and various synthetic

CB<sub>1</sub> agonists reinstate drug seeking for cannabinoids (Justinova et al. 2008b; Spano et al. 2004), opioids (De Vries et al. 2003; Fattore et al. 2003, 2005), ethanol (Lopez-Moreno et al. 2004; McGregor et al. 2005), nicotine (Biala and Budzynska 2008; Gamaledin et al. 2012a), and cocaine (De Vries et al. 2001). Conversely, CB<sub>1</sub> receptor antagonism attenuates drug-seeking behavior associated with a variety of abused substances. Rimonabant (SR141716A) significantly reduces operant responding for conditioned cues previously associated with  $\Delta$ 9-THC (Justinova et al. 2008b), heroin (De Vries et al. 2003; Fattore et al. 2003; 2005), nicotine (Cohen et al. 2005; De Vries et al. 2005; Diergaarde et al. 2008), and ethanol (Cippitelli et al. 2005; Economidou et al. 2006). CB<sub>1</sub> antagonism also reduces excessive ethanol intake exhibited following periods of abstinence (an animal model of relapse-like alcohol consumption) (Gessa et al. 2005), and the novel CB<sub>1</sub> antagonist SLV330 reduces both drug- and cue-induced reinstatement of ethanol- and nicotine-seeking behavior (de Bruin et al. 2011). Studies employing site-specific antagonist infusions have uncovered important contributions of CB<sub>1</sub> receptors in the PFC and NAc shell in cue-induced reinstatement of both heroin- and nicotine-seeking behavior, and CB<sub>1</sub> receptors in the BLA appear to contribute to cue-induced nicotine-seeking, but not heroin-seeking, behavior (Alvarez-Jaimes et al. 2008; Kudas et al. 2007). Although CB<sub>1</sub> receptor inactivation produces subtle and inconsistent effects on psychostimulant self-administration as compared with other drugs of abuse, substantial evidence indicates a strong CB<sub>1</sub> receptor influence on the reinstatement of psychostimulant-seeking behavior. CB<sub>1</sub> antagonism attenuates both drug-primed and cue-induced reinstatement of cocaine-seeking (De Vries et al. 2001; Filip et al. 2006; Xi et al. 2006; Adamczyk et al. 2012b) and methamphetamine-seeking behavior in rats (Anggadiredja et al. 2004; Boctor et al. 2007). Further, both drug- and cue-induced reinstatement of cocaine and methamphetamine seeking is attenuated by the negative allosteric CB<sub>1</sub> modulator ORG27569 (Jing et al. 2014). Interestingly, although footshock-induced reinstatement of cocaine seeking is not blocked by either rimonabant or the CB<sub>1</sub> antagonist AM251 (De Vries et al. 2001; Kupferschmidt et al. 2012a), AM251 blocks the reinstatement of cocaine seeking induced by forced swim stress and exogenous CRF administration (Vaughn et al. 2012; Kupferschmidt et al. 2012a), suggesting a CB<sub>1</sub> influence on some forms of stress-induced reinstatement of drug seeking. These latter findings may relate specifically to an AM251-induced modulation of the effects produced by the stress peptide CRF, given that AM251 also attenuates the anxiogenic effects of both cocaine withdrawal (an effect mediated by increased CRF signaling (DeVries and Pert 1998)) and exogenously administered CRF (Kupferschmidt et al. 2012b). However, the mechanisms for this putative interaction are not clear, and these findings are at odds with evidence that CB<sub>1</sub> signaling generally suppresses the physiological and behavioral responses to stress (see discussion below).

Thus, CB<sub>1</sub> receptor signaling is implicated in drug-seeking behavior for a variety of abused substances that differ substantially in pharmacodynamic mechanisms including cannabinoids, opioids, alcohol, nicotine, and psychostimulants. Moreover, CB<sub>1</sub> receptor antagonism blocks both cue- and “prime”-induced

reinstatements of seeking behavior for nondrug rewards such as sucrose and corn oil ((De Vries et al. 2005; Ward et al. 2009), but see Xi et al. (2006)). Accordingly, CB<sub>1</sub> receptor signaling appears to participate in the modulation of conditioned reward in general.

