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Endocannabinoid-mediated synaptic plasticity and addiction-related behavior

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Abstract

Endogenous cannabinoids (eCBs) are retrograde messengers that provide feedback inhibition of both excitatory and inhibitory transmission in brain through the activation of presynaptic CB₁ receptors. Substantial evidence indicates that eCBs mediate various forms of short- and long-term plasticity in brain regions involved in the etiology of addiction. The present review provides an overview of the mechanisms through which eCBs mediate various forms of synaptic plasticity and discusses evidence that eCB-mediated plasticity is disrupted following exposure to a variety of abused substances that differ substantially in pharmacodynamic mechanism including alcohol, psychostimulants and cannabinoids. The possible involvement of dysregulated eCB signaling in maladaptive behaviors that evolve over long-term drug exposure is also discussed, with a particular focus on altered behavioral responses to drug exposure, deficient extinction of drug-related memories, increased drug craving and relapse, heightened stress sensitivity and persistent affective disruption (anxiety and depression).

Keywords

Synaptic plasticity; endocannabinoid; addiction; relapse; stress; affective disorder

1. Introduction

A crucial aspect of brain neuronal signaling is synaptic plasticity that modulates the strength and number of connections between neurons. 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 and Hyman, 2000; Everitt et al., 2001; Everitt et al., 1999; Hyman, 2005; Hyman et al., 2006; Jentsch and Taylor, 1999; Kalivas and O’Brien, 2008; Kauer, 2004; Kauer and Malenka, 2007; Kelley, 2004; Thomas et al., 2008; Torregrossa et al., 2011; White, 1996). Substantial evidence supports a fundamental role of synaptic plasticity in the ventral tegmental area (VTA) and regions innervated by VTA dopamine projections in the behavioral response to

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initial drug exposure. Moreover, plastic events in regions such as the nucleus accumbens (NAc), prefrontal cortex (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 and O'Brien, 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).

The recent discovery that endocannabinoids (eCBs) mediate retrograde synaptic signaling has unveiled a novel concept of how diffusible messengers modify synaptic plasticity. Endocannabinoids are well known to suppress neurotransmitter release at excitatory and inhibitory synapses with both short- and long-term effects (Alger, 2002; Chevalleyre et al., 2006; Diana and Marty, 2004; Kano et al., 2009; Lovinger, 2008; Marsicano and Lutz, 2006; Wilson and Nicoll, 2002). The present review discusses the mechanisms through which eCBs mediate various forms of synaptic plasticity in brain regions involved in drug addiction and the possible functional implications of disrupted eCB signaling to addiction-related pathologies. Because much of this work is predicated on knowledge of the mechanisms regulating endocannabinoid signaling in brain we begin with a brief review of eCB synthesis, clearance and signaling.

2. Endocannabinoid synthesis, clearance and signaling mechanisms

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 a signaling molecule at CB₁ and CB₂ receptors (Mechoulam et al., 1995; Sugiura et al., 1995). Other endogenous molecules have been identified that exert cannabinoid-like effects including 2-arachidonoyl-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 -linolenylethanolamine (HEA) and *N*-docosatetraenylethanolamine (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 such 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.

Because eCBs are lipids their physiochemical properties preclude intracellular vesicular storage. Rather, eCBs are synthesized on an "as needed" basis by cleavage from membrane lipid precursors and immediate extrusion from neurons. AEA derives from the phospholipid precursor *N*-arachidonoyl-phosphatidylethanolamine (NAPE) (Cadas et al., 1996; Piomelli, 2003) and its release from membrane is catalyzed by a specific phospholipase D (NAPE-PLD) (Okamoto et al., 2004) whose activity is regulated by depolarization and/or activation of ionotropic (Piomelli, 2003; Stella and Piomelli, 2001) or metabotropic receptors (Giuffrida et al., 1999; Kim et al., 2002; Varma et al., 2001). Although this is believed to be the primary pathway for AEA synthesis alternative biosynthetic routes have recently been proposed (Leung et al., 2006; Liu et al., 2008; Liu et al., 2006; Simon and Cravatt, 2006). 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 and Jarrahian, 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 is abundantly expressed in the CNS and FAAH-positive neurons are found in proximity to CB₁ receptor-containing terminals, supporting a role for this enzyme in eCB inactivation (McKinney and Cravatt, 2005). 2-AG hydrolysis is performed by multiple enzymes, though the primary mechanism for 2-AG clearance appears to be mediated by MAGL (Blankman et al., 2007; Dinh et al., 2002). In addition to MAGL, the enzymes ABHD6 and ABHD12 also appear to play an important role in 2-AG metabolism (Blankman et al., 2007; Marrs et al., 2010). Interestingly, while FAAH is present in postsynaptic cells (e.g. near the origin of eCB synthesis) both MAGL and CB₁ receptors are localized in presynaptic terminals (Gulyas et al., 2004; Ludanyi et al., 2010; Straiker et al., 2009). This orientation suggests that FAAH may play a general role in regulating interstitial AEA levels, while MAGL may be more specifically involved in 2-AG inactivation near its site of action. This organization is consistent with emerging thoughts that AEA exerts a general influence on tonic CB₁ receptor activation while 2-AG plays a greater role in mediating “on demand” forms of short- and long-term plasticity (Kim and Alger, 2010).

