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ENDOCANNABINOID INFLUENCE IN DRUG REINFORCEMENT, DEPENDENCE AND ADDICTION-RELATED BEHAVIORS

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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 etiology of drug addiction which is characterized by compulsive drug seeking, loss of control in limiting drug intake, emergence of a negative emotional state in the absence of drug use and a persistent vulnerability toward relapse to drug use during protracted abstinence. In this review we discuss the effects of drug intake on brain endocannabinoid signaling, evidence implicating the endocannabinoid system in the motivation for drug consumption, and drug-induced alterations in endocannabinoid function that may contribute to various aspects of addiction including dysregulated synaptic plasticity, increased stress responsivity, negative affective states, drug craving and relapse to drug taking. Current knowledge of genetic variants in endocannabinoid signaling associated with addiction is also discussed.

Keywords

endocannabinoid; CB1 receptor; addiction; craving; relapse; synaptic plasticity

1. Introduction

The recreational use of psychoactive substances by humans has been documented for centuries, and it is well known that the repeated use of many abused drugs can lead to dependence and a progression toward addiction. Addiction is a persistent state characterized by compulsion to seek and take a drug, a loss of control in limiting drug intake even when serious negative consequences ensue and the emergence of a negative emotional state (e.g. anxiety, depression, irritability) when access to the drug is prevented (Hyman, 2005; Hyman *et al*., 2006; Jaffe, 1990; Koob *et al*., 2010; O'Brien *et al*., 1996; O'Brien *et al*., 2005). Addicts often have a persistent vulnerability to relapse to drug use after days or even years

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of abstinence, and this aspect of addiction presents the greatest difficulty in treating this psychiatric disease (Nestler, 2002; O'Brien, 1997; O'Brien, 2008; Shaham *et al*., 2005; Yahyavi-Firouz-Abadi *et al*., 2009).

An important goal of addiction research is to understand the neuropharmacological and neuroadaptive mechanisms that mediate the transition from occasional, controlled drug use to the loss of behavioral control over drug-seeking and drug-taking that defines addiction. Investigations of the neural substrates mediating the positive reinforcing properties of various drugs have dominated the field of addiction research for several decades. This work has established an important role for increased mesolimbic dopamine signaling in the mediation of acute drug reward. Indeed, all drugs of abuse have been shown to increase extracellular dopamine levels in the nucleus accumbens (NAc) (Di Chiara *et al*., 2004) though this effect is relatively less pronounced for ethanol, nicotine and opioids as compared with psychostimulants. Further studies have demonstrated significant involvement of serotonin, glutamate, GABA, acetylcholine, and various neuroactive peptides in the positive reinforcing effects of various abused drugs (Bardo, 1998; Hyman *et al*., 2006; Koob *et al*., 2004; Ross *et al*., 2009) and the relative importance of a large number of brain structures in addition to the mesolimbic system has been characterized (Bardo, 1998; McBride *et al*., 1999; Paulus, 2007).

In recent years there has been substantial effort to characterize the neural mechanisms underlying the shift from controlled to compulsive drug use and the associated transfer in motivational drive from positive to negative reinforcement that results from long-term drug exposure. The data suggest that the transition to drug dependence and addiction involves adaptations in many of the neurochemical systems implicated in the positive reinforcing effects of acute drug use, a dysregulation of synaptic plasticity and the development of maladaptive stress responses (Chen *et al*., 2010; Kalivas, 2009; Kalivas *et al*., 2008; Koob, 2008; Koob, 2009; Martin-Fardon *et al*., 2010; Wise *et al*., 2010).

A growing body of evidence points to an involvement of the endogenous cannabinoid system (ECS) in the acquisition and maintenance of drug taking behavior and in various physiological and behavioral processes associated with addiction. An assessment of this evidence is presented in the sections that follow, with a focus on the potential endocannabinoid (eCB) influence on drug reinforcement, drug-related synaptic plasticity, drug-seeking behavior (relapse), stress responsivity and affective state. We will first provide a brief overview of the ECS and a consideration of the behavioral effects produced by enhanced eCB signaling.

2. The endogenous cannabinoid system

In the early 1990s two arachidonic acid derivatives were identified as endogenous cannabinoid receptor ligands. The first eCB to be discovered was anandamide (*N*-arachidonoyl-ethanolamine; AEA) (Devane *et al*., 1992) and within two years a second endogenous lipid, 2-arachidonoyl-glycerol (2-AG), was shown to function as signaling molecule at CB_1 and CB_2 receptors (Mechoulam *et al*., 1995; Sugiura *et al*., 1995). Other endogenous molecules have been identified that exert cannabinoid-like effects including 2-arachidonyl-glycerol ether (noladin ether) (Hanus *et al*., 2001), *N*-arachidonoyl-dopamine (NADA) (Bisogno *et al*., 2000; Huang *et al*., 2002), virodhamine (Porter *et al*., 2002), *N*-homo-γ-linolenoylethanolamine (HEA) and *N*-docosatetraenoylethanolamine (DEA) (Hanus *et al*., 1993; Pertwee *et al*., 1994). However, the presence of many of these lipids in intact tissue has been a matter of debate and their pharmacological activity and metabolism have not yet been thoroughly characterized. Endocannabinoid congeners including palmitoylethanolamide (PEA) (Re *et al*., 2007), and oleoylethanolamide (OEA) (Rodriguez

de Fonseca *et al*., 2001) have also been identified, though these moieties do not interact with cannabinoid receptors. Accordingly, AEA and 2-AG are still considered the primary endogenous mediators of cannabinoid signaling.

Unlike classical neurotransmitters, eCBs are not stored in intracellular compartments but are synthesized on an "as needed" basis by cleavage from membrane lipid precursors and immediate extrusion from neurons through distinct calcium-dependent mechanisms. AEA derives from the phospholipid precursor *N*-arachidonoyl-phosphatidylethanolamine (NAPE) (Cadas *et al*., 1996; Piomelli, 2003). The precise pathways through which NAPE is converted to AEA remain controversial, and at least four routes have been proposed including a direct transacylation-phosphodiesterase pathway catalyzed by a *N*-acyl-phosphatidylethanolamine-selective phosphodiesterase (NAPE-PLD) (Di Marzo *et al*., 2007; Liu *et al*., 2008; Okamoto *et al*., 2004) whose activity is regulated by depolarization and/or activation of ionotropic (Piomelli, 2003; Stella *et al*., 2001) or metabotropic receptors (Giuffrida *et al*., 1999; Kim *et al*., 2002; Varma *et al*., 2001). Although this has been considered to be a major route for AEA production, NAPE-PLD knockout mice were found to have unaltered AEA levels in brain (Leung *et al*., 2006) clearly pointing to the presence of additional metabolic pathways for AEA formation. At least two pathways distinct from NAPE-PLD have been proposed. One pathway involves the double-*O*-deacylation of NAPEs by α,β-hydrolase (ABHD4) to form glycerophospho-*N*-acylethanolamines (GP-NAEs), followed by conversion of these intermediates to NAEs by glycerophosphodiesterase-1 (GDE1) (Simon *et al*., 2006; Simon *et al*., 2008). Another pathway utilizes a phospholipase C (PLC) to produce phopho-*N*-arachidonoylethanolamine (pAEA) from NAPE, followed by conversion of pAEA into AEA by phosphatases such as PTPN22 and SHIP1 (Liu *et al*., 2006; Liu *et al*., 2008). 2-AG derives primarily from the hydrolytic metabolism of 1,2-diacylglycerol (DAG) mediated by two sn-1-selective DAG lipases, DAGL-α and DAGL-β (Bisogno *et al*., 2003; Piomelli, 2003; Stella *et al*., 1997) though alternate biosynthetic routes have been described (Sugiura *et al*., 1995).

Inactivation of eCB signaling is mediated by cellular reuptake into both neurons and glial cells (Beltramo *et al*., 1997; Hillard *et al*., 2000) and subsequent intracellular hydrolysis. Fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) have been identified as enzymes primarily responsible for the degradation of AEA and 2-AG, respectively. FAAH can also hydrolyze 2-AG (Goparaju *et al*., 1998) and other fatty acid primary amides, N-acyltaurines and N-acyl amino acids. The cloning, structural and kinetic properties, distribution in the body and crystal structure of FAAH have been described (Ahn *et al*., 2008; McKinney *et al*., 2005). FAAH is abundantly expressed in the CNS and FAAH-positive neurons are found in proximity to CB_1 receptor-containing terminals, supporting a role for this enzyme in eCB inactivation (McKinney *et al*., 2005). 2-AG hydrolysis is performed by multiple enzymes, though the primary mechanism of clearance appears to be mediated by MAGL (Blankman *et al*., 2007; Dinh *et al*., 2002). MAGL cloning, structural and catalytic properties have recently been reviewed (Saario *et al*., 2007). In addition to MAGL, the enzymes ABHD6 and ABHD12 appear to play an important role in 2-AG metabolism (Blankman *et al*., 2007; Marrs *et al*., 2010).

Two major types of cannabinoid receptors have been characterized and cloned: CB_1 and CB_2. CB_1 receptors are highly expressed in brain and are also found in peripheral tissues (Batkai *et al*., 2001; Herkenham *et al*., 1991a; Herkenham *et al*., 1991b; Herkenham *et al*., 1990; Howlett *et al*., 1990). CB_2 receptors are mainly located in immune cells (Munro *et al*., 1993), although there is evidence for CB_2 receptor expression on neurons, glia and endothelial cells in brain (Ashton *et al*., 2007; Atwood *et al*., 2010; Brusco *et al*., 2008a; Brusco *et al*., 2008b; Jhaveri *et al*., 2008; Onaivi *et al*., 2006; Onaivi *et al*., 2008; Van Sickle *et al*., 2005; Viscomi *et al*., 2009). CB_1 and CB_2 receptors are both coupled to similar

transduction systems through G_i or G_o proteins. Their activation reduces adenylate cyclase activity and Ca^{2+} influx through N-, P/Q- and L-type Ca^{2+} channels (Gebremedhin *et al*., 1999; Mackie *et al*., 1992; Twitchell *et al*., 1997). CB receptor activation also stimulates inwardly rectifying potassium channels and the mitogen-activated protein kinase pathway (Howlett, 2005; Mackie *et al*., 1995).

AEA and 2-AG each exert agonist activity at both CB_1 and CB_2 receptors. AEA binds with slightly higher affinity to CB_1 than CB_2, and similar to Δ9-THC it functions as a partial agonist at both CB receptors, though it is less efficacious at CB_2 as compared with CB_1 receptors (Pertwee, 2010). 2-AG binds with more or less equal affinity to CB_1 and CB_2 receptors, and has greater potency and efficacy than AEA at these receptors (Pertwee, 2010). AEA and 2-AG also function as agonists at orphan G-protein coupled receptors that may be members of the cannabinoid receptor family such as GPR55 and GPR119 (Godlewski *et al*., 2009; Lauckner *et al*., 2008; Overton *et al*., 2006; Pertwee, 2010; Ryberg *et al*., 2007; Sharir *et al*., 2010), and AEA potently activates non-cannabinoid receptors such as transient receptor potential vanilloid type-1 (TRPV1) receptors (Di Marzo *et al*., 2010; Zygmunt *et al*., 1999). Thus, the physiological and behavioral effects produced by eCBs result from agonist effects at both cannabinoid (CB_1 and CB_2) and non-cannabinoid receptors. For purposes of clarity, however, this review will focus primarily on the influence of eCB signaling through CB_1 receptors.

Since its discovery the ECS has been implicated in the regulation of a range of physiological processes including neural development (Fride, 2008), immune function (Pandey *et al*., 2009; Stella, 2009), metabolism and energy homeostasis (Viveros *et al*., 2008), synaptic plasticity and learning (Heifets *et al*., 2009), pain (Guindon *et al*., 2009) and emotional state (Lutz, 2009). There has also been substantial interest in the possible involvement of the ECS in the etiology of drug abuse and addiction, largely due to the dense CB_1 receptor expression in brain regions involved the motivational and addictive properties of abused drugs, and the similar pharmacological effects produced by eCBs and exogenous cannabinoids such as Δ9-tetrahydrocannabinol (Δ9-THC).

3. Behavioral effects produced by endocannabinoids

In the early 1990s Billy Martin and colleagues developed a battery of behavioral tests as an *in vivo* assay for evaluating cannabimimetic effects (Martin *et al*., 1991). Collectively these procedures were shown to provide a sensitive index of a drug affinity and efficacy at centrally located cannabinoid receptors. Although the full battery includes various tests in multiple species, the primary collection of tests is the rodent “tetrad”. Cannabinoid agonists such as Δ9-THC, WIN 55,212-2, and CP 55,940 produce a characteristic combination of four symptoms; hypoactivity, catalepsy, hypothermia and analgesia. Each of these effects are reversed by the CB_1 receptor antagonist SR 141716, providing good evidence for the involvement of CB_1-mediated mechanisms. Exogenous AEA administration produces behavioral effects similar to the CB_1 agonists mentioned above, though with much lower potency and of shorter duration (Crawley *et al*., 1993; Fride *et al*., 1993; Smith *et al*., 1994), most likely due to the rapid metabolism of this eCB. Although initial evaluations demonstrated that the hypothermia, analgesia and catalepsy induced by AEA are not reversed by the CB_1 receptor antagonist SR141716A (Adams, Compton, & Martin, 1998) subsequent tests revealed that the hypothermic effects of AEA and two AEA analogs (ACEA and ACPA) are attenuated by SR141716A pretreatment (Hillard *et al*., 1999). Further studies have revealed that selective FAAH and MAGL inhibitors produce an intriguing subset of the behavioral effects observed with direct CB_1 agonists (Kinsey *et al*., 2009; Lichtman *et al*., 2004; Long *et al*., 2009a; Long *et al*., 2009c; Russo *et al*., 2007). For example, inhibition of MAGL, but not FAAH, causes CB_1-dependent hypomotility (Long *et*

al., 2009c) and neither FAAH nor MAGL inhibition induces catalepsy as typically observed with direct CB_1 agonists. Thus, while AEA and 2-AG each produce some behavioral responses characteristic of Δ9-THC there are notable distinctions between the behavioral effects of eCBs and CB_1 agonists.