Few studies have characterized the influence of eCB signaling on drug-seeking behavior through more direct manipulations of eCB processing such as the inhibition of hydrolytic clearance mechanisms. Three studies have found that both drug-primed and cue-induced nicotine- and cocaine-seeking behaviors are reduced by URB597 and the less selective FAAH inhibitor PMSF (Forget et al. 2009; Scherma et al. 2008; Adamczyk et al. 2009). This is somewhat surprising given that CB<sub>1</sub> receptor stimulation enhances both nicotine- and cocaine-seeking behavior (Biala and Budzynska 2008; De Vries et al. 2001). However, because tonic eCB production is believed to be low, the inhibition of eCB clearance is anticipated to preferentially amplify eCB signaling in circuits/synapses activated by a given stimulus (in this case, drug-seeking behavior), rather than producing more widespread indiscriminate CB<sub>1</sub> activation as is produced by exogenous CB<sub>1</sub> agonists. Moreover, FAAH hydrolyzes a large variety of fatty acid moieties (Ahn et al. 2008), and it is conceivable that the effects of FAAH inhibition on drug seeking are mediated through actions of non-cannabinoid lipids. In this regard, it's notable that the putative eCB uptake inhibitor VDM11 also attenuates both nicotine- and cue-induced nicotine-seeking behavior (Gamaledin et al. 2011). This latter finding is of interest as unlike URB597, VDM11 elevates AEA levels with reduced effects on non-cannabinoid FAAH substrates that may influence behavior through PPAR $\alpha$  signaling (De Petrocellis et al. 2000; van der Stelt et al. 2006). Similar to the effects of VDM11, the putative eCB uptake inhibitor AM404 dose-dependently attenuates both nicotine- and cue-induced nicotine-seeking behavior, though AM404 did not alter nicotine self-administration itself (Gamaledin et al. 2013). In contrast to the effects on nicotine- and cocaine-seeking behavior, neither URB597 nor AM404 alters either cue- or stress-induced reinstatement of alcohol-seeking behavior (Cipitelli et al. 2007; 2008).

Recent data demonstrate that detoxified alcoholics present significantly lower baseline plasma AEA levels as compared with nondependent social drinkers (Mangieri et al. 2009). Further, a significant negative relationship between resting plasma AEA levels and the severity of cue-induced craving was evident in social drinkers but not alcoholics. In social drinkers, alcohol-related cues significantly increased both craving and plasma AEA levels, and the relative magnitude of cue-induced increases in AEA was significantly correlated with the severity of craving. However, cue-induced changes in AEA were indexed by a percentage change from baseline, and thus this index is substantially influenced by baseline AEA levels (e.g., the same absolute change in AEA content will be reflected as a greater percentage change in subjects with lower vs. higher baseline AEA levels). Accordingly, the positive correlation between cue-induced changes in plasma AEA and craving intensity further supports the importance of baseline AEA levels in cue-induced craving in social drinkers. Interestingly, although alcohol-related cues elicited more intense craving in alcoholics vs. social drinkers, alcoholics did not

present significant cue-induced increases in plasma AEA. Based on these observations, it was concluded that cue-induced increases in plasma AEA contributes to interoceptive signaling that moderates the desire for alcohol in social drinkers. It may also be concluded that deficits in plasma AEA levels confer increased susceptibility to cue-induced alcohol craving. While cue-induced elevations in plasma AEA may contribute to craving responses, it is curious that elevations in AEA were not evident in alcoholics who also presented the greatest level of cue-induced craving. It is conceivable that cue-induced increases in plasma AEA reflect an adaptive response, and its absence in alcoholics somehow contributes to excessive craving responses to alcohol-related cues. Further evaluations in humans are clearly needed to investigate these issues.