Two major types of cannabinoid receptors have been characterized and cloned: CB₁ and CB₂. CB₁ receptors are highly expressed presynaptic terminals 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). CB₂ receptors are mainly located in immune cells of the spleen, tonsils and thymus gland (Galiegue et al., 1995; Munro et al., 1993), though evidence also suggests CB₂ localization in activated microglial in the CNS (Cabral et al., 2008; Maresz et al., 2007; Stella, 2004) and on neurons in cerebellum and brainstem (Ashton and Glass, 2007; Onaivi et al., 2008; Onaivi et al., 2006; Van Sickle et al., 2005). CB₁ and CB₂ receptors are both coupled to similar transduction systems through G_i or G_o proteins. Their activation reduces adenylate cyclase activity and Ca²⁺ influx through N-, P/Q- and L-type Ca²⁺ channels (Gebremedhin et al., 1999; Mackie and Hille, 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 CB₁ and CB₂ receptors. AEA binds with slightly higher affinity to CB₁ than CB₂ and is a partial agonist at both CB receptors with lesser efficacy at CB₂ versus CB₁ receptors (Pertwee, 2010). 2-AG binds with more or less equal affinity to CB₁ and CB₂ 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 and Abood, 2010). AEA also potently activates non-cannabinoid receptors such as transient receptor potential vanilloid type-1 (TRPV1) receptors (Di Marzo and De Petrocellis, 2010; Zygmunt et al., 1999) and this action may exert important influences on plasticity that are distinct from cannabinoid receptor-mediated signaling (see section 3.2 below). Accordingly, the physiological and behavioral effects produced by eCBs result from interactions with CB₁ and CB₂ receptors and non-CB receptors. For purposes of clarity, however, this review will focus primarily on the influence of eCB signaling through CB₁ receptors.

3. Endocannabinoid-mediated synaptic plasticity

It is now well established that eCBs serve as retrograde messengers at various synapses in the CNS (Kreitzer and Regehr, 2001; Maejima et al., 2001; Ohno-Shosaku et al., 2001; Wilson and Nicoll, 2001) and contribute to different forms of short- and long-term synaptic plasticity. Following synthesis and release from postsynaptic neurons, eCBs activate presynaptic CB₁ receptors to suppress release of both excitatory (e.g., glutamate) and inhibitory (e.g., GABA) neurotransmitters in a transient (short-term plasticity) or persistent (long-term plasticity) manner. These different forms of eCB-mediated plasticity are discussed in the sections that follow, along with consideration of brain regional differences in the mechanisms underlying these processes.

3.1 Endocannabinoid-mediated short-term plasticity

The first evidence for eCB-mediated neural plasticity came from brain slice electrophysiological experiments characterizing the phenomena of depolarization-induced suppression of inhibition (DSI) that dampens presynaptic GABA release (Ohno-Shosaku et al., 2001; Wilson and Nicoll, 2001), and depolarization-induced suppression of excitation (DSE) that dampens presynaptic glutamate release (Kreitzer and Regehr, 2001). These transient forms of plasticity typically persist for a minute or less. Induction of DSE/DSI requires specific stimulation protocols to depolarize postsynaptic cells, open voltage-gated Ca²⁺ channels and elevate intracellular Ca²⁺ concentrations. Endocannabinoids were implicated in this process based on observations that DSE/DSI are prevented by CB₁ receptor antagonism (CB₁ receptors are primarily located on presynaptic terminals) and evidence that direct acting CB₁ agonists and eCB transport inhibitors induce DSE/DSI (Kreitzer and Regehr, 2001; Maejima et al., 2001; Wilson and Nicoll, 2001). Although the specific eCB species involved in the production of DSI/DSE remain unclear several findings point to a role for 2-AG. For example, while AEA can clearly produce DSI-like effects (Heinbockel et al., 2005), inhibition of AEA clearance (e.g. FAAH inhibition or FAAH deletion) does not alter the temporal profile of DSI (Kim and Alger, 2004; Pan et al., 2009). In contrast, enhanced 2-AG signaling produced by MAGL inhibition prolongs DSE/DSI (Makara et al., 2005; Pan et al., 2009; Straiker et al., 2009; Szabo et al., 2006) and hippocampal DSI is lost in DAGLα(−/−) mice that are characterized by an 80% reduction in brain tissue 2-AG content (Gao et al., 2010). Interestingly, hippocampal LTD is largely unaltered in DAGLβ(−/−) mice that exhibit lesser reductions (50%) in brain 2-AG, which may suggest that disruption of hippocampal DSI requires severe decrements in 2-AG signaling. Overall, these findings provide strong evidence that DSE/DSI is more reliant on 2-AG signaling than AEA signaling.