Several preclinical studies have investigated whether enhanced eCB signaling produces rewarding effects, and much of this work has compared eCB-induced behaviors with those produced by CB_1 agonists. With one published exception (Wiley *et al*., 1995), exogenous AEA has not substituted for Δ9-THC in drug discrimination tests except at quite high doses that also produce substantial motor disturbances (Burkey & Nation, 1997; Wiley, et al., 1997; Wiley, Ryan, Razdan, & Martin, 1998; Solinas, et al., 2007). Very rapid AEA metabolism likely confers a very short duration of action, and this may be responsible for the lack of generalization observed in most studies. Consistent with this hypothesis is evidence that the metabolically stable AEA analogs (R)-methanandamide and O-1812 as well as the CB_1-selective AEA analog AM1346 each fully substitute for Δ9-THC in discrimination tasks performed in rats (Alici *et al*., 2004; Burkey *et al*., 1997; Jarbe *et al*., 2000; Jarbe *et al*., 2001; Jarbe *et al*., 2006; Jarbe *et al*., 1998; Solinas *et al*., 2007; Wiley *et al*., 2004) though (R)-methanandamide does not generalize to the Δ9-THC stimulus in C58BL/6J mice or Rhesus monkeys (McMahon, 2006; McMahon *et al*., 2008). In rats and mice, treatment with the selective FAAH inhibitor URB597 or the non-selective serine hydrolase inhibitor PMSF potentiates the discriminative stimulus properties of AEA sufficiently to fully substitute for Δ9-THC (Solinas *et al*., 2007; Vann *et al*., 2009), though URB597 alone does not produce Δ9-THC appropriate responding (Gobbi *et al*., 2005; Solinas *et al*., 2007). Recent studies have also shown that Δ9-THC and (R)-methanandamide each fully generalize to the discriminative stimulus produced by the CB_1-selective AEA analog AM1346 (Jarbe *et al*., 2009) and Δ9-THC, WIN 55,212-2 and the selective CB_1 agonist AM678 fully generalize to the discriminative stimulus of (R)-methanandamide through a CB_1 receptor-sensitive mechanism (Jarbe *et al*., 2010). The discriminative properties of (R)-methanandamide, AEA (following URB597 administration), WIN 55,212-2, AM678, AM1346 and Δ9-THC are each blocked by SR 141716A and are therefore thought to be CB_1 receptor dependent (Jarbe *et al*., 2000; Jarbe *et al*., 2001; Jarbe *et al*., 2009; Jarbe *et al*., 2010; Jarbe *et al*., 1998; Solinas *et al*., 2007). These studies provide strong evidence of similar pharmacological effects produced by phytocannabinoids (e.g. Δ9-THC), synthetic CB_1 agonists and AEA-like moieties. However, reported differences in discriminative stimulus potency and CB_1 antagonist surmountability suggest that CB_1 receptor activation by these ligands may engage distinct signaling pathways (Jarbe *et al*., 2009; Jarbe *et al*., 2010). Recent work has shown that the MAGL inhibitor JZL184 produces only partial generalization to the Δ9-THC discriminative stimulus, though dual inhibition of MAGL and FAAH by JZL195 produces much more reliable Δ9-THC appropriate responding (Long *et al*., 2009b). Collectively these findings indicate that systemic administration of eCBs produces CB_1-dependent Δ9-THC-like discriminative stimulus effects, particularly following inhibition of eCB clearance mechanisms. In addition, recent evidence from the Goldberg lab suggests that enhanced AEA production induced by overt dopamine D_2 receptor activation can augment the discriminative stimulus properties of Δ9-THC (Solinas *et al*., 2010).

Neither exogenous AEA administration (Mallet *et al*., 1998) nor the FAAH inhibitor URB597 (Gobbi *et al*., 2005) produce place-conditioning effects and moderate doses of the FAAH inhibitors URB597 and PMSF or the putative eCB clearance inhibitor OMDM-2 do not alter brain stimulation reward thresholds (Vlachou *et al*., 2006), suggesting that enhancement of AEA tone does not produce rewarding effects in these paradigms. In contrast, the eCB transport and FAAH inhibitor AM404 produces rewarding effects in rats in the CPP paradigm (Bortolato, et al., 2006). AM404 enhances brain levels of both AEA

and 2-AG (Beltramo & Piomelli, 2000; Beltramo, et al., 1997; Hajos, Kathuria, Dinh, Piomelli, & Freund, 2004) and this more broad increase in eCB tone may contribute to the reinforcing properties of this compound. Similar to Δ9-THC (Justinova *et al*., 2003; Tanda *et al*., 2000) intravenous AEA infusion supports operant self-administration behavior in squirrel monkeys in a CB_1 receptor-dependent manner (Justinova *et al*., 2005). Intravenous AEA administration significantly increases extracellular dopamine (DA) levels in the NAc of rats in a CB_1 receptor-dependent manner (Solinas *et al*., 2006) and it's likely this effect contributes to the reinforcing effects of exogenous AEA. However, the FAAH inhibitor URB597 does not support operant self-administration in squirrel monkeys despite the fact that its delivery produces a substantial elevation in AEA throughout the monkey brain (Justinova *et al*., 2008b).

Two studies have evaluated whether repeated AEA administration produces physical dependence, and the sum of these reports is inconclusive. Aceto and colleagues characterized the effects of continuous intraperitoneal AEA infusion (10 – 100 mg/kg/24h) in rats over the course of 4 days. While significant behavioral effects were observed during the AEA infusion (immobility, eyelid ptosis), no somatic symptoms of withdrawal were observed when AEA administration was abruptly terminated (Aceto *et al*., 1998). Treatment with SR141716A at the end of the AEA administration period also did not precipitate a withdrawal syndrome. In contrast, Costa and colleagues observed that daily i.p. administration of 20 mg/kg AEA to rats resulted in significant withdrawal symptoms under conditions of both spontaneous (e.g. cessation of AEA treatment) and precipitated (e.g. SR141716A challenge) withdrawal conditions (Costa *et al*., 2000). Significant tolerance to some of the behavioral effects of AEA was observed over the course of treatment (including hypothermia, catalepsy, and splayed hind limbs), which could reflect a downregulation of systems activated by AEA, or an increase in AEA clearance. Withdrawal symptoms were similar to those observed during Δ9-THC withdrawal including ptosis, wet dog shakes, teeth chattering, forepaw fluttering and piloerection and these were substantially more pronounced during precipitated vs. spontaneous withdrawal. In one experiment in this report the spontaneous withdrawal symptoms were remarkably short-lived (<30 min), though SR141716A challenge produced clear withdrawal symptoms that persisted for >80 min. Recent studies have also evaluated subchronic administration of selective FAAH and MAGL inhibitors in tests of dependence (Schlosburg *et al*., 2009; Schlosburg *et al*., 2010). Mice given daily injections of URB597 or the more potent FAAH inhibitor PF-3845 for 6 days and subsequently challenged with SR141716A displayed no significant withdrawal symptoms (paw tremors, head twitching), suggesting prolonged FAAH inhibition does not lead to physical dependence. In contrast, significant SR141716A-induced somatic withdrawal was observed following 6 days of treatment with the selective MAGL inhibitor JZL184. This treatment regimen also resulted in significant reductions in CB_1 receptor expression and function, suggesting that long-term reductions in 2-AG clearance produces a dependent state similar to that produced by repeated Δ9-THC administration (Schlosburg *et al*., 2010). It is worth noting that the JZL184 dose employed in this study is more than 3-fold higher than required to elicit significant behavioral effects in animal models of pain, anxiety and drug withdrawal (Kinsey *et al*., 2011; Kinsey *et al*., 2009; Schlosburg *et al*., 2009). It is presently unclear whether repeated treatment with low, behaviorally efficacious JZL184 doses also dysregulates CB_1 receptor signaling.

Collectively these findings suggest that administration of exogenous eCBs can induce behavioral effects similar to those produced by CB_1 agonists, including reinforcing effects in a variety of paradigms. However, most evidence indicates that pharmacological compounds that enhance eCB tone (e.g. eCB clearance inhibitors) do not produce robust CB_1 agonist-like effects and likely do not possess abuse liability. It is notable, however, that much of this work has focused on AEA and FAAH due to the limited availability of tools for

manipulating 2-AG. As described above, the recent development of selective MAGL inhibitors and dual FAAH and MAGL inhibitors (Long *et al*., 2009b; Long *et al*., 2009c) will allow for important additional analyses regarding the behavioral processes modulated by eCB signaling.

4. Endocannabinoid modulation of non-cannabinoid drug reinforcement

The motivational and addictive properties of abused drugs are mediated through drug-induced changes in neurotransmitter and neuromodulatory signaling in the CNS. Although there are differences in effects caused by various classes of abused drugs, substantial evidence points to an involvement of monoamines (dopamine, serotonin, norepinephrine), excitatory and inhibitory amino acids (primarily glutamate and GABA, respectively), acetylcholine, opioid peptides and stress-related peptides in the etiology of addiction. As reviewed below, there is now substantial evidence implicating the ECS in the motivational effects produced by several classes of abused drugs such as ethanol, nicotine, opiates and psychostimulants. Much of this is based on the influence of CB_1 receptor signaling on drug-induced behaviors, though some studies have more directly evaluated manipulations of eCB tone on drug reinforcement.

4.1 Alcohol

A large amount of evidence points to an important influence of CB_1 receptor signaling on ethanol-related behaviors. CB_1 receptor knockout mice exhibit less ethanol-induced conditioned place preference than do wildtype controls (Houchi *et al*., 2005; Thanos *et al*., 2005) suggesting a role for CB_1 receptors in the mediation of ethanol reward and/or interoreceptive-related conditioned associations. CB_1 receptors also exert substantial regulatory influence on ethanol consumption. The selective CB_1 receptor antagonist SR 141716A decreases ethanol consumption in alcohol-preferring C57BL/6 mice (Arnone *et al*., 1997; Wang *et al*., 2003), Sardinian alcohol-preferring sP rats (Colombo *et al*., 1998), Long Evans rats (Freedland *et al*., 2001), and both non-dependent (Freedland *et al*., 2001; Gallate *et al*., 1999) and alcohol-dependent (Lallemand *et al*., 2001) Wistar rats. Repeated administration of SR 141716A or the more selective CB_1 antagonist SR147778 also prevents the acquisition of ethanol drinking by Sardinian alcohol-preferring rats given free choice between 10% ethanol (v/v) and water (Gessa *et al*., 2005; Serra *et al*., 2001). CB_1 receptor knockout mice display low ethanol preference and intake compared with wild-type mice, and the suppressive effects of SR141716A on ethanol preference and consumption are absent in these mice (Hungund *et al*., 2003; Naassila *et al*., 2004; Thanos *et al*., 2005; Wang *et al*., 2003). Moreover, ethanol-induced increases in NAc dopamine levels are absent in CB_1 knockout mice and are attenuated in wildtype animals by SR141716A pretreatment (Cohen *et al*., 2002; Hungund *et al*., 2003). Based on these data most investigators have concluded that ethanol reward depends in part on intact CB_1 receptor signaling, though some evidence suggests that reduced ethanol preference and consumption in CB_1 knockout mice results from an increased sensitivity to ethanol intoxication and severity of withdrawal (Naassila *et al*., 2004). It is also possible that CB_1 antagonist-induced suppression of ethanol consumption results in part from non-specific reductions in consummatory behavior. For example, although some studies report that SR 141716A reduces ethanol intake at doses that do not attenuate food consumption (Arnone *et al*., 1997; Colombo *et al*., 1998), this antagonist can produce comparable dose-dependent reductions in the consumption of both ethanol and sucrose (Arnone *et al*., 1997; Freedland *et al*., 2001). Although not fully explored, it is conceivable such an influence results from interactions between the cannabinoid, opioid and dopamine systems in the regulation of palatable food consumption and reward (Cooper, 2004; Cota *et al*., 2006; Gardner, 2005). It is notable, however, that CB_1 receptor knockout mice do not display phenotypic differences in sucrose, quinine or food consumption (Hungund *et al*., 2003; Naassila *et al*., 2004). Finally, some evidence

suggests that the CB_1 receptor influence on ethanol intake may also be dependent on the animals' stress state (Racz *et al*., 2003).

Despite these caveats, the findings described above suggest that CB_1 receptors exert a facilitory influence on ethanol preference and consumption. Consistently CB_1 receptor activation has been shown to increase ethanol consumption. The synthetic CB_1 agonists WIN 55,212-2 and CP 55,940 dose-dependently increase spontaneous drinking in Sardinian alcohol preferring sP rats (Colombo *et al*., 2002) and C57BL/6J mice (Wang *et al*., 2003) and CP 55,940 dose-dependently increases the breaking point of responding for beer by Wistar rats on a lick-based progressive ratio schedule of reinforcement (Gallate *et al*., 1999). In each case the CB_1 agonist-induced increase in ethanol intake was reversed by SR141716A doses that by themselves did not alter ethanol consumption. CB_1 agonist pretreatment non-selectively increased the consumption of beer, non-alcoholic beer ("near-beer") and sucrose by Wistar rats (Gallate, et al., 1999) suggesting a non-specific stimulatory effect of CB_1 receptor stimulation on appetite for palatable beverages. In contrast, both WIN 55,212-2 and CP 55,940 selectively increased ethanol, but not sucrose or food intake in alcohol-preferring sP rats (Colombo, et al., 2002). These differential effects may result from innate differences in CB_1 receptor expression and function in this line of alcohol-preferring rats (Vinod *et al*., 2011). It is worth noting, however, that not all studies have observed CB_1 agonist-induced facilitation of ethanol intake. Cippitelli and colleagues did not observe any alteration in ethanol self-administration by Wistar rats following pretreatment with the selective CB_1 agonists ACEA or HU-210, and observed a dose-dependent reduction in ethanol self-administration by WIN 55,212-2 (Cippitelli *et al*., 2007).

Studies in FAAH knockout mice provide more direct evidence for an eCB influence on EtOH consumption. These animals display an increased preference for ethanol and consume significantly more ethanol than do wildtype mice, though there is no genotypic difference in consumption of non-alcoholic tastants such as saccharine or quinine (Basavarajappa *et al*., 2006; Blednov *et al*., 2007; Vinod *et al*., 2008). Similarly, acute administration of the FAAH inhibitor URB597 increases ethanol preference and consumption in wildtype mice. This effect is not observed in FAAH or CB_1 receptor knockout mice, indicating that the effects of URB597 are mediated through its actions on FAAH, and that the resultant effect of FAAH inhibition on ethanol consumption relies on CB_1 receptor signaling. There is some evidence that increased ethanol consumption by FAAH deficient mice results from a diminished sensitivity to ethanol-induced motor incoordination and intoxication (Blednov *et al*., 2007), and this is analogous to the association between decreased ethanol consumption and increased sensitivity to ethanol intoxication in CB_1 deficient mice (Naassila *et al*., 2004). In addition to these findings in mice, Hansson and colleagues reported that rats selectively bred for high ethanol preference and consumption are characterized by reduced FAAH expression and activity in the prefrontal cortex (PFC) (Hansson *et al*., 2007). Moreover, these authors found that localized URB597 administration into the PFC increases ethanol consumption by outbred Wistar rats. In contrast, Cippitelli and colleagues reported that systemically administered URB597 does not alter voluntary homecage ethanol consumption by Marchigian Sardinian alcohol-preferring (msP) rats, and does not facilitate operant ethanol self-administration by Wistar rats under either continuous or progressive ratio schedules of reinforcement (Cippitelli *et al*., 2008). In a separate study these authors observed that the putative eCB reuptake inhibitor AM404 significantly reduces operant ethanol self-administration by Wistar rats at doses that do not alter saccharin self-administration (Cippitelli *et al*., 2007). Thus, while FAAH inhibition appears to consistently increase ethanol preference and consumption in mice, less consistent effects are observed in rats.