### ***13.2 Extinction Learning***

The potent motivational effects of drug-related cues create substantial difficulties during periods of attempted drug abstinence and are causal in the reinstatement of drug intake (e.g., relapse) (Carter and Tiffany 1999). One approach for lessening the motivational impact of drug-associated cues is through extinction learning, wherein a subject learns that a drug-associated cue no longer has predictive value. However, extinction therapy for addiction is generally ineffective for reducing relapse in both humans (Conklin and Tiffany 2002) and rodents (Crombag and Shaham 2002), and it is conceivable that this results from disruptions in the learning mechanisms that override the original association memory (Bouton 2004; Rescorla 1996). The ECS plays a prominent role in memory extinction, particularly the extinction of aversive memory. Substantial evidence demonstrates that CB<sub>1</sub> signaling blockade results in impaired extinction of cued fear memory, contextual fear memory, and fear-potentiated startle and spatial memory under aversive mildly stressful conditions (Marsicano et al. 2002; Suzuki et al. 2004; Chhatwal et al. 2005, 2009; Niyuhire et al. 2007; Varvel et al. 2005; Varvel and Lichtman 2002; Pamplona et al. 2006, 2008). Moreover, recent findings demonstrate that a line of mice selectively bred for high alcohol consumption exhibits excessive fear-potentiated startle responses and that the nonselective FAAH inhibitor LY2183240 facilitates extinction of fear-potentiated startle in these mice but not mice bred for low alcohol consumption (Powers et al. 2010). This suggests that FAAH inhibition influences memory-related processes regulating the expression of conditioned fear in animals genetically predisposed toward high alcohol consumption. However, it has consistently been reported that CB<sub>1</sub> inactivation does not alter the extinction of behaviors motivated by appetitive and non-aversive memories (Holter et al. 2005; Niyuhire et al. 2007; Ward et al. 2007; Harloe et al. 2008; Hernandez and Cheer 2011). Because aversive memory may be involved in relapse to drug taking (Kaplan et al. 2011; Quirk and Gehlert 2003; Stewart and Kushner 2001), deficient eCB signaling following long-term drug exposure may contribute to the limited efficacy of extinction therapy for addiction.

### ***13.3 Amygdala: Cortical Communication as a Possible Mechanism for eCB Modulation of Drug-Seeking Behavior***

Considerable evidence highlights the importance of functional communication between the basolateral amygdala and prefrontal cortex (BLA->PFC) as a mediator of emotionally salient learning, memory, and synaptic plasticity. Distinct subpopulations of neurons in the PFC control the processing of aversive fear-related memory (Laviolette et al. 2005; Lauzon et al. 2009; Laviolette and Grace 2006) and rewarding and appetitive memory (Bishop et al. 2011; Sun et al. 2011), and both of these subpopulations are influenced by CB<sub>1</sub> modulation of BLA inputs (Tan et al. 2014). Growing evidence demonstrates that excessive activation of CB<sub>1</sub> receptors in either the BLA or PFC leads to amplification of aversive emotional information, while deficient CB<sub>1</sub> signaling in these areas blunts the salience of normally aversive events while enhancing the salience of sub-reward threshold stimuli (Tan et al. 2010, 2014; Laviolette and Grace 2006). These processes appear to be mediated through direct interactions with subcortical DAergic motivational systems arising from the VTA, and through these interactions, cortical CB<sub>1</sub> receptors are capable of modulating reward processing, even the switching of emotional valence from normally rewarding conditioned stimuli to aversive stimuli (Ahmad et al. 2013). The specific contribution of these mechanisms in the pathologically elevated motivational salience to drug-predictive cues and/or motivational effects of aversive memory contributing to drug seeking and relapse remains to be characterized (Tan et al. 2014). However, the potential involvement of these mechanisms not only in addiction but also in abnormal emotional learning and memory in other neuropsychiatric conditions is worth noting.

## **14 Cognitive Function**

Impairments in cognitive processing are hallmarks of addiction. The progression from initial, intermittent, controlled drug use to compulsive drug seeking and consumption in the addicted state is conceptualized as a progressive deterioration of executive control over behavior (primarily reliant on frontal-cortical and hippocampal function) and the emergence of habitual or compulsive behaviors that drive drug seeking and drug taking (mediated in large part through dorsal striatal signaling) (Everitt and Robbins 2005; Jentsch and Taylor 1999). Endocannabinoids exert prominent control of frontal-cortical, hippocampal, and striatal synaptic signaling, and growing evidence implicates dysregulated eCB signaling in both aberrant executive function and habit-based behaviors driven by dorsal striatal signaling.