Several studies have sought to characterize the neurochemical mechanisms and neuronal substrates through which CB_1 receptors modulate ethanol intake. Pharmacological blockade

or genetic deletion of CB_1 receptors diminishes ethanol-induced increases in dopamine levels and dopamine transients in the NAc (Cheer *et al*., 2007; Hungund *et al*., 2003; Perra *et al*., 2005) and ethanol-induced increases in the firing of ventral tegmental area (VTA) dopamine cells that project to the NAc appear to involve a CB_1 receptor mechanism (Perra *et al*., 2005). Localized administration of SR141716A into VTA reduces ethanol self-administration by Wistar rats (Alvarez-Jaimes *et al*., 2009a; Malinen *et al*., 2008) and this effect appears to be restricted to the posterior aspect of the VTA (Alvarez-Jaimes *et al*., 2009a) consistent with evidence of a specific involvement of the posterior VTA in the regulation of ethanol intake (Gatto *et al*., 1994; Rodd *et al*., 2004; Rodd-Henricks *et al*., 2000). Ethanol self-administration is also dose-dependently reduced by SR141716A infusions into the NAc shell, but is unaffected by infusions of this antagonist into the medial PFC (Alvarez-Jaimes *et al*., 2009a). This regional pattern of CB_1 receptor influence on ethanol consumption is consistent with the regional specificity of ethanol-induced increases in interstitial eCB levels determined by microdialysis (Alvarez-Jaimes *et al*., 2009a; Caille *et al*., 2007) (see discussion below).

4.2 Nicotine

Nicotinic acetylcholine (nACh) receptors are the primary pharmacological target of nicotine. The overlapping distribution of CB_1 and nACh receptors in several brain structures such as the hippocampus and the amygdala (Picciotto *et al*., 2000) allows the possibility of functional interactions between these two systems. Indeed, nicotine facilitates several physiological and behavioral effects induced by acute Δ9-THC administration, including hypothermia, antinociception, hypolocomotion and anxiolytic-like responses (Valjent *et al*., 2002). Co-administration of sub-threshold doses of nicotine and Δ9-THC induces significant anxiolytic-like effects in the light-dark transfer test and open field, and a significant conditioned place preference (Valjent *et al*., 2002). Moreover, co-administration of Δ9-THC and nicotine produces a strong potentiation of c-*Fos* immunoreactivity in various limbic and cortical structures, including the shell of the NAc, central and basolateral nucleus of amygdala (CeA & BLA, respectively), dorsolateral bed nucleus stria terminalis (BNST), cingulate and piriform cortices and PVN (Valjent *et al*., 2002).

Several studies implicate a CB_1 receptor involvement in the rewarding effects of nicotine. For example, nicotine doses that produce significant conditioned place preference in wildtype mice do not produce place preference in CB_1 knockout mice (Castane *et al*., 2002). Similarly, SR 141716A blocks the acquisition of nicotine-induced conditioned place-preference in rats (Forget *et al*., 2005; Le Foll *et al*., 2004) and wildtype mice (Merritt *et al*., 2008). SR141716A also blocks short-term expression of previously established nicotine place preference (24h after the final nicotine pairing), but not the long-term expression of nicotine-conditioned preference (3 or 12 weeks after nicotine pairing) (Forget *et al*., 2005; Forget *et al*., 2006). SR 141716A and the more selective CB_1 antagonist AM251 (Krishnamurthy *et al*., 2004; Lan *et al*., 1999) each dose-dependently reduce nicotine self-administration by rats (Cohen *et al*., 2002; Shoaib, 2008) and CB_1 receptor knockout mice self-administer less nicotine than wildtypes (Cossu *et al*., 2001). Further, *in vivo* microdialysis evaluations reveal that SR141716A blocks the dopamine-releasing effects of nicotine in limbic regions of the rat (Cohen *et al*., 2002) though subsequent studies failed to observe a significant effect of SR 141716A on nicotine-induced increases in mesolimbic dopamine cell firing (Melis *et al*., 2008). Finally, SR141716A does not alter the discriminative stimulus properties of nicotine (Cohen *et al*., 2002; Le Foll *et al*., 2004).

Two recent studies have characterized the effect of FAAH inhibition on nicotine-induced conditioned place preference and self-administration. In the first study, Merritt and colleagues observed that FAAH knockout mice and URB597-treated wildtype mice display enhanced sensitivity to low nicotine doses relative to vehicle treated wildtype mice in the

conditioned place-preference assay (Merritt *et al*., 2008). The genotypic and URB597-related enhanced effect on nicotine conditioning was lost with higher nicotine doses. The enhanced sensitivity to the rewarding effects of low dose nicotine was blocked by the SR141716A in FAAH knockout mice, confirming an involvement of CB_1 receptors in this behavioral effect. The URB597-induced enhancement of nicotine conditioned place preference occurred without a significant effect on locomotor activity, and URB597 did not alter the potency of nicotine in acute antinociception or hypothermia tests, suggesting that the FAAH-related enhancement of nicotine reward was not due to a general increase in sensitivity to nicotine. Collectively these results suggest that FAAH inhibition enhances nicotine reward in mice through a CB_1 receptor mechanism, most likely due to elevated levels of AEA.

In contrast, Scherma and colleagues reported that URB597 blocks the development of nicotine-induced conditioned place preference in rats (Scherma *et al*., 2008a). This effect was observed across a wide range of nicotine doses that included a subthreshold dose for inducing place preference. URB597 pretreatments also attenuated acquisition of intravenous nicotine self-administration, and reduced the effect of acute nicotine on NAc DA levels. These findings suggest that while FAAH inhibition enhances the rewarding effects of low nicotine doses in mice (Merritt *et al*., 2008) the reinforcing and neurochemical effects of nicotine in rats are reduced by FAAH inhibition. Further *in vivo* studies using anesthetized rats revealed that FAAH inhibition attenuates nicotine-induced excitation of VTA dopamine cells in a CB_1-independent manner through activation of nuclear peroxisome proliferator-activated receptor-α (PPAR-α) receptors by oleoylethanolamide (OEA) and/or palmitoylethanolamide (PEA) (Luchicchi *et al*., 2010; Melis *et al*., 2008). Similar to AEA, both OEA and PEA are metabolized by FAAH and thus FAAH inhibition results in enhanced levels of these and other ethanolamines in brain (Ahn *et al*., 2008). However, unlike AEA neither OEA nor PEA possess significant CB_1 receptor affinity. The effects of PPAR-α activation on drug-induced dopamine cell activation are selective for nicotine (Luchicchi *et al*., 2010) and administration of the metabolically stable OEA analog methOEA and the selective PPAR-α agonist WY14643 selectively decrease nicotine, but not cocaine or food self-administration in both rats and monkeys (Mascia *et al*., 2011).

In summary, the behavioral, physiological and neurochemical effects of nicotine appear to be facilitated by CB_1 receptor activation. While some evidence suggests that enhanced eCB tone resulting from FAAH inhibition increases the rewarding effects of low nicotine doses in mice, similar effects of FAAH inhibition have not been observed in rats or monkeys due to a dominant opposing influence of non-CB_1 mechanisms engaged by increased OEA and PEA levels.

4.3 Opioids

Opioids, such as heroin and morphine exert their physiological and behavioral effects through specific interactions with mu (μ)-, delta (δ)- and, kappa (κ)-opioid receptors, though opiate dependence appears to primarily involve μ receptors (Kieffer, 1999; Matthes *et al*., 1996). CB_1 and μ-opioid receptors are similarly expressed in many brain areas involved in reward processes (Delfs *et al*., 1994; Herkenham *et al*., 1991b; Mansour *et al*., 1995; Matsuda *et al*., 1993; Navarro *et al*., 1998; Rodriguez *et al*., 2001), and these receptors share common signaling cascades (Childers *et al*., 1992; Howlett, 2002; Reisine *et al*., 1996). Growing evidence suggests a functional interaction between the endogenous cannabinoid and opioid systems (for review see (Corchero *et al*., 2004; Maldonado *et al*., 2003; Manzanares *et al*., 1999b; Vigano *et al*., 2005)). Activation of each system produces similar behavioral responses including motor suppression, analgesia and reward (Manzanares *et al*., 1999b; Massi *et al*., 2001) and the ECS appears to exert a modulatory influence on many opiate-induced processes (Corchero *et al*., 2004; Hine *et al*., 1975; Manzanares *et al*., 1999b;

Valverde *et al*., 2000; Vela *et al*., 1995). CB_1 receptor efficacy is diminished in the striatum of μ-opioid receptor knockout mice (Berrendero *et al*., 2003) while heroin self-administration or repeated morphine administration leads to increased CB_1 receptor function in reward-related brain regions (Fattore *et al*., 2007; Gonzalez *et al*., 2002a). The rewarding effects of Δ9-THC are suppressed in opioid receptor knockout mice (Castane *et al*., 2003; Ghozland *et al*., 2002) and are attenuated by opioid receptor antagonists (Braida *et al*., 2001; Justinova *et al*., 2004). In contrast, CB_1 receptor deletion increases δ- and κ-opioid receptor efficacy in the caudate putamen without altering the density of opioid receptor expression (Uriguen *et al*., 2005). CB_1 receptor activation increases the release of endogenous opioid peptides in various brain regions (Corchero *et al*., 1997; Manzanares *et al*., 2005; Pugh *et al*., 1997; Valverde *et al*., 2001) and opiate-induced increases in brain eCB content have also been reported (Caille *et al*., 2007; Vigano *et al*., 2004; Vigano *et al*., 2003) (see section 5).

Several studies have demonstrated an important CB_1 receptor influence in the rewarding effects of opiates. The CB_1 receptor antagonist SR141716A blocks the development of morphine-induced conditioned place preference in rats and mice (Chaperon *et al*., 1998; Navarro *et al*., 2001; Singh *et al*., 2004), and mice lacking CB_1 receptors display reduced morphine-induced CPP (Martin *et al*., 2000) though this effect was not observed in another test of CB_1 knockouts (Rice *et al*., 2002). CB_1 receptor knockout mice do not acquire heroin self-administration (Cossu *et al*., 2001; Ledent *et al*., 1999) and SR141716A dose-dependently reduces heroin self-administration in rats (Caille *et al*., 2003; De Vries *et al*., 2003; Navarro *et al*., 2001; Solinas *et al*., 2003). The suppressant effect of SR141716A on heroin self-administration is more pronounced under schedules that require high levels of operant behavior (Caille *et al*., 2003; De Vries *et al*., 2003; Solinas *et al*., 2003).

Increased CB_1 receptor signaling appears to facilitate opiate reward. Pre-exposure to the CB_1 receptor agonist WIN 55,212-2 potentiates morphine-induced conditioned place preference (Manzanedo *et al*., 2004), and both WIN 55,212-2 and Δ9-THC pretreatment increase operant responding for heroin self-administration under a progressive ratio schedule in rats (Solinas *et al*., 2005). However, neither the FAAH inhibitor URB597 nor the putative eCB uptake inhibitor AM404 increase progressive ratio responding for heroin (Solinas *et al*., 2005). These findings suggest that while direct CB_1 receptor agonists facilitate opioid reward, opioid-induced increases in eCB formation (Caille *et al*., 2007) likely do not influence the motivation for opiate self-administration.

CB_1 and opioid agonists appear to increase NAc dopamine levels through a common mechanism (Tanda *et al*., 1997), and thus it is possible that CB_1 receptors modulate opiate reward through a mesolimbic dopamine mechanism. However, while morphine-induced increases in NAc dopamine are attenuated in CB_1 knockout mice (Mascia *et al*., 1999), acute administration of the CB_1 receptor antagonist SR141716A does not alter morphine- or heroin-induced increases in NAc dopamine (Caille *et al*., 2003; Caille *et al*., 2006; Tanda *et al*., 1997). Moreover, recent evidence demonstrates that FAAH inhibition by URB597 does not alter morphine-induced alterations in VTA dopamine cell firing, though as previously reviewed this manipulation does block nicotine-induced increases in VTA dopamine cell firing in a CB_1-dependent manner (Luchicchi *et al*., 2010). In addition to the mesolimbic dopamine system, opiate reward is mediated in part through reduced GABA signaling in the ventral pallidum (Bardo, 1998; Caille *et al*., 2004; Xi *et al*., 2000; Xi *et al*., 2002) and SR 141716A dose-dependently prevents morphine-induced reductions in ventral pallidal GABA release through a dopamine-independent mechanism (Caille *et al*., 2006). Similarly, WIN 55,212-2 induced reductions in ventral pallidal GABA release are reversed by the opiate receptor antagonist naloxone, suggesting a cross talk between opioid and cannabinoid signaling mechanisms in this neurochemical response. However, this effect appears to be selective for opiates as CB_1 antagonism does not alter cocaine-induced reductions in pallidal

GABA (Caille *et al*., 2006). Finally, heroin self-administration is dose-dependently reduced by SR 141716A infusions into the NAc, but not ventral pallidum (Caille *et al*., 2006). Collectively these findings suggest that NAc CB_1 receptors may modulate opiate reward by regulating opiate-induced inhibition of GABAergic medium spiny neurons projecting to the ventral pallidum.

4.4 Psychostimulants

The behavioral and addictive effects of psychostimulants such as cocaine, 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") and methamphetamine are produced by direct interactions with the brain monoamine neurotransmitters (dopamine, serotonin and norepinephrine). Substantial evidence indicates that dopamine is the primary monoamine involved in psychostimulant reward (Howell *et al*., 2008; Rothman *et al*., 2003) and drugs in this class increase extracellular dopamine concentrations through inhibition of dopamine reuptake (e.g. cocaine) or the promotion of impulse-independent dopamine release (e.g. amphetamine and MDMA) (Riddle *et al*., 2005; Ritz *et al*., 1987; Sulzer *et al*., 1990). This direct influence on dopamine release and clearance differentiates psychostimulants from other classes of abused drugs (i.e. nicotine, alcohol, opiates) that primarily increase dopamine cell firing through indirect mechanisms (Brodie *et al*., 1999; Gysling *et al*., 1983; Matthews *et al*., 1984; Pierce *et al*., 2006).

The distinct mechanisms through which these drugs increase mesolimbic dopamine levels may underlie the apparent differential influence of CB_1/eCB signaling on the reinforcing effects of psychostimulants vs. other classes of abused drugs. In contrast to reports that CB_1 receptor deletion attenuates the reinforcing effects of alcohol, nicotine and opiates, CB_1 receptor deletion does not affect psychostimulant-induced place conditioning (Houchi *et al*., 2005; Martin *et al*., 2000) or self-administration (Cossu *et al*., 2001). In addition, doses of the CB_1 antagonist SR141716A that significantly reduce alcohol, nicotine and opiate self-administration do not alter cocaine self-administration by squirrel monkeys (Tanda *et al*., 2000), rats (Caille *et al*., 2006; Caille *et al*., 2007; De Vries *et al*., 2001; Fattore *et al*., 1999; Filip *et al*., 2006) or mice (Lesscher *et al*., 2005). Cocaine-induced increases in NAc dopamine levels are unaltered by SR141716A pretreatment or CB_1 receptor deletion (Caille *et al*., 2003; Soria *et al*., 2005) and cocaine-induced enhancement in the sensitivity to brain stimulation reward is unaffected by SR141716A (Vlachou *et al*., 2003; Xi *et al*., 2008).