Endocannabinoid signaling regulates neural activity, structural plasticity, and functional output of the medial prefrontal cortex (McLaughlin et al. 2014) and is implicated in several PFC-mediated cognitive functions including attentional set



shifting (Klugmann et al. 2011) and reversal learning in the Morris water maze (Varvel and Lichtman 2002; Lee et al. 2014). CB<sub>1</sub> receptor antagonism or deletion results in shorter and less complex dendrites of neurons in layer II/III of the prefrontal cortex (Hill et al. 2011; Lee et al. 2014) and impairments in cognitive flexibility that resemble behaviors in mPFC-lesioned animals (Lacroix et al. 2002; Lee et al. 2014). Conversely, genetic deletion or pharmacological inhibition of FAAH enhances the acquisition of the Barnes maze task (Wise et al. 2009), enhances memory acquisition in a passive avoidance task (Mazzola et al. 2009), and facilitates acquisition and extinction of a spatial memory task (Varvel et al. 2007). Physical activity increases circulating AEA levels in both humans and rodents (Sparling et al. 2003; Hill et al. 2010b; Raichlen et al. 2013; Heyman et al. 2012), and this may contribute to the beneficial effects of exercise on hippocampal cell proliferation, neurogenesis, and synaptic plasticity (Hill et al. 2010b; Wolf et al. 2010; Madronal et al. 2012). Treadmill running increases spatial working memory through a CB<sub>1</sub>-reliant mechanism, and similar working memory enhancement is observed in sedentary animals treated with URB597 (Ferreira-Vieira et al. 2014).

Despite growing evidence for an eCB influence in cognitive functions mediated by the mPFC and hippocampus, few studies have investigated disruptions in these mechanisms following long-term drug exposure. Drug-induced impairments in recognition memory may result from altered hippocampal CB<sub>1</sub> receptor function, and blockade of CB<sub>1</sub> receptors during drug exposure has been shown to prevent deficits in recognition memory produced by chronic morphine, MDMA, and nicotine exposure (Nawata et al. 2010; Vaseghi et al. 2012, 2013; Saravia et al. 2016). Regarding drug-induced disruptions in frontal cortical function, the Woodward lab recently demonstrated that alcohol withdrawal is associated with deficient CB<sub>1</sub>-mediated inhibition of GABAergic signaling in layers II/III of the PFC and possible increases in CB<sub>1</sub>-mediated inhibition of GABAergic signaling in layers V/VI (Pava and Woodward 2014), suggesting a role for dysregulated CB<sub>1</sub> signaling in altered cortical network activity that may underlie impaired cognitive function in detoxified alcoholics.

## 15 Food Addiction and Eating Disorders

Food addiction is defined as “a loss of control over food intake,” and growing evidence demonstrates that food and drug addiction have overlapping neuroadaptations in the mesolimbic system (Lutter and Nestler 2009). Indeed, eating disorders such as binge eating disorder (BED), anorexia nervosa (AN), and bulimia nervosa (BN) are hypothesized to derive in part from aberrant brain reward function (Kaye 2008; Marco et al. 2012; Scherma et al. 2014; Stoving et al. 2009). Similar to drug addiction, food addiction is defined in part by compulsive eating, continued aberrant feeding behavior despite negative consequences, and unsuccessful attempts to “normalize” dysfunctional eating (Cassin and von Ranson 2007;

**Table 2** Summary of ECS involvement in food intake and eating disorders

Pharmacological manipulation	Healthy animals	Binge eating disorder	Anorexia nervosa
Baseline ECS	↑↓ Energy balance <sup>a</sup> ↑↓ Food intake ↑↓ Hedonic aspects of feeding	↑ AEA levels in blood <sup>b</sup>	↑ AEA levels in blood <sup>c</sup> ↑ CB <sub>1</sub> mRNA in blood ↑ CB <sub>1</sub> binding in brain ↓ FAAH activity
CB <sub>1</sub> R antagonist	↓ Motivation for food <sup>d</sup> ↓ Preference for palatable foods ↓ Hedonic effects of food	↓ Compulsive eating <sup>e</sup> ↑ Weight loss	
CB <sub>1</sub> R agonist	↑ Motivation for food <sup>f</sup> ↑ Preference for palatable foods ↑ Hedonic effects of food		↑ Weight gain <sup>g</sup>

<sup>a</sup>Silvestri and Di Marzo (2013), Melis et al. (2007), Di Marzo et al. (2001), Bermudez-Silva et al. (2012), Kirkham et al. (2002), Hanus et al. (2003), Berridge et al. (2010), Jyotaki et al. (2010), Yoshida et al. (2010), Cervino et al. (2009)

<sup>b</sup>Monteleone et al. (2005)

<sup>c</sup>Monteleone et al. (2005, 2009), Frieling et al. (2009), Gerard et al. (2011)

<sup>d</sup>Simiand et al. (1998), South et al. (2007), Mathes et al. (2008), Chaperon et al. (1998), Gallate and McGregor (1999), Gallate et al. (1999), Solinas and Goldberg (2005), Jarrett et al. (2007), Melis et al. (2007)

<sup>e</sup>Scherma et al. (2013), Pataky et al. (2013)

<sup>f</sup>Kirkham and Williams (2001), Farrimond et al. (2011), Kirkham et al. (2002), Williams and Kirkham (1999), Martinez-Gonzalez et al. (2004), Solinas and Goldberg (2005), Guegan et al. (2013), Dipatrizio and Simansky (2008), Shinohara et al. (2009), Higgs et al. (2003), Jarrett et al. (2005, 2007), Mahler et al. (2007), Gallate et al. (1999), Dodd et al. (2009), Anderson-Baker et al. (1979), Jamshidi and Taylor (2001), Verty et al. (2005), Soria-Gomez et al. (2007)

<sup>g</sup>Andries et al. (2014)

Gearhardt et al. 2012). The influence of cultural pressures and stress in these disorders is well documented, though there are also strong genetic contributions to these diseases (Kaye 2008; Klump et al. 2001). Furthermore, it is estimated that more than 50% of individuals with BED meet the criteria for food addiction (Cassin and von Ranson 2007; Gearhardt et al. 2012).

Several findings suggest an ECS involvement in eating disorders, including aberrant reward processing associated with these conditions (Table 2). For example, abnormal eating behaviors like self-starvation (in AN) or binge eating (in BN or BED) become rewarding in their own right, and this may be influenced by disrupted eCB function (Monteleone et al. 2012; Cervino et al. 2009). Patients with AN or BED (but not BN) present with increased blood AEA levels as compared with controls, though no changes in blood 2-AG levels are associated with these disorders (Monteleone et al. 2005). Moreover, blood AEA levels are significantly and inversely correlated with plasma leptin levels in women with AN, consistent with the inhibitory influence of leptin on AEA synthesis (Di Marzo et al. 2001) and

leptin deficiency in these eating disorders. It should be noted, however, that although plasma eCB levels provide a potential index of disrupted eCB processing, they do not directly reflect dynamic changes in eCB signaling in the brain or other tissues. A *CNR1* polymorphism is associated with vulnerability to AN (Siegfried et al. 2004) (but see Muller et al. (2008)),  $CB_1$  mRNA levels are increased in the blood of AN and BN patients (Frieling et al. 2009), and increased brain  $CB_1$  binding has been observed in patients with AN and BN (Gerard et al. 2011). Specifically, AN and BN patients exhibit increased  $CB_1$  availability in the bilateral insular cortex (a region critically involved in reward and emotional processing as well as interoception), and increased  $CB_1$  availability is evident in the inferior frontal and temporal cortices of AN patients (regions involved in emotional processing and executive function). An association between the *C385A* polymorphism in the gene encoding FAAH (leading to diminished FAAH activity) and the *CNR1* polymorphism rs1049353 has been observed in higher frequency in patients with AN and BN (Monteleone et al. 2009) with a synergistic effect of these polymorphisms evident in patients with AN. The *C385A* polymorphism is also significantly associated with obesity (Monteleone et al. 2008; Sipe et al. 2005), though the relative contributions of possible disruptions in metabolism and hedonic mechanisms have not been determined. An association between a nonsynonymous *CNR2* polymorphism and both AN and BN has also recently been reported (Ishiguro et al. 2010).