These findings suggest that CB_1 receptors do not play a critical role in the rewarding effects of cocaine. However, these reports are countered by several studies that provide evidence for a CB_1 receptor modulation of cocaine-induced behavioral and neurochemical events. For example, WIN 55,212-2 dose-dependently reduces both cocaine-induced facilitation of brain stimulation reward in rats (Vlachou *et al*., 2003) and cocaine self-administration by rats through a CB_1 receptor-dependent mechanism (Fattore *et al*., 1999). Soria and colleagues observed that CB_1 receptor deletion impairs the acquisition of cocaine self-administration by mice, and both genetic and pharmacological CB_1 receptor blockade reduces the motivation for cocaine under a progressive ratio schedule of reinforcement (Soria *et al*., 2005). Moreover, in contrast to SR141716A the structurally similar CB_1 receptor antagonist AM251 significantly attenuates the motivation for cocaine self-administration under a progressive ratio schedule of reinforcement (Xi *et al*., 2008), reduces methamphetamine self-administration (Vinklerova *et al*., 2002) and attenuates cocaine-induced enhancement in the sensitivity to brain stimulation reward (Xi *et al*., 2008). Additionally, Li and colleagues recently reported that CB_1 receptor deletion results in diminished basal dopamine release and attenuated cocaine-induced increases in NAc dopamine (Li *et al*., 2009).

A recent report from Orio and colleagues suggests that the CB_1 receptor influence on cocaine reward is enhanced by long periods of cocaine self-administration that result in

progressive increases in cocaine intake (Orio *et al*., 2009). For example, SR 141716A dose-dependently reduces the breakpoint for cocaine self-administration under a progressive ratio schedule selectively in rats previously given daily 6h access to cocaine with much lesser efficacy in rats given only 1h daily access to cocaine. Similar group-related differences in SR141716A efficacy were observed following direct SR141716A infusions into the NAc. Consistent with these findings levels of both phosphorylated and total CB_1 receptor protein were increased in the NAc and amygdala of rats given extended daily access to cocaine. These observations suggest that neuroadaptations induced by extended cocaine exposure may recruit a CB_1 receptor involvement in a progressive escalation of drug intake that results from extended periods of cocaine use.

Few studies have directly evaluated an eCB influence in psychostimulant reinforcement through manipulation of eCB clearance mechanisms. Two recent reports demonstrate that FAAH inhibition does not alter fixed ratio cocaine self-administration by either squirrel monkeys (Justinova *et al*., 2008b) or rats (Adamczyk *et al*., 2009), though both URB597 and PMSF attenuate cocaine- and cue-induced reinstatement of cocaine-seeking behavior in rats (Adamczyk *et al*., 2009) (see section 7). Luchicchi and colleagues have observed that URB597 does not affect cocaine-induced alterations in dopamine cell activity in the rat VTA, though this FAAH inhibitor does attenuate cocaine-induced alterations in the firing of medium spiny neurons in the shell of the NAc (Luchicchi *et al*., 2010). In contrast, the eCB uptake/FAAH inhibitor AM404 attenuates cocaine-induced facilitation of brain stimulation reward through a CB_1 receptor-dependent mechanism (Vlachou *et al*., 2008) in a manner similar to the effects of the synthetic CB_1 agonist WIN 55,212-2 (Vlachou *et al*., 2003). Collectively these findings suggest that increased levels of AEA (and other FAAH substrates) do not substantially alter the reinforcing effects of cocaine or cocaine-induced alterations in mesolimbic dopamine transmission, though eCB reuptake blockade by AM404 appears to attenuate cocaine-induced enhancement of reward function. Because AM404 increases brain levels of both AEA and 2-AG (Beltramo *et al*., 2000; Beltramo *et al*., 1997; Hajos *et al*., 2004) these latter findings may suggest a more potent influence of 2-AG than AEA on cocaine-induced behavioral effects, though this possibility clearly requires further investigation of the effects of MAGL inhibition on cocaine-related behaviors.

Overall, while there is some evidence for a CB_1 receptor and/or eCB involvement in the reinforcing and neurochemical effects of psychostimulants the comparable number of papers reporting negative findings suggests a relatively modest eCB influence in the behavioral effects of this class of abused drugs.

5. Drug-induced alterations in brain eCB content

As reviewed above, a substantial literature indicates that the reinforcing effects of various non-cannabinoid drugs are modulated by CB_1 receptor manipulations and in some cases by manipulations of eCB signaling (through administration of clearance inhibitors). From these observations it has been hypothesized that brain eCB levels are altered by exposure to drugs of abuse.

The most common approach for quantifying brain eCB content has been lipid extraction and purification from bulk postmortal brain tissue, with subsequent analysis by liquid or gas chromatography coupled with mass spectrometry (for review see (Buczynski *et al*., 2010)). Several groups have employed this approach to evaluate the effects of acute or repeated drug exposure on eCB levels in reward-relevant brain regions. In general the findings demonstrate that brain AEA and 2-AG content is altered following administration of abused drugs, though dissimilar effects on these two eCBs are often observed, with distinct profiles produced by different classes of drugs.

For example, while repeated Δ9-THC administration (10 mg/kg 1x/day for 8 days) significantly reduces both AEA and 2-AG content in the caudate putamen, only AEA content was decreased in the midbrain and diencephalon (Di Marzo *et al*., 2000; Gonzalez *et al*., 2004b). In contrast, this Δ9-THC exposure regimen robustly increased AEA (but not 2-AG) content in the limbic forebrain, while 2-AG (but not AEA) content is significantly increased in the hippocampus, brainstem and cerebellum. Interestingly, one clinical study in humans revealed that antipsychotic-naïve schizophrenics who used cannabis at least 20 time in their life had lower CSF AEA levels compared with subjects who had 5 or fewer lifetime exposures, though no group differences in serum AEA levels were evident (Leweke *et al*., 2007). Although preliminary and perhaps selective to a specific patient population, these findings provide some indication that cannabis use can alter eCB function in the CNS. Results of one preclinical study also suggest that prenatal CB_1 agonist exposure can result in long-term alterations in brain eCB levels. Castelli and colleagues observed that adult rats exposed to moderate WIN 55,212-2 doses (0.5 mg/kg, 1x/day) on gestation days 5 – 20 are characterized by significantly increased striatal AEA content and significantly reduced AEA levels in the limbic forebrain (Castelli *et al*., 2007). Interestingly, these effects may have resulted from altered AEA clearance mechanisms as FAAH activity was significantly reduced in striatum and increased in the limbic forebrain of animals give prenatal WIN 55,212-2 exposure.

Several lines of evidence indicate that ethanol exposure stimulates central eCB production and leads to alterations in eCB signaling mechanisms. Pioneering work in this area was performed in the laboratory of Basalingappa Hungund demonstrating that chronic ethanol exposure increases both 2-AG and AEA formation in human neuroblastoma cells and primary cultures of rodent cerebellar granule neurons (Basavarajappa *et al*., 1999; Basavarajappa *et al*., 2000; Basavarajappa *et al*., 2003). Consistently it was shown that chronic ethanol vapor inhalation downregulates CB_1 receptor expression an desensitizes cannabinoid-activated signal transduction in Swiss-Webster mice (Basavarajappa *et al*., 1999; Basavarajappa *et al*., 1998; Vinod *et al*., 2006) similar to the effects produced by chronic exposure to both synthetic and endogenous CB_1 agonists (Oviedo *et al*., 1993; Romero *et al*., 1995; Romero *et al*., 1998). The effects of voluntary ethanol consumption on brain eCB content has been evaluated by several groups, and while the results clearly demonstrate alcohol-induced alterations in brain eCBs it is difficult to define a clear picture of regional effects from the published literature. For example, while some studies report increased AEA content in the limbic forebrain and NAc of alcohol-exposed rats (Gonzalez *et al*., 2002b; Gonzalez *et al*., 2004a; Malinen *et al*., 2009), other studies report significant AEA decreases in components of the limbic forebrain such as the amygdala, hippocampus, PFC (Malinen *et al*., 2009; Rubio *et al*., 2007). Moreover, ethanol consumption is reported to both increase and decrease AEA content in the caudate putamen, and to increase and decrease 2-AG content in the PFC (Malinen *et al*., 2009; Rubio *et al*., 2007). These differential findings may result from differences in rat strain, gender, amount of daily ethanol consumption duration of ethanol exposure, and post-exposure time that was evaluated. Moreover, quantification of tissue eCB content is highly sensitive to the procedures employed for tissue harvesting, eCB extraction and analysis and methodological differences likely also underlie between-study differences in observations (Buczynski *et al*., 2010).

Nicotine-induced alterations in brain eCB content have also been reported. For example, repeated nicotine administration (1 mg/kg/day for 7 days) significantly increases both AEA and 2-AG levels in the brainstem and significantly decreases levels of these eCBs in the cortex, while some regions such as limbic forebrain and caudate putamen display significant elevations in AEA but not 2-AG content. (Gonzalez *et al*., 2002b). Marco and colleagues observed a significant increase in hippocampal CB_1 receptor expression and decrease in

striatal CB_1 receptor expression 1 month after a 10-day period of nicotine administration in Wistar rats, though no changes in CB_1 expression were observed in tissue harvested 2h after the final nicotine treatment (Marco *et al*., 2007). Werling and colleagues compared the effects of subchronic nicotine exposure on CB_1 receptor expression in periadolescent and adult Sprague Dawley rats (Werling *et al*., 2009). Twenty-four hours after the final nicotine exposure CB_1 receptor binding was significantly increased in the prelimbic PFC, VTA and hippocampus of adolescent, but not adult rats. Collectively these findings suggest that repeated nicotine exposure alters CB_1 receptor function presumably through nicotine-induced alterations in brain eCB levels.

Opiate administration has also been shown to differentially alter both AEA and 2-AG content in rat brain. Vigano and colleagues report that repeated morphine injections significantly reduce 2-AG content in the striatum, cortex, hippocampus, hypothalamus and limbic forebrain, while AEA content in these same samples was unaltered (Vigano *et al*., 2003). Higher morphine doses also significantly reduce 2-AG content in the ventral striatum and hippocampus, but increase AEA content in the dorsal and ventral striatum, hippocampus and PFC (Vigano *et al*., 2004). Chronic morphine exposure significantly alters CB_1 receptor expression in several brain regions including the NAc, caudate, hippocampus and amygdala (Gonzalez *et al*., 2002a) and this may result from morphine-induced alterations in brain eCB production.

Several studies have evaluated the effect of psychostimulant administration on brain eCB levels. Patel and colleagues observed that AEA or 2-AG content in mouse limbic forebrain tissue was unaltered by acute cocaine doses up to 10 mg/kg (Patel *et al*., 2003). However, 20 mg/kg cocaine produced a subtle, but significant increase in limbic forebrain 2-AG content with no concurrent alteration in tissue AEA content. Gonzalez and colleagues reported that repeated cocaine exposure (15 mg/kg, 2x/day for 10 days) does not alter AEA or 2-AG content in hippocampus, cerebral cortex, caudate putamen, midbrain, mesencephalon, brainstem or cerebellum (Gonzalez *et al*., 2002b). Unlike the stimulatory effects of acute cocaine on 2-AG content in mouse limbic forebrain (Patel *et al*., 2003), 10 days' exposure to cocaine induced subtle but significant reductions in 2-AG levels in rat limbic forebrain tissue (AEA content was unaltered (Gonzalez *et al*., 2002b)). In contrast to the subtle effects of cocaine observed in whole animal studies, i*n vitro* studies in rat brain striatal slices have shown that acute superfusion with 10 μM cocaine robustly increases AEA levels in the superfusion media, most likely through a combined increase in NAPE-PLD activity and decrease in FAAH activity (e.g. both increased AEA formation and decreased AEA clearance (Centonze *et al*., 2004)). Interestingly, these cocaine-induced effects were reliant on dopamine D_2 receptor signaling, and were mimicked by superfusion with the D_2-selective agonist quinpirole (Centonze *et al*., 2004), consistent with other evidence of a facilitory D_2 receptor influence on brain AEA levels (Giuffrida *et al*., 1999; Giuffrida *et al*., 2004; Patel *et al*., 2003). Moreover, cocaine-induced reductions in GABA mediated spontaneous IPSCs were significantly attenuated by SR141716A (Centonze *et al*., 2004), suggesting an AEA involvement in cocaine-induced inhibition of presynaptic GABA transmission in the striatum. The effects of cocaine on striatal 2-AG levels were not evaluated in this study. The more robust effects of cocaine on eCB levels observed in *in vitro* vs. *in vivo* preparations may result from the simplified neuronal environment provided by the isolated brain slice preparation, or possibly from differences in sustained brain cocaine concentrations in these paradigms. In addition to cocaine, Patel and colleagues evaluated the effects produced by acute administration of the dopamine/norepinephrine releasing drug methylphenidate (Ritalin) and the selective dopamine transport inhibitor GBR12909 (Patel *et al*., 2003). Both of these stimulant drugs dose-dependently reduced AEA levels in limbic forebrain tissue, and methylphenidate also significantly reduced 2-AG content in these samples (a non-significant trend toward GBR12909-induced reductions in

2-AG was also evident). The differential eCB effects produced by cocaine, GBR12909 and methylphenidate may result from differences in monoaminergic selectivity or perhaps differences in pharmacodynamic mechanism.

Collectively these studies indicate that Δ9-THC, ethanol, nicotine and opiates can alter rat brain eCB content. Although drug-induced increases and decreases have been reported, these findings are generally consistent with the substantial literature demonstrating a CB_1 receptor influence in the behavioral effects of each of these drugs. Although there is relatively less information available on cocaine-induced alterations in brain eCB content, the subtle changes in eCB levels observed following relatively high dose cocaine administration correlates with behavioral evidence suggesting only a subtle CB_1 influence on psychostimulant-induced behaviors.

As a complement to eCB measures from bulk brain tissue *in vivo* microdialysis methods have recently been developed for quantifying eCB levels in the brain interstitial space (Buczynski *et al*., 2010) and a few studies have utilized this approach to evaluate drug-induced alterations in brain eCB levels. Bequet and colleagues observed that acute systemic WIN 55,212-2 administration significantly increases 2-AG and decreases AEA levels in rat hypothalamic microdialysates (Bequet *et al*., 2007). This effect of WIN 55,212-2 was blocked by moderate SR141716A doses, and high dose SR141716A administration itself was found to produce an opposite effect (e.g. decrease in 2-AG, increase in AEA). These data suggest that CB_1 receptor activation activates 2-AG production and inhibits AEA production in the rat hypothalamus. Caillé and colleagues observed that ethanol, heroin and cocaine self-administration results in dose-dependent and drug-specific alterations in eCB levels in microdialysates collected from the NAc (Caille *et al*., 2007). Ethanol self-administration increased 2-AG levels without altering dialysate AEA levels, and the rise and fall of dialysate 2-AG content followed the pattern of blood alcohol concentrations typically observed following oral consumption. In contrast, heroin self-administration led to dose-dependent increases in dialysate AEA content with delayed decreases in dialysate 2-AG levels, while cocaine self-administration did not alter dialysate levels of either AEA or 2-AG. Consistent with the drug-specific alterations in NAc eCB levels ethanol and heroin self-administration were dose-dependently reduced by either systemic or intra-accumbens CB_1 antagonist administration, while these same antagonist treatments did not alter cocaine self-administration (Caille *et al*., 2006; Caille *et al*., 2007). These findings suggest that drug-induced increases in NAc eCB formation modulate the reinforcing properties of certain abused substances. Regionally specific effects of drug intake on interstitial eCB levels have also been observed. For example, ethanol self-administration increases 2-AG content in dialysates collected from the NAc (Caille *et al*., 2007) and ventral tegmental area (Parsons, unpublished observations), but does not alter either 2-AG or AEA levels in dialysates collected from the medial PFC (Alvarez-Jaimes *et al*., 2009a). Additional studies have revealed that several factors can affect drug-induced alterations in interstitial eCB levels, including the route, dose and contingency of drug administration as well as the prior history of drug exposure (Alvarez-Jaimes *et al*., 2009b; Ferrer *et al*., 2007; Orio *et al*., 2009). These factors have also been shown to affect measures of drug-induced alterations in bulk tissue eCB content.

Collectively these observations provide initial evidence that brain eCB levels are altered following exposure to various drugs of abuse. However, due to the variability associated with between-study quantitative measures of brain eCB content (Buczynski *et al*., 2010) and differences in drug dosing regimen, a clear picture of the effects of distinct classes of abused drugs on brain eCB formation has yet to emerge, and more work is needed in this regard.

6. Endocannabinoids, synaptic plasticity and addiction

Synaptic plasticity is considered one of the primary mechanisms underlying learning and memory processes, and is thought to be vital for experience-dependent modifications in neural function that underlies behavioral flexibility. Several conceptualizations of addiction posit that drugs of abuse "hijack" plasticity mechanisms in circuits responsible for reinforcement and reward, and in this way addiction represents a powerful pathological form of learning and memory (Berke *et al*., 2000; Everitt *et al*., 2001; Everitt *et al*., 1999; Hyman, 2005; Hyman *et al*., 2006; Jentsch *et al*., 1999; Kalivas *et al*., 2008; Kauer, 2004; Kauer *et al*., 2007; Kelley, 2004; Thomas *et al*., 2008; Torregrossa *et al*., 2011; White, 1996). Substantial evidence supports a fundamental role of synaptic plasticity in the VTA and regions innervated by VTA dopamine projections in the behavioral response to initial drug exposure. Moreover, plastic events in regions such as the NAc, PFC and other limbic structures likely participate in the formation of conditioned associations between drug reward and a variety of internal and external cues associated with drug intake. These conditioned cues subsequently exert powerful motivational effects on drug intake and relapse to drug consumption following periods of abstinence (Kalivas *et al*., 2008). Drug-induced alterations in long-term plastic events in limbic circuitry involved in stress, reward and emotional memory have also been described (Childress *et al*., 1999; Dumont *et al*., 2005; Fu *et al*., 2007; Grueter *et al*., 2006; Weitlauf *et al*., 2004), and these processes likely contribute to dysregulated stress responses and affective state associated with drug dependence and protracted withdrawal (Koob, 2008).

Endocannabinoids are well known to suppress neurotransmitter release at both excitatory and inhibitory synapses with both short- and long-term effects (Alger, 2002; Chevaleyre *et al*., 2006; Diana *et al*., 2004; Kano *et al*., 2009; Lovinger, 2008; Marsicano *et al*., 2006; Wilson *et al*., 2002). Endocannabinoid-mediated short-term synaptic plasticity includes depolarization-induced suppression of excitation (DSE) that results from suppression of presynaptic glutamate release, and depolarization-induced suppression of inhibition (DSI) resulting from inhibition of presynaptic GABA release. These effects typically persist for a minute or less. Endocannabinoids are also involved in long-term forms of synaptic plasticity including long-term potentiation (LTP) that is a long-lasting increase in the strength of synaptic signaling, and long-term depression (LTD) that is a prolonged weakening of synaptic strength. LTP and LTD can persist for hours to weeks and are particularly important for various forms of learning and memory.

In 2003 the Lupica group reported that eCB-mediated LTD of excitatory signaling in the rat NAc is abolished following chronic treatment with either Δ9-THC or WIN 55,212-2, and this effect was correlated with decreased CB_1 receptor influence at both excitatory and inhibitory synapses (Hoffman *et al*., 2003). Soon thereafter the Manzoni lab reported that a single Δ9-THC exposure abolishes eCB-mediated LTD of both excitatory and inhibitory transmission in the mouse NAc and hippocampus (Mato *et al*., 2004). This effect was transient (< 24h) and associated with tolerance to CB_1 receptor agonists, consistent with the findings by Hoffman and colleagues. Subsequently the Manzoni group reported that LTD of NAc excitatory transmission is not altered following chronic Δ9-THC treatment despite the presence of diminished CB_1 receptor G-protein coupling and tolerance to CB_1 receptor agonist effects on excitatory transmission (Mato *et al*., 2005). This surprising preservation of LTD following repeated Δ9-THC exposure was found to result from recruitment of mGluR2/3 mechanisms that were posited to compensate for reduced eCB influence resultant from desensitized CB_1 receptor function. The reasons for the differential reported effects of repeated Δ9-THC exposure on NAc LTD are not clear, though several experimental factors distinguish these studies including nearly 7-fold differences in Δ9-THC dose and the rodent species under study (Sprague Dawley rats vs. C57Bl/6 mice).

Acute and repeated alcohol exposure also disrupts eCB-mediated synaptic plasticity. Short periods of low-frequency stimulation produce a CB_1-dependent long-lasting disinhibition (DLL) of striatal output neurons as a result of reduced synaptic strength at inhibitory synapses (Adermark *et al*., 2009). Acute exposure of striatal slices to moderate ethanol doses substantially reduces eCB-mediated DLL in the dorsolateral striatum (Clarke *et al*., 2010). DLL is also significantly reduced in the dorsolateral striatum of rats following long-term voluntary alcohol consumption (Adermark *et al*., 2011). Endocannabinoid-mediated LTD at inhibitory striatal synapses is also reduced by acute ethanol, though no significant ethanol effects are evident on LTD of excitatory synapses (Clarke *et al*., 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 ethanol-induced interference in eCB-LTD contributes to maladaptive habitual behavior associated with addiction.

Similar to Δ9-THC, a single injection of a moderately high cocaine dose (20 mg/kg) abolishes eCB-mediated LTD of excitatory transmission in the mouse NAc (Fourgeaud *et al*., 2004), thereby resulting in heightened excitatory signaling in this region. This was not associated with reduced CB_1 receptor function but was correlated with reduced mGluR5 expression and influence suggesting that cocaine-induced abolition of eCB-LTD results from diminished mGluR5-mediated eCB production. In concert with this, repeated cocaine exposure reduces the inhibition of rat VTA dopamine cells through facilitated induction of eCB-mediated LTD of GABAergic cells (Pan *et al*., 2008). This effect is reliant on dopamine D_2, mGluR5 and CB_1 receptors (Liu *et al*., 2005), and is attenuated following inhibition of PLC or DAGL function (Pan *et al*., 2008), implicating a role for 2-AG in this process. Collectively these findings suggest that cocaine-induced disruption of eCB-LTD results in imbalanced mesolimbic dopamine function characterized by diminished inhibitory control over VTA dopamine cells and heightened excitatory signaling in the NAc. Cocaine-induced disruption of eCB-mediated LTD of excitatory transmission has also been observed in the BNST (Grueter *et al*., 2006). This effect was induced by either repeated administration of non-contingently administered cocaine injections or response-contingent cocaine self-administration. However, in contrast to the effects reported in NAc (Fourgeaud *et al*., 2004; Swanson *et al*., 2001), cocaine-induced disruption of eCB-LTD in the BNST was evident only after repeated cocaine exposure and was not present following a single cocaine injection. The BNST is a stress-responsive structure and excitatory transmission in this region is critical in mediating stress – reward interactions and anxiety-like behavior (Delfs *et al*., 2000; McElligott *et al*., 2009; Stewart, 2000). The BNST extends a substantial projection to the VTA (Dong *et al*., 2006) and accordingly drug-related disruption of BNST plasticity is likely to influence motivational responses to stress. As reviewed below, dysregulation of stress reactivity is a major adverse consequence of long-term drug exposure that plays a primary role in relapse to drug use.

7. Endocannabinoids, drug-seeking and relapse

Drug addiction is characterized by compulsive drug-seeking and use that is associated with a high incidence of relapse to drug use following periods of abstinence (Leshner, 1997; McLellan *et al*., 2000; O'Brien *et al*., 1996; O'Brien *et al*., 1998). Substantial difficulties with relapse have been described for a range of abused substances including opiates, ethanol, nicotine and cocaine (Chutuape *et al*., 2001; Cooney *et al*., 1997; Covey *et al*., 2000; Gossop *et al*., 1989; Kaplan *et al*., 1985; Laberg, 1986; Mendelson *et al*., 1996; O'Brien, 1997; Silagy *et al*., 2004). Several factors are believed to be causal in drug relapse including craving induced by exposure to environments or situations previously associated with drug use (e.g. conditioning factors) (Carter *et al*., 1999; O'Brien *et al*., 1992), acute exposure to the drug itself or a pharmacologically related agent during abstinence (e.g. drug

priming) (de Wit, 2000; Jaffe *et al*., 1989) and stressful events (Kosten *et al*., 1986; Kreek *et al*., 1998; Sinha *et al*., 1999).

Recently developed animal models of drug seeking have contributed substantially to our understanding of the neurobiological mechanisms underlying drug relapse (See, 2005; Shaham *et al*., 2000; Shalev *et al*., 2002; Stewart, 2000; Weiss, 2005). These models have identified important roles for glutamate, dopamine, GABA, serotonin, opioid peptides and stress-related peptides (e.g. CRF) in relapse-related behavior (Crombag *et al*., 2008; Weiss, 2005; Yahyavi-Firouz-Abadi *et al*., 2009). Recent studies have also demonstrated an important influence of cannabinoid signaling in the re-initiation of drug-seeking and taking behaviors. For example, direct acting CB_1 agonists such as Δ9-THC, HU-210, WIN 55,212-2, and CP 55,940 reinstate extinguished drug-seeking behavior for cannabinoids (Justinova *et al*., 2008a; Spano *et al*., 2004), opioids (De Vries *et al*., 2003; Fattore *et al*., 2003; Fattore *et al*., 2005b), ethanol (Lopez-Moreno *et al*., 2004; McGregor *et al*., 2005), nicotine (Biala *et al*., 2008) and cocaine (De Vries *et al*., 2001).

Drug-seeking behavior associated with a variety of abused substance is attenuated following CB_1 receptor antagonism. For example, SR141716A significantly reduces operant responding by squirrel monkeys reinforced by a conditioned cue that was previously paired with Δ9-THC self-administration (Justinova *et al*., 2008a). In a similar manner, SR1417161A dose-dependently attenuates cue-induced and heroin-primed reinstatement of heroin-seeking behavior in rats (De Vries *et al*., 2003; Fattore *et al*., 2003; Fattore *et al*., 2005a). Bilateral SR141716A infusions into the PFC and NAc shell dose-dependently attenuate cue-induced reinstatement of heroin-seeking behavior (Alvarez-Jaimes *et al*., 2008), consistent with evidence that expression of goal-directed behaviors in response to drug-paired stimuli relies on these structures (Kalivas *et al*., 2005). However, despite substantial evidence of an important involvement of the BLA in cue-induced drug-seeking behavior (See, 2005; Weiss, 2005) and the dense expression of CB_1 receptors in this region (Herkenham *et al*., 1991b), cue-induced heroin-seeking behavior was unaltered by intra-BLA SR141716A administration (Alvarez-Jaimes *et al*., 2008).

CB_1 receptor antagonism also attenuates ethanol-seeking behavior. SR 141716A reduces cue-induced reinstatement of ethanol-seeking behavior (Cippitelli *et al*., 2005; Economidou *et al*., 2006) and reduces excessive ethanol intake present following periods of abstinence (an animal model of relapse-like alcohol consumption (Spanagel *et al*., 2000)). Both SR141716A and the similar CB_1 antagonist SR147778 reduce this “alcohol deprivation effect” when the antagonists are systemically administered prior to the post-deprivation access to alcohol (Gessa *et al*., 2005; Serra *et al*., 2002). In contrast, subchronic WIN 55,212-2 administration during alcohol abstinence increases the magnitude and duration of post-deprivation elevations in alcohol consumption (Alen *et al*., 2008; Lopez-Moreno *et al*., 2004). These observations suggest that CB_1 receptors exert a facilitory influence on post-abstinence increases in alcohol consumption.

Reinstatement of nicotine-seeking behavior evoked by non-contingent presentation of a drug-paired stimulus is dose-dependently reduced by SR 141716A (Cohen *et al*., 2005; De Vries *et al*., 2005) as is nicotine-seeking behavior precipitated by exposure to environments previously paired with nicotine self-administration (Diergaarde *et al*., 2008). These findings suggest that CB_1 receptor blockade reduces the motivational saliency of both discrete and contextual cues associated with drug intake. However, as demonstrated by De Vries and colleagues (De Vries *et al*., 2005) SR 141716A also suppresses cue-induced sucrose-seeking behavior, suggesting a CB_1 receptor influence on both drug-associated and generalized conditioned reinforcement. Similar to the work on heroin-seeking behavior described above, bilateral SR141716A infusions into the NACsh dose-dependently reduce cue-induced

nicotine-seeking behavior (Kodas *et al*., 2007). Significant reductions were also observed following CB_1 antagonist infusion into the PFC and BLA.

Despite inconsistent and subtle CB_1 receptor effects on psychostimulant self-administration, growing evidence demonstrates a substantial CB_1 receptor influence on psychostimulant-seeking behavior. In fact, the first evidence of CB_1 antagonist effects on drug-seeking behavior was gathered by De Vries and colleagues who observed that SR 141716A dose-dependently attenuates both cocaine-primed and cue-induced reinstatement of cocaine-seeking behavior in rats (De Vries *et al*., 2001). These findings were subsequently replicated by others using higher SR 141716A doses (Filip *et al*., 2006) and the more selective CB_1 receptor antagonist AM251 (Xi *et al*., 2006). Interestingly, Xi and colleagues observed that AM251 selectively attenuates reinstatement of cocaine- but not sucrose-seeking behavior which stands in contrast to earlier work demonstrating that SR141716A significantly reduces both drug- and sucrose-seeking (De Vries *et al*., 2005). Cue-induced reinstatement of cocaine self-administration by C57/BL6 mice is also significantly reduced by SR 141716A, as is “priming”-induced reinstatement of oral corn oil self-administration (Ward *et al*., 2009). This latter finding again suggests that CB_1 receptors modulate the motivational saliency of cues conditioned to both drug and non-drug rewards. A CB_1 receptor influence on psychostimulant-seeking may not be restricted to cocaine, as SR 141716A also significantly reduces both priming- and cue-induced reinstatement of methamphetamine-seeking behavior (Anggadiredja *et al*., 2004) though comparable effects were not observed using AM251 (Boctor *et al*., 2007). Finally, a recent study by Gerdeman and colleagues demonstrates that expression of behavioral sensitization to cocaine is reduced by SR 141716A in a context-dependent manner, such that attenuation is observed only when the animals are tested in a cocaine-paired environment and not when tested with identical drug treatments in a non-paired environment (Gerdeman *et al*., 2008). This observation further supports a CB_1 receptor involvement in modulation of the perception and/or motivational saliency of drug-paired cues.