Limited research has been conducted on the effects of CB manipulations in animal models of eating disorders. Sub-chronic  $\Delta 9$ -THC treatment (0.5–2 mg/kg/day) was found to increase food intake and reduce body weight loss in an activity-based rat model of anorexia nervosa (Verty et al. 2005), though these effects were not evident in similar studies conducted in mice (Lewis and Brett 2010). Conversely,  $CB_1$  receptor antagonism selectively reduces binge-like vs. normal patterns of consumption for highly palatable sweet and high-fat foods (Scherma et al. 2013). It is possible this latter finding involves a mesolimbic DA mechanism in light of evidence that binge-like consumption of palatable or high-fat foods elicits increased NAc DA release upon repeated bouts of consumption (Rada et al. 2005; Liang et al. 2006), while the DAergic response to normal patterns of consumption abates upon repeated exposure to palatable foods (Bassareo and Di Chiara 1999b). Regarding clinical studies in humans, two small initial trials assessing the efficacy of  $\Delta 9$ -THC treatments for AN failed to demonstrate significant benefits on weight gain, though some beneficial effects on depression and perfectionism were evident (for review see Stoving et al. 2009). However, a more recent and larger trial demonstrated that a 4-week treatment with dronabinol induced a small but significant weight gain in women suffering from severe-enduring AN (Andries et al. 2014). Further, a recent randomized, placebo-controlled, double-blind trial in 289 obese subjects with binge eating disorders demonstrated that a 6-month treatment with rimonabant significantly reduced binge eating and led to significant weight loss with modest presentation of adverse psychiatric side effects (Pataky et al. 2013).

## 16 Conclusions and Future Directions

Endocannabinoid signaling participates in the mediation and modulation of both natural reward (such as food consumption, exercise, sex, and social interaction) and drug-induced reward. Most natural rewards and drugs of abuse alter brain eCB levels, and there is a robust CB<sub>1</sub>R influence on the motivation for both natural and drug rewards. Chronic drug use results in a neuroadaptive downregulation of CB<sub>1</sub>R and/or CB<sub>2</sub>R availability and function and may also lead to disruptions in eCB biosynthesis and clearance. The resulting deficit in eCB signaling may contribute to increased stress responsivity, increased negative affect, impaired extinction of drug-related memories, and drug seeking/craving that are known contributors to relapse. Recent animal studies suggest that eCB clearance inhibitors may have therapeutic potential for ameliorating these behavioral abnormalities related to addiction disorders. This therapeutic approach may present fewer unwanted behavioral effects than that produced by exogenous cannabinoids, given that eCBs are generally produced in a synapse-specific manner, and as such, eCB clearance inhibition may preferentially facilitate eCB signaling in specific circuits engaged by distinct stimuli (e.g., stress, drug-associated cues, etc.).

There are a number of notable gaps in our understanding of the eCB influence on reward and addiction. The ECS plays a prominent role in neuronal guidance and brain development (Maccarrone et al. 2014), and as such, disruptions in eCB function at an early age likely have substantial consequences for adult brain function. This is underscored by increasing evidence of the long-term consequences of prenatal or adolescent cannabinoid exposure (Hurd et al. 2014; Calvigioni et al. 2014). Though the effects of early-life exposure to non-cannabinoid drugs are well studied, the specific contributions of persistent drug-induced disruptions in eCB signaling on adult neural function and behavior are not understood. Robust bidirectional interactions between the ECS and sex hormones are now recognized (Gorzalka and Dang 2012), but few studies have characterized possible sex differences in the eCB influence on reward function, addiction, stress, and cognitive processing. There are also substantial limitations in the interpretation and replication of genetic analyses of the eCB influence in addiction due to heterogeneity of the populations studied, drug class, polysubstance use, and even drug use phenotypes examined. Large-scale future studies across different populations and drug classes will be critical to understand the relative impact and causal nature of ECS-related genetic mutations in the vulnerability to addictive disorders. Filling these gaps of knowledge is critical given the important need for scientific data to help guide current discussions and changes being made in marijuana legalization policies.

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