Recent studies have begun evaluating the effect of eCB clearance inhibitors on drug-seeking behavior as a more direct means of investigating the effect of eCB tone on relapse-related behaviors. In squirrel monkeys administration of the FAAH inhibitor URB597 does not promote reinstatement of drug-seeking behavior previously maintained by Δ9-THC, cocaine or AEA (Justinova *et al*., 2008b). Similarly, neither URB597 nor the eCB reuptake inhibitor AM404 alter cue- or stress-induced reinstatement of ethanol-seeking behavior in rats (Cippitelli *et al*., 2007; Cippitelli *et al*., 2008). However, two studies have determined that URB597 significantly reduces both drug priming- and cue-induced nicotine-seeking behavior (Forget *et al*., 2009; Scherma *et al*., 2008b), and both URB597 and PMSF significantly attenuate both priming- and cue-induced cocaine-seeking behavior (Adamczyk *et al*., 2009). These observations are somewhat surprising in light of evidence that CB_1 receptor stimulation enhances drug-seeking and FAAH inhibition is expected to produce substantial increases in brain AEA levels. However, FAAH hydrolyzes a large number of fatty acid moieties in addition to AEA (Ahn *et al*., 2008) and it is conceivable that the effects of FAAH inhibition on drug-seeking are mediated through a non-AEA lipid signaling molecule. Moreover, it should be borne in mind that AEA potently activates non-CB_1 signaling mechanisms such as TRPV1 receptors that are known to mediate behavioral effects that are sometimes opposite to those produced by CB_1 activation (Micale *et al*., 2009; Santos *et al*., 2008; Terzian *et al*., 2009).

8. Endocannabinoids, stress responsivity and addiction

A substantial clinical and preclinical literature indicates that various forms of stress are involved in the etiology and maintenance of drug dependence. Stress often precedes the

development of substance use disorders (Jose *et al*., 2000; Richman *et al*., 1996; Rospenda *et al*., 2000), and preclinical studies have shown that stress and glucocorticoids increase the acquisition of drug self-administration (Goeders, 2002; Goeders *et al*., 1996; Koob *et al*., 2007; Lynch *et al*., 1999; Vengeliene *et al*., 2003). There is some evidence to suggest that both stress- and drug-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis sensitizes the function of reward pathways through glucocorticoid mechanisms (Piazza *et al*., 1998; Rouge-Pont *et al*., 1998; Rouge-Pont *et al*., 1995; Tidey *et al*., 1997). High glucocorticoid levels and increased levels of stress-related peptides have been proposed to contribute to an allostatic state that results from long-term drug exposure. In the context of drug use, initial exposure produces a positive hedonic response followed by a minor negative response (e.g. withdrawal, or "hangover") that is hypothesized to involve recruitment of brain stress systems. Continued drug use prior to the resolution of the negative response prevents the reestablishment of homeostasis, and is hypothesized to lead to the transition to an allostatic reward state that is driven in part by an overactive HPA axis and recruitment of stress peptide systems ultimately resulting in an escalation of drug consumption (Koob *et al*., 2007; Koob *et al*., 1997; Le Moal, 2009).

In this context, 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; Hill *et al*., 2010). There is substantial CB_1 receptor expression in brain regions involved in stress responsivity, including the hippocampus, PFC, amygdala, hypothalamus and midbrain monoaminergic nuclei such as the locus coeruleus and dorsal raphe. Tasker and colleagues have demonstrated that CB_1 receptor activation inhibits glutamatergic activation of CRF neurosecretory neurons, and that glucocorticoid inhibition of CRF release is mediated by eCB/CB_1 signaling (Di *et al*., 2003). CB_1 receptor knockout mice exhibit enhanced HPA axis activity with heightened basal plasma ACTH and corticosterone levels, enhanced pituitary ACTH secretion in response to CRF and increased CRF mRNA levels in the PVN (Barna *et al*., 2004; Cota *et al*., 2007; Haller *et al*., 2004). CB_1 receptor deficient mice also exhibit exaggerated stress-induced secretion of both ACTH and corticosterone as compared with wildtypes (Barna *et al*., 2004; Haller *et al*., 2004; Uriguen *et al*., 2004; Valverde, 2006). Consistently, CB_1 antagonist administration increases basal and stress-induced corticosterone secretion and enhances stress-induced neuronal activation in the PVN (Manzanares *et al*., 1999a; Patel *et al*., 2004; Wade *et al*., 2006) while CB_1 agonists and eCB clearance inhibitors significantly attenuate stress-induced corticosterone secretion (Patel *et al*., 2004). Collectively these findings indicate that eCB signaling is capable of dampening HPA axis activity.

Several studies indicate that eCB production is increased in response to stress. In humans the Trier social stress test rapidly increases circulating levels of 2-AG without affecting circulating levels of AEA (Hill *et al*., 2009a). Both *in vitro* and *in vivo* studies in rodents have demonstrated that glucocorticoids such as corticosterone increase AEA and 2-AG production in the PVN, amygdala, hippocampus and hypothalamus (Di *et al*., 2003; Di *et al*., 2009; Di *et al*., 2005a; Di *et al*., 2005b; Hill *et al*., 2010; Malcher-Lopes *et al*., 2006). Moreover, brief footshock stress increases eCB levels in the periaqueductal grey (Hohmann *et al*., 2005) and acute restraint stress produces 2-AG elevations in PFC, hippocampus and hypothalamus. Sensitization of stress-induced increases in forebrain and amygdalar 2-AG levels following repeated episodes of restraint has been linked to the behavioral and physiological habituation to repeated homotypic stress (Patel *et al*., 2005b; Patel *et al*., 2004). These findings demonstrate that stress can increase eCB levels in the CNS, and that this effect provides a homeostatic feedback mechanism dampening stress responses.

An alternate hypothesis posits that eCBs exert a tonic steady-state regulation of HPA activity, and that stress-induced reductions in AEA content in the amygdala, PFC and

hippocampus (Hill *et al*., 2008b; Hill *et al*., 2009b; Patel *et al*., 2005b; Rademacher *et al*., 2008) allow for enhanced HPA axis activation and the subsequent expression of stress responses (Patel *et al*., 2004). Restoration of AEA tone or the prevention of AEA decrements (through eCB clearance inhibition) would therefore maintain constraint of the HPA axis and attenuate stress responses. Regardless of the specific mechanism that prevails, it is evident that eCB signaling serves to limit HPA axis activation and may contribute to the termination of stress responses.

In light of the evidence for an eCB influence in the regulation of stress responses, it is conceivable that an alteration in eCB function following long-term drug exposure may contribute to the allostatic shift toward persistent dysregulation of HPA axis function and increased sensitivity to stress that contributes to the maintenance of high levels of drug intake and vulnerability toward relapse associated with drug dependence (Koob *et al*., 2007; Koob *et al*., 1997; Le Moal, 2009). However, direct tests of this hypothesis have not been published and this remains an open question for investigation.

9. Endocannabinoids and affective state related to drug dependence

Withdrawal is a critical component of most definitions of drug dependence and is characterized by impaired physiological function and increased negative affect. Physical symptoms of withdrawal can include fatigue, tremor, perspiration, convulsions and nausea. These symptoms may vary as a function of drug class and typically dissipate after the first few days of abstinence. While unpleasant, physical withdrawal symptoms are not thought to play a significant role in relapse to drug taking (with the exception of opiates). Withdrawal from most classes of abused drugs is also associated with increased negative affective symptoms such as anxiety and depression (Alling *et al*., 1982; Carmody, 1992; Coffey *et al*., 2000; Janiri *et al*., 2005; Nunes *et al*., 2004a; Nunes *et al*., 2004b; Voltaire-Carlsson *et al*., 1996). These negative affective states can persist for many months during protracted abstinence and their severity is hypothesized to be closely associated with susceptibility to relapse (Annis *et al*., 1998; Miller *et al*., 2000). Accordingly there has been substantial interest in elucidating the neural mechanisms contributing to withdrawal-related affective dysregulation with the aim of identifying viable treatment targets for the prolongation of abstinence.

As discussed below, substantial evidence implicates the ECS in the regulation of affective state, and dysfunctional eCB signaling has been associated with increased anxiety and depression. In light of the evidence for drug-induced changes in brain eCB formation and subsequent alterations of eCB signaling following long-term drug exposure (see sections 4 – 6) it is conceivable that dysregulated eCB function contributes to affective disturbances associated with drug dependence and protracted withdrawal.

9.1 Anxiety

CB_1 receptors are expressed in high density in key regions implicated in the regulation of anxiety such as the amygdala, hippocampus, anterior cingulate cortex and PFC (Glass *et al*., 1997; Herkenham *et al*., 1991a; Herkenham *et al*., 1991b; Herkenham *et al*., 1990; Katona *et al*., 2001). It has long been recognized that cannabis produces a bimodal effect on anxiety in humans, with low doses having anxiolytic effects and high doses having anxiogenic effects (Ashton, 2001; Dannon *et al*., 2004; Hall *et al*., 1998; Tournier *et al*., 2003). Similar biphasic effects of cannabinoid agonists on anxiety-like behaviors have been observed in rats and mice (Viveros *et al*., 2005). The mechanisms contributing to these dose-related differences in cannabinoid-induced anxiety-like behavior have not been fully characterized. It is possible that different behavioral effects are produced by activation of CB_1 receptors versus novel non-CB_1 cannabinoid sensitive receptors (Hajos *et al*., 2002; Haller *et al*.,

2002). For example, Rubino and colleagues observed that activation of CB_1 receptors by low doses of exogenous AEA produces an anxiolytic-like effect, while higher AEA doses produce an anxiogenic-like effect through the activation of transient receptor potential vanilloid (TRPV1) receptors (Rubino *et al*., 2008). Opposing influences of these receptors in the control of anxiety-like behavior has been well documented in rodent studies (Aguiar *et al*., 2009; Micale *et al*., 2009; Terzian *et al*., 2009). It is also possible that the CB_1 receptor-mediated effects on anxiety-like behavior vary in a region-dependent manner, with anxiolytic-like effects produced in the PFC, ventral hippocampus and periaqueductal grey (Lisboa *et al*., 2008; Moreira *et al*., 2007; Rubino *et al*., 2008) and anxiogenic-like effects produced in dorsal hippocampus and amygdala (Onaivi *et al*., 1995; Roohbakhsh *et al*., 2007; Rubino *et al*., 2008).

In addition, there is considerable evidence that manipulation of the ECS can substantially modulate anxiety-related behavioral responses. Elevation of interstitial eCB levels through inhibition of eCB clearance mechanisms produces anxiolytic-like effects in the elevated zero-maze, elevated plus-maze, light-dark transfer test, defensive withdrawal tests and the isolation-induced ultrasonic emission test in pups (Bortolato *et al*., 2006; Braida *et al*., 2007; Haller *et al*., 2009; Kathuria *et al*., 2003; Micale *et al*., 2009; Moise *et al*., 2008; Moreira *et al*., 2008; Naderi *et al*., 2008; Naidu *et al*., 2007; Patel *et al*., 2006; Rutkowska *et al*., 2006; Scherma *et al*., 2008a). Unlike traditional anxiolytics such as benzodiazepines, enhancement of eCB tone appears to produce effects on anxiety-like behavior only under aversive or stressful conditions (Haller *et al*., 2009; Naidu *et al*., 2007). Moreover, unlike exogenous CB_1 receptor agonists, eCB clearance inhibitors do not produce dramatic bi-phasic effects on anxiety-like behavior but appear to only produce anxiolytic-like behavioral effects. Thus, increased eCB tone produces anxiolytic-like effects, particularly under stressful or aversive conditions.

In contrast, reduced CB_1 receptor signaling produces anxiogenic-like behavioral effects. CB_1 knockout mice display increased aggression in the resident-intruder test, and anxiogenic-like responses in the light/dark box, elevated plus-maze and social interaction tests and hypersensitivity to the effects of restraint stress on HPA activation (Haller *et al*., 2002; Martin *et al*., 2002; Uriguen *et al*., 2004). There is some indication that the anxiogenic profile observed in CB_1 knockout mice is most apparent under conditions of heightened stress such as bright light on the EPM and an unfamiliar environment in the social interaction test (Haller *et al*., 2002), and this may explain why some investigators have not observed anxiogenic-like responses on the EPM (Marsicano *et al*., 2002). In wildtype mice SR141716A produces anxiogenic-like effects in the defensive withdrawal and elevated plus maze tests, and the isolation-induced ultrasonic emission test in pups (Arevalo *et al*., 2001; McGregor *et al*., 1996; Navarro *et al*., 1997). SR141716A also increases Fos expression in anxiety-related structures (Patel *et al*., 2005a). Based on these observations, deficient eCB tone appears to increase anxiety-like behavior with effects more consistently observed under stressful or aversive conditions.

In addition to the expression of generalized symptoms of anxiety, the ECS may play a particular role in phobias and post-traumatic stress disorder (PTSD) that are characterized by a reduced capacity to suppress emotionally aversive memories. Disruption of CB_1 receptor signaling impairs the extinction of aversive memories (Cannich *et al*., 2004; Chhatwal *et al*., 2005; Chhatwal *et al*., 2006; Chhatwal *et al*., 2009; de Oliveira Alvares *et al*., 2008; Harloe *et al*., 2008; Kamprath *et al*., 2006; Marsicano *et al*., 2002; Niyuhire *et al*., 2007; Pamplona *et al*., 2008; Pamplona *et al*., 2006; Reich *et al*., 2008; Suzuki *et al*., 2004) without altering the capacity to extinguish appetitive memories (Harloe *et al*., 2008; Holter *et al*., 2005; Niyuhire *et al*., 2007). Conversely, CB_1 receptor activation either through direct pharmacologic stimulation or facilitation of eCB signaling accelerates the extinction of

aversive memory (Bitencourt *et al*., 2008; Chhatwal *et al*., 2005; de Oliveira Alvares *et al*., 2008; Pamplona *et al*., 2008; Pamplona *et al*., 2006). This appears to be mediated primarily in the BLA where eCB levels are increased during extinction trials that serve to suppress aversive memories (Marsicano *et al*., 2002).

Collectively the evidence published to date indicates the eCB system participates in a negative feedback system that limits the expression of anxiety under stressful circumstances and that contributes to the suppression of aversive or fearful memories. Accordingly, dysregulation of eCB function may contribute to abnormal anxiety-like responses to stress and reduced capacity to recover from emotionally traumatic and stressful experiences. To the extent that aversive memory is involved in relapse to drug taking behavior (Kaplan *et al*., 2011; Quirk *et al*., 2003; Stewart *et al*., 2001) these findings suggest the ECS as a potential pharmacological target for enhancing the efficacy of extinction therapy for addiction.

9.2 Depression

Deficiencies in CB_1 receptor signaling appear to produce depressive-like symptoms in rodents and humans. CB_1 knockout mice more rapidly become anhedonic during chronic mild stress exposure than do wildtype mice (Martin *et al*., 2002) and exhibit increased passive stress coping behaviors in paradigms such as the forced swim test and tail suspension test (Aso *et al*., 2008; Steiner *et al*., 2008). As previously noted, CB_1 knockout mice display a heightened HPA axis response to stress (Uriguen *et al*., 2004), in line with one of the most consistent findings in major depressive disorder. Although acute CB_1 receptor antagonist administration produces antidepressive-like responses in rodents (Griebel *et al*., 2005; Shearman *et al*., 2003; Takahashi *et al*., 2008; Tzavara *et al*., 2003), recent evidence suggests that a depression-like profile is evident following chronic antagonist administration (Beyer *et al*., 2010). Long-lasting CB_1 receptor blockade induces a depressive behavioral phenotype in rats that is associated with well-known biochemical markers of depression along with diminished neuroplasticity and synaptic efficiency in the PFC (Rubino *et al*., 2009; Rubino *et al*., 2008). Perhaps the most important data in this regard are clinical reports from the use of Rimonabant (SR141716A) for the treatment of obesity in which significant signs of anxiety and depression were presented even in individuals with no prior history of these affective disorders (Christensen *et al*., 2007; Nissen *et al*., 2008). Similar effects were observed in trials with the structurally distinct CB_1 receptor antagonist Taranabant (Aronne *et al*., 2010). Recent evidence also suggests that a single nucleotide polymorphism (SNP) in the CB_1 receptor gene (rs7766029) is highly associated with increased symptoms of depression following recent negative life events (Juhasz *et al*., 2009), and a different CB_1 receptor gene SNP (rs1049353) is associated with a diminished neuronal response to social reward stimuli and increased resistance to antidepressant treatment (Domschke *et al*., 2008). Reductions in circulating eCBs have also been documented in women with major depression (Hill *et al*., 2008a). All of these data support the hypothesis that impairment of CB_1 receptor signaling leads to depression-like sympomatology.

In general, enhancement of CB_1 receptor signaling produces antidepressant-like behavioral effects. Systemic administration of direct CB_1 receptor agonists reverses behavioral despair in the forced swim test under both acute (Adamczyk *et al*., 2008; Bambico *et al*., 2007; Hill *et al*., 2005; Rutkowska *et al*., 2004) and chronic conditions (Jiang *et al*., 2005; Morrish *et al*., 2009). Enhancement of eCB tone through inhibition of FAAH activity also produces antidepressant-like effects in the forced swim and tail suspension tests, as well as in the chronic stress-induced anhedonia model (Adamczyk *et al*., 2008; Bortolato *et al*., 2006; Gobbi *et al*., 2005; Hill *et al*., 2005; McLaughlin *et al*., 2007; Naidu *et al*., 2007; Rademacher *et al*., 2007). FAAH knockout mice also display an antidepressant profile in the forced swim and tail suspension tests (Bambico *et al*., 2007; Naidu *et al*., 2007). Finally,

administration of direct CB_1 receptor agonists or enhancement of eCB tone through eCB clearance inhibition increases hippocampal neurogenesis (Goncalves *et al*., 2008; Hill *et al*., 2006; Jiang *et al*., 2005; Marchalant *et al*., 2009), which may play a role in the antidepressant profile produced by these manipulations (Drew *et al*., 2007; Perera *et al*., 2008).

10. Genetic variants in endocannabinoid signaling and addiction

10.1 CNR1 polymorphisms

Several genetic polymorphisms of eCB-related genes have been linked to drug and alcohol abuse. Most studies have focused the CNR1 gene that encodes the cannabinoid receptor CB_1. Among the first polymorphisms reported in this system was a triplet repeat of varying number (AAT)n in the 3′-flanking region of the CNR1 (CB_1) genetic locus (Dawson *et al*., 1995). In a 1997 report Comings and colleagues reported a significant linkage to psychostimulant and cannabis dependence in non-Hispanic Caucasians who are homozygous for more than 5 repeats of (AAT)n (Comings *et al*., 1997), and a linkage between this polymorphism was subsequently confirmed for cocaine dependence in an African-Caribbean population (Ballon *et al*., 2006). In addition, a significant relationship between this triplet repeat marker and decreased P300 event-related potential amplitudes in subjects with alcohol and substance abuse disorders has been reported (Johnson *et al*., 1997). A 6-repeat allele of the triplet repeat polymorphism (AATn/A6) was recently found to be significantly associated with impulsivity in a Native American population with a high lifetime prevalence of substance dependence (Ehlers *et al*., 2007) and a similar polymorphism is reportedly associated with ADHD in Spanish alcoholics (Ponce *et al*., 2003). However, other studies have failed to find a significant linkage between the (AAT)n polymorphism and drug dependence (Covault *et al*., 2001; Heller *et al*., 2001; Li *et al*., 2000; Zhang *et al*., 2004).

Another CNR1 gene polymorphism is a silent mutation that results in the substitution of G to A at nucleotide position 1359 in codon 435 (Thr) (Gadzicki *et al*., 1999; Hoehe *et al*., 1991). A modest association between the A/A genotype and alcohol withdrawal delirium has been reported in German patients who are A/A homozygous (Schmidt *et al*., 2002), though further studies in a similar population did not replicate this finding (Preuss *et al*., 2003).

Several single nucleotide polymorphisms (SNPs) in CNR1 appear to be associated with problem drug and alcohol use. A ‘TAG’ haplotype resulting from a combination of three SNPs in intron 2 (rs806379, rs1535255, rs2023239) has been associated with substance abuse in European-Americans, African-Americans and Japanese populations (Zhang *et al*., 2004). Consistent with these observations, two recent reports indicate that SNPs proximal to the TAG haplotypes (rs806380, rs806368) are associated with susceptibility to cannabis dependence while other haplotypes (rs6454674, rs806380, rs806377, rs1049353) are associated with fewer cannabis dependence problems in adolescent and adult European- and African-Americans (Agrawal *et al*., 2009; Hopfer *et al*., 2006). However, these findings were not replicated in a more recent study (Hartman *et al*., 2009). Another CNR1 SNP (rs2023239) is proposed to be a significant predictor of a cannabis withdrawal syndrome and overall levels of cannabis craving during abstinence (Haughey *et al*., 2008). Carriers the rs2023239 G allele also display significantly greater activity in reward-related brain areas during exposure to marijuana-associated cues as compared with carriers of the A/A genotype for this SNP (Filbey *et al*., 2010).

CNR1-associated SNPs, particularly rs6454674 and rs806368, are also associated with cocaine, opioid and alcohol dependence in European Americans and African-Americans (Zuo *et al*., 2007; Zuo *et al*., 2009). However, other studies have not found linkages between CNR1 SNP haplotypes and cocaine, opioid, cannabis or polysubstance dependence (Herman

et al., 2006), though one SNP (rs1535255 T/G) has been linked to alcohol dependence (Herman *et al*., 2006). The C allele of rs2023239 appears to be associated with greater CB_1 binding in the PFC, greater alcohol cue–elicited brain activation in the midbrain and PFC and greater subjective reward when consuming alcohol (Filbey *et al*., 2008; Hutchison *et al*., 2008). Interestingly, this allele is also associated with more positive outcomes in individuals receiving Olanzapine, a medication that targets mesocorticolimbic circuitry (Hutchison *et al*., 2008). Four SNPs in or near the CNR1 gene (rs1535225, rs2023239, rs1049353, rs806368) are associated with increased impulsivity in a Native American population characterized by a high prevalence of alcoholism and substance abuse (Ehlers *et al*., 2007). Finally, three SNPs (rs2023239, rs12720071, rs806368) are associated with nicotine dependence in Caucasian American females (Chen *et al*., 2008).

Recently Benyamina and colleagues systematically reviewed all association studies of CNR1 polymorphisms with drug dependence, and identified 11 studies that were used for meta-analysis of rs1049353, rs806379 and the AAT repeat (Benyamina *et al*., 2010). Of these polymorphisms only the AAT repeat showed a significant association with illicit substance dependence, and only in Caucasian populations with a risk allele definition of >16 repeats. However, a wide heterogeneity between studies was acknowledged with particular regard to between study differences in ethnic population, lack of gender delineation, differences in phenotype definition and ambiguity regarding illicit substances. Thus, while this meta-analysis indicates a significant influence of the CNR1 AAT repeat polymorphism in drug dependence, it also highlights the need for a greater body of well-described studies to determine the relative influence of CNR1 polymorphisms in addiction.

10.2 FAAH polymorphisms

Several recent reports suggest that genetic alterations in FAAH expression or function confer susceptibility to problem drug and alcohol use. For example, FAAH expression and function are reduced in the PFC of rats selectively bred for high ethanol preference and consumption (Hansson *et al*., 2007). Consistently, genetic deletion of FAAH results in increased ethanol preference and consumption in mice (Basavarajappa *et al*., 2006; Blednov *et al*., 2007; Vinod *et al*., 2008). Animals lacking FAAH are also less sensitive to ethanol-induced motor incoordination and exhibit reduced signs of ethanol withdrawal, leading to the theory that reductions in the aversive effects of ethanol intake confer increased motivation for ethanol consumption. FAAH knockout mice also display enhanced sensitivity to both the rewarding effects of nicotine and the aversive effects of nicotine withdrawal (Merritt *et al*., 2008), though Δ9-THC dependence and precipitated withdrawal appear to be unaltered by FAAH deletion (Schlosburg *et al*., 2009). Collectively these findings in rodents suggest that genetic disruption of FAAH function results in altered sensitivity to some abused drugs such as alcohol and nicotine.

In humans, a missense SNP in the FAAH DNA sequence has been identified (C385A, rs324420) that leads to a conserved proline to threonine (P129T) conversion in the FAAH amino acid sequence (Chiang *et al*., 2004). The resultant enzyme variant is more susceptible to proteolytic degradation, thereby resulting in substantially reduced FAAH activity and a presumed increase in levels of AEA and other FAAH substrates. Initial reports described a significant association between the C385A polymorphism and problem drug use (Flanagan *et al*., 2006; Sipe *et al*., 2002). Further characterization has shown this FAAH mutation to be strongly associated with risk for frequent sedative use, though individuals with this SNP do not appear to be at greater risk for alcohol, nicotine or methamphetamine use or dependence (Iwasaki *et al*., 2007; Tyndale *et al*., 2007). Among human marijuana users the C allele of this SNP has been associated with increased risk of cannabis dependence including increased severity of withdrawal symptoms, increased craving during abstinence from marijuana use and heightened happiness after renewed marijuana smoking (Haughey *et al*.,

2008; Schacht *et al*., 2009; Tyndale *et al*., 2007). Moreover, a recent study by Filbey and colleagues determined that individuals homozygous for the C allele of this FAAH SNP have a heightened neural response to marijuana-associated cues in reward-related structures (orbitofrontal cortex, anterior cingulated gyrus and NAc) (Filbey *et al*., 2010). A similar increase in cue-induced neural activity was observed in carriers of the G allele of rs2023239 in CNR1, though the genetic effects were greater for the FAAH gene than for the CNR1 gene in terms of activation cluster size. This pattern of heightened response to marijuana cues was found to increase as the number of risk alleles increased. Another recent study found that carriers of the FAAH C385A SNP display increased ventral striatal reactivity associated with delay discounting, a behavioral index of impulsivity and reward sensitivity (Hariri *et al*., 2009). Moreover, C385A carriers exhibited a markedly decreased relationship between threat-related amygdala reactivity and trait anxiety, similar to patterns observed in individuals with high familial risk for alcoholism (Glahn *et al*., 2007). These findings suggest dysregulation of FAAH function through the C385A polymorphism confers increased impulsivity and decreased threat perception that result in increased risk-taking behavior associated with addiction.

11. Concluding remarks

While enhancement of eCB signaling per se does not produce robust addiction-related behaviors, growing evidence implicates eCB signaling in the modulation of the motivational effects produced by ethanol, nicotine, opiates and to a lesser degree psychostimulant drugs. Endocannabinoids have also recently been implicated in mediating the effects of abused inhalants (such as toluene) on prefrontal cortical neural activity (Beckley *et al*., 2011). Further, preclinical studies point to an important involvement of CB_1 receptors in drug-seeking behaviors induced by exposure to both drug-conditioned cues and drug administration itself.

Most preclinical investigations of an eCB influence in drug abuse-related behaviors have focused on pharmacological or genetic manipulations of CB_1 receptor function. In this regard it should be noted that the inverse agonist properties of SR141716A and AM251 (Bergman *et al*., 2008; Janero *et al*., 2009; Pertwee, 2005) might produce effects that are distinct from the simple blockade of eCB-mediated CB_1 receptor activation. In addition, while both of these compounds are typically used to characterize CB_1 receptor-mediated processes it is worth bearing in mind that AM251 also activates GPR55 receptors (Henstridge *et al*., 2009; Kapur *et al*., 2009; Whyte *et al*., 2009; Yin *et al*., 2009) and SR141716A binds to non-CB_1, non-CB_2 G protein-coupled receptors (including μ and κ opioid receptors and tachykinin NK_2 receptors) and ion channels (including TRPV1 receptors) in the low micromolar range (vs. a low nanomolar interaction with CB_1) (Cinar *et al*., 2009; De Petrocellis *et al*., 2001; Kathmann *et al*., 2006; Price *et al*., 2004). Despite these caveats, the aforementioned preclinical studies along with growing clinical evidence for an association between CNR1 polymorphisms and problem drug use/dependence strongly support a cannabinoid receptor influence in the etiology of addiction.

More direct evaluations of an eCB influence on drug-related behaviors have focused on the effects of increased eCB tone induced by inhibition of eCB clearance mechanisms. Inhibition of eCB clearance significantly alters the behavioral effects of alcohol and nicotine, suppresses drug-seeking behavior and ameliorates affective disruptions commonly associated with drug dependence and withdrawal. While many of these tests provide evidence of CB_1-dependent eCB influences, not all results are consistent with this pharmacological mechanism. eCBs interact with several non-CB_1 putative cannabinoid receptors such as GPR55 and GPR119 (Godlewski *et al*., 2009; Lauckner *et al*., 2008; Overton *et al*., 2006; Pertwee, 2010; Ryberg *et al*., 2007; Sharir *et al*., 2010) and the

influence of these receptors on addiction-related behaviors has not been characterized. The agonist effects of eCBs at CB_2 receptors should also not be discounted as these receptors are present on brain neuronal cells and emerging evidence suggests a possible CB_2 receptor influence on drug-related behaviors (Garcia-Gutierrez *et al*., 2011; Garcia-Gutierrez *et al*., 2010; Ishiguro *et al*., 2007; Onaivi *et al*., 2008). Moreover, AEA and other eCB-like moieties potently activate non-cannabinoid receptors such as TRPV1 receptors (Di Marzo *et al*., 2010; Zygmunt *et al*., 1999) and peroxisome proliferators-ativated receptors (PPAR)-α and -γ receptors (O'Sullivan, 2007). As such, behavioral effects produced by manipulations of eCB clearance may result from activation of these non-cannabinoid targets that may produce distinct effects from CB_1 receptors. An example of this circumstance is the anxiogenic-like behavioral effects produced by AEA activation of TRPV1 receptors following FAAH inhibition that counters the anxiolytic-like effects of CB_1 receptor activation (Micale *et al*., 2009). Inhibition of eCB clearance mechanisms can also produce effects mediated by non-cannabinoid lipids. A good example of this is the inhibitory effects of PPAR activation on nicotine-induced behaviors and neurochemical effects resulting from increased OEA and/or PEA levels following FAAH inhibition (Luchicchi *et al*., 2010; Melis *et al*., 2008; Melis *et al*., 2010; Scherma *et al*., 2008b). Thus the behavioral effects produced by eCB clearance inhibition likely result from activation of both CB_1 and non-CB_1 receptor mechanisms, and this may in part explain some incongruities in the literature such as the attenuation of drug-seeking behavior by either CB_1 receptor antagonism (Alvarez-Jaimes *et al*., 2008; Cippitelli *et al*., 2005; Cohen *et al*., 2005; De Vries *et al*., 2005; De Vries *et al*., 2003; De Vries *et al*., 2001; Economidou *et al*., 2006; Fattore *et al*., 2003; Justinova *et al*., 2008a; Xi *et al*., 2006) or eCB clearance inhibition (Adamczyk *et al*., 2009; Forget *et al*., 2009; Scherma *et al*., 2008b) and the attenuation of nicotine-induced activation of mesolimbic dopamine cells by either CB_1 receptor antagonism (Cohen *et al*., 2002) or eCB clearance inhibition (Luchicchi *et al*., 2010; Melis *et al*., 2008; Scherma *et al*., 2008b).

Because several classes of abused drugs appear to increase eCB formation in brain it is possible that long-term drug exposure results in neuroadaptations that serve to diminish the influence of eCB signaling. Indeed, drug exposure generally leads to a transient loss of eCB-mediated synaptic plasticity at both inhibitory and excitatory synapses and this may be related to a downregulation of CB_1 receptor expression and/or function (for review see (Sidhpura *et al*., 2011)). Drug dependence and withdrawal may also be associated with deficient eCB levels resulting from altered eCB biosynthetic and/or clearance mechanisms, or disruptions in non-cannabinoid mechanisms that can stimulate eCB production (e.g. mGluR5, dopamine D_2, etc.). Deficits in eCB signaling may contribute to decreased extinction of drug-related memories, drug craving and relapse, increased stress responsivity and affective disruptions (including anxiety and depression) that are associated with drug dependence and protracted withdrawal. Accordingly, therapeutic approaches aimed at restoring or bolstering cannabinoid signaling may have clinical benefit for the treatment of addiction. The use of exogenous CB_1 receptor agonists for this purpose would likely be problematic as these compounds induce drug craving, increase relapse and exacerbate abstinence-related affective disorders at higher doses. However, enhancement of eCB tone through inhibition of eCB clearance may be a viable therapeutic approach in light of evidence that these manipulations facilitate extinction of aversive memory, decrease drug-seeking behavior, constrain excessive stress responses and produce anxiolytic- and antidepressive-like behaviors. Importantly, because eCBs are generally produced in response to specific stimuli, the behavioral effects of moderate eCB clearance inhibition may be preferentially evident in limited circumstances such as exposure to stress or drug-associated cues. Supporting this hypothesis is *in vivo* evidence that eCB clearance inhibition does not alter extracellular eCB levels under quiescent conditions but enhances and prolongs elevations in extracellular eCB levels induced by neural activation (Alvarez-Jaimes *et al*., 2009b; Buczynski *et al*., 2010; Long *et al*., 2009c). Endocannabinoid clearance inhibition

may also facilitate region-specific increases in brain eCB signaling as a result of regionally distinct stimulus-induced eCB production. For this reason moderate doses of eCB clearance inhibitors may produce fewer unwanted behavioral effects than exogenous CB_1 agonists that induce widespread CB_1 receptor activation. These and related considerations have supported the proposed therapeutic use of eCB clearance inhibitors for a variety of pathologies (Gaetani *et al*., 2009; Hwang *et al*., 2010; Lutz, 2004; Petrosino *et al*., 2010).

Nearly all evaluations of the behavioral effects of eCB clearance inhibition have employed acute dosing procedures and further studies characterizing the effects of long-term administration of eCB clearance inhibitors are needed. The importance of this is underscored by clinical evidence that polymorphisms in the FAAH gene (C385A) conferring reduced FAAH activity are associated with problem sedative use and cannabis dependence. Moreover, although several preclinical studies have characterized the behavioral effects of FAAH inhibition, knowledge of the effects of MAGL inhibition on addiction-related behaviors is sparse. Work in this area will be greatly facilitated by the recent development of selective and efficacious MAGL inhibitors (e.g. (Long *et al*., 2009c)).

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Abbreviations

AEA	anandamide (*N*-arachidonoyl-ethanolamine)
2-AG	2-arachidonoylglycerol
BLA	basolateral amygdala
BNST	bed nucleus of the stria terminalis
CB1	cannabinoid receptor type 1
CeA	central nucleus of the amygdala
CNR1	cannabinoid receptor type 1 gene
CPA	conditioned place aversion
CPP	conditioned place preference
ECS	endogenous cannabinoid system
FAAH	fatty acid amide hydrolase
MAGL	monoacylglycerol lipase
NAc	nucleus accumbens
nACh	nicotinic acetylcholine ion channel receptors
OEA	oleoylethanolamide
PEA	palmitoylethanolamide
PVN	paraventricular nucleus of the hypothalamus
sP	Sardinian alcohol-preferring rats
THC	Δ9-tetrahydrocannabinol

VTA ventral tegmental area

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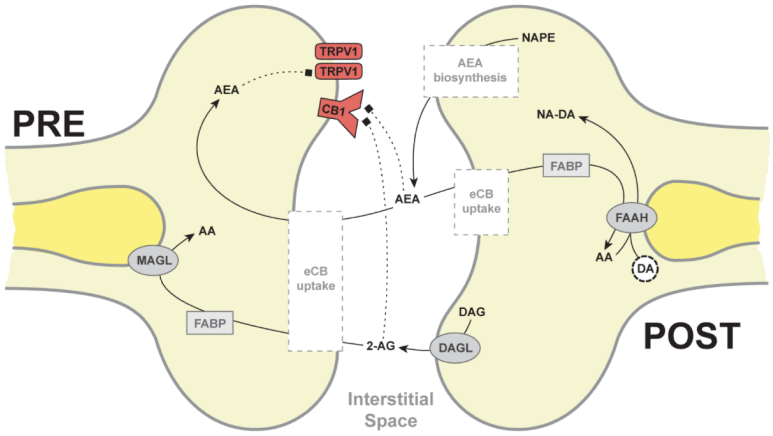

Figure 1. Synaptic organization of the endocannabinoid system

AEA and 2-AG are synthesized from phospholipids in the postsynaptic cell. The most commonly accepted route for AEA synthesis involves its direct formation from *N*-arachidonoyl-phosphatidylethanolamine (NAPE) via catalysis by a specific phospholipase D (NAPE-PLD). Alternatively, recent evidence points to AEA formation via the ABHD4/GDE1 pathway and also through the PLC pathway via either PTPN22 or SHIP1 activity. Because the specific enzymes for AEA generation remain unclear no specific pathway is represented in this figure. 2-AG derives primarily from the hydrolytic metabolism of 1,2-diacylglycerol (DAG) via the sn-1-selective DAG lipases DAGLα and DAGLβ. Once released into the synaptic cleft AEA and 2-AG exert signaling effects through CB_1 and other receptors including CB_2 and GPR55 (Pertwee, 2010). CB_1 receptors are expressed on presynaptic terminals, though the synaptic positions of CB_2 and GPR55 in the CNS have not been confirmed. AEA also functions as a potent agonist at transient receptor potential vanilloid receptor 1 (TRPV1), though unlike GPCRs these receptors contain an intracellular lipid binding site. Termination of extracellular eCB signaling is initiated by cellular reuptake, and once inside the cell eCBs are shuttled via chaperone mechanisms (including fatty acid binding proteins (FABPs; (Maccarrone *et al*., 2010)) to specific enzymes for hydrolytic cleavage. Degradation of 2-AG is attributed primarily to presynaptic monoacylglycerol lipase (MAGL) that cleaves 2-AG into arachidonic acid (AA) and glycerol. Degradation of AEA occurs in postsynaptic cells through fatty acid amide hydrolase (FAAH) that cleaves AEA into AA and ethanolamine. Evidence suggests that FAAH can also conjugate AA and various neurotransmitters into *n*-arachidonoyl moieties such as *n*-arachidonoyl dopamine (NADA) (Hu *et al*., 2009) that have potent bioactivity at TRPV1 and CB_1 receptors (Pertwee, 2010).

Table 1

Pharmacological agents frequently cited in this review

CB_1 Agonist		**CB_1 Antagonist**		**eCB clearance inhibitors**	
Δ9-THC	($CB_1 = CB_2$)	SR141716A	($CB_1 > CB_2$)	URB597	FAAH
		SR147778	($CB_1 > CB_2$)	PF-3845	FAAH
WIN 55,212-2	($CB_1 \leq CB_2$)	AM251	($CB_1 > CB_2$)		
CP 55,940	($CB_1 = CB_2$)			JZL184	MAGL
HU-210	($CB_1 = CB_2$)				
AM678 (JWH-018)	($CB_1 \geq CB_2$)			JZL195	Dual FAAH/MAGL
R-methanandamide	($CB_1 \geq CB_2$)			PMSF	Non-selective serine hydrolase
ACEA	($CB_1 > CB_2$)				
O-1812	($CB_1 \geq CB_2$)			AM404	Reuptake/FAAH
AM1346	($CB_1 \geq CB_2$)			OMDM-2	Reuptake

Table 2

Discriminative Stimulus effects of eCBs

Training Drug	Test Drug	Effect
Δ9-THC	exogenous AEA	no generalization
	FAAH inhibition	no generalization
	AEA + FAAH inhibition	full generalization
	R-methanandamide	full generalization
	O-1812	full generalization
	AM1346	full generalization
	JZL184	partial generalization
	JZL195	full generalization
R-methanandamide	Δ9-THC	full generalization
	WIN 55,212-2	full generalization
	AM678	full generalization
AM1346	Δ9-THC	full generalization
	R-methanandamide	full generalization

Table 3

Rewarding effects of increased eCB signaling

Paradigm	Test Drug	Effect
Place Conditioning	AEA	no conditioning effect
	URB597	no conditioning effect
	AM404	significant place preference
Brain stimulation reward	URB597	no effect
	PMSF	no effect
	OMDM-2	no effect
Intravenous self-administration	AEA	supports operant behavior (squirrel monkey)
	URB597	does not support operant behavior (squirrel monkey)
	AM404	supports operant behavior (squirrel monkey)

Table 4

Endocannabinoid influence on alcohol-related behaviors

Manipulation		Effect
CB_1 receptor	CB_1 knockout	Reduced alcohol conditioned place preference
		Reduced alcohol preference and consumption
		Absence of alcohol-induced increase in NAc dopamine
		Increased sensitivity to intoxication
		Increased withdrawal
	CB_1 antagonists	Attenuate acquisition of alcohol consumption
		Reduce alcohol preference and consumption
		Attenuate alcohol-induced increases in NAc dopamine
	CB_1 agonists	WIN 55,212-2 and CP 55,940 increase the motivation for and quantity of alcohol consumption
eCB clearance inhibition	FAAH knockout	Increased alcohol preference and consumption
	Rats selectively bred for high alcohol preference	Decreased FAAH expression and activity in PFC
	Pharmacological Manipulations	URB597 increases alcohol preference and consumption in mice, but not rats
		AM404 decreases alcohol consumption in rats
Alcohol-induced alterations in brain eCB function		Increased 2-AG and AEA formation in culture
		Regionally distinct alterations in brain tissue eCB content
		Alcohol self-administration increases interstitial levels of 2-AG but not AEA in the NAc
		Decreased CB_1 expression and function by chronic alcohol

Table 5

Endocannabinoid influence on nicotine-related behaviors

Manipulation		Effect
CB_1 receptor	CB_1 knockout	Reduced nicotine conditioned place preference
		Reduced intravenous nicotine self-administration
	CB_1 antagonists	Reduce nicotine conditioned place preference
		Reduce intravenous nicotine self-administration
		Attenuate nicotine-induced increases in NAc dopamine
		No effect on nicotine-induced discriminative stimulus
eCB clearance inhibition	FAAH knockout	Increased sensitivity to low-dose nicotine place preference
	Pharmacological Manipulations	URB597 blocks nicotine place preference in rats (CB_1 receptor independent)
		URB597 attenuates nicotine self-administration in rats (CB_1 receptor independent)
		URB597 attenuates nicotine-induced increases in NAc dopamine in rats (CB_1 receptor independent)
Nicotine-induced alterations in brain eCB function		Regionally distinct alterations in brain tissue eCB content
		Increased CB_1 expression during protracted nicotine withdrawal

Table 6

Endocannabinoid influence on opioid-related behaviors

Manipulation		Effect
CB_1 receptor	CB_1 knockout	Reduced morphine conditioned place preference
		Reduced intravenous heroin self-administration
	CB_1 antagonists	Reduce morphine conditioned place preference
		Reduce intravenous heroin self-administration
	CB_1 agonists	WIN 55,212-2 enhaces morphine conditioned place preference
		WIN 55,212-2 and Δ9-THC increase the motivation for heroin self-administration
eCB clearance inhibition	Pharmacological Manipulations	Neither URB597 nor AM404 alter heroin self-administration
Opiate-induced alterations in brain eCB function		Regionally distinct alterations in brain tissue eCB content
		Heroin self-administration increases interstitial levels of AEA but not 2-AG in the NAc
		CB_1 expression significantly altered by chronic morphine

Table 7

Endocannabinoid influence on psychostimulant-related behaviors

Manipulation		Effect
CB_1 receptor	CB_1 knockout	Unaltered cocaine place preference
		Modest or no change in cocaine self-administration
	CB_1 antagonists	AM251, but not SR141716A, decreases cocaine self-administration
		AM251 decreases methamphetamine self-administration
		AM251, but not SR141716A, decreases cocaine-induced facilitation of brain stimulation reward
		SR141716A does not alter cocaine-induced increases in NAc dopamine
	CB_1 agonists	WIN 55,212-2 reduces cocaine self-administration and blocks cocaine-induced facilitation of brain stimulation reward
eCB clearance inhibition	Pharmacological Manipulations	URB597 does not alter cocaine self-administration
		URB597 does not modulate cocaine-induced alterations in VTA dopamine cell activity
		AM404 attenuates cocaine-induced facilitation of brain stimulation reward
Cocaine-induced alterations in brain eCB function		Tissue eCB content unaltered by chronic cocaine exposure
		Cocaine self-administration does not alter interstitial eCB levels in the NAc
		Extended periods of cocaine self-administration result in increased levels of phosphorylated and total CB_1 protein in the NAc and amygdala

Table 8

Endocannabinoid influence on drug-seeking behaviors (relapse)

Manipulation	Effect
CB_1 receptor	CB_1 agonists reinstate extinguished drug-seeking for:
	cannabinoids
	alcohol
	opioids
	nicotine
	cocaine
	CB_1 antagonists block:
	Cue-induced reinstatement of drug-seeking for:
	Δ9-THC
	Alcohol
	Heroin
	Nicotine
	cocaine
	sucrose
	Drug-primed reinstatement of drug-seeking for:
	Alcohol (deprivation effect)
	Heroin
	Cocaine
eCB clearance inhibition	URB597 does not reinstate extinguished drug-seeking for:
	Δ9-THC
	Cocaine
	AEA
	URB597 blocks cue-induced reinstatement of drug-seeking for:
	nicotine
	cocaine
	URB597 blocks drug-primed reinstatement of drug-seeking for:
	nicotine
	cocaine
	Neither URB597 nor AM404 block cue- or stress-induced reinstatement of alcohol-seeking