Another form of eCB-mediated short-term plasticity is driven by activation of postsynaptic metabotropic receptors that couple to Gq-like G-proteins, such as group I metabotropic glutamate receptors (mGluRs) and the M1 and M3 subtypes of muscarinic acetylcholine receptors (mAChRs) (Edwards et al., 2006; Fukudome et al., 2004; Kim et al., 2002; Martin and Alger, 1999; Ohno-Shosaku et al., 2003; Ohno-Shosaku et al., 2002; Varma et al., 2001). In distinction from initial descriptions of DSI/DSE, metabotropic receptor-driven eCB formation does not require increased postsynaptic Ca²⁺, though increased intracellular Ca²⁺ can enhance the process. The eCB formation governed by these Gq-coupled receptors is dependent on phospholipase C (PLC) and DAGL, as confirmed by the loss of endocannabinoid-mediated short-term depression in cerebellar, hippocampal and VTA neurons following PLC and/or DAGL inhibition (Edwards et al., 2006; Galante and Diana, 2004; Melis et al., 2004) or genetic deletion of PLC (Hashimoto et al., 2005; Maejima et al., 2005). Further, mGluR activation in the hippocampus or striatum preferentially stimulates the production of 2-AG over AEA (Jung et al., 2005). Collectively these findings suggest a preferential influence of 2-AG in this form of plasticity. However, evidence for

mechanisms involving PLC-induced AEA synthesis (Liu et al., 2006) suggests a possible role for AEA in eCB-mediated short-term depression at certain synapses.

Endocannabinoid-mediated short-term plasticity driven by DSI/DSE and Gq-coupled receptors has been observed in several brain areas relevant to drug reward and addiction including the VTA (Melis et al., 2004), basolateral amygdala (BLA) (Zhu and Lovinger, 2005), dentate gyrus of the hippocampus (Isokawa and Alger, 2005), neocortex (Bodor et al., 2005; Trettel and Levine, 2003) and substantia nigra (Yanovsky et al., 2003). Endocannabinoid-dependent short-term plasticity mediated by Gq-coupled receptors is thought to influence various neurotransmitter systems involved in addiction-related behavior including dopamine D₂ receptor-mediated inhibition of striatal glutamate release (Yin and Lovinger, 2006) (likely involving group I mGluRs but not mAChRs (Narushima et al., 2006)) and short-term suppression of GABA transmission in the CA1 region of hippocampus (which likely involves interactions between CB₁ and kainate receptors) (Lourengo et al., 2010).

3.2 Endocannabinoid-mediated long-term plasticity

Endocannabinoids are also involved in more persistent forms of synaptic plasticity including long-term potentiation (LTP; a long-lasting increase in the strength of synaptic signaling), and long-term depression (LTD; 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. Initiation of eCB-LTD typically occurs in response to a transient increase in activity at glutamatergic afferents resulting in stimulation of postsynaptic group I mGluRs and/or increase in intracellular Ca²⁺ concentrations. Endocannabinoids released from the postsynaptic cell activate presynaptic CB₁ receptors on the original afferents (homosynaptic eCB-LTD) or afferents in close proximity (heterosynaptic eCB-LTD) to produce a long-lasting decrease in neurotransmitter release (Heifets and Castillo, 2009). As discussed below, eCB-LTD has been reported in brain regions such as the dorsal striatum, NAc, amygdala, hippocampus, PFC and VTA, which are critically involved in various stages of the addiction cycle.

3.2.1 Dorsal striatum—Initial evidence for eCB-LTD came from studies reporting that CB₁ receptor activation suppresses glutamate release in the dorsal striatum (Gerdeman and Lovinger, 2001), that striatal LTD is blocked by CB₁ receptor antagonists and is absent in CB₁ receptor knockout mice (Gerdeman et al., 2002). AEA has been implicated in this process based on evidence that loading of postsynaptic cells with AEA transport inhibitors prevents eCB-LTD (Ronesi et al., 2004). Striatal LTD appears to involve multiple signaling pathways as mGluR1 receptor antagonists prevent induction of LTD during high frequency stimulation of corticostriatal glutamatergic afferents (Sung et al., 2001) and eCB-LTD at afferent glutamatergic synapses requires dopamine D₂ receptors on postsynaptic medium spiny neurons (Kreitzer and Malenka, 2005). While most striatal studies have focused on eCB-LTD at glutamatergic afferents, a recent report has revealed that eCB-LTD also occurs at GABAergic synapses which appear to be more sensitive to eCB signaling than their excitatory counterparts (Adermark and Lovinger, 2009).

3.2.2 Nucleus accumbens—As observed in the dorsal striatum, NAc CB₁ receptors provide inhibitory control over local glutamate and GABA release (Hoffman and Lupica, 2000, 2001; Pistis et al., 2002; Robbe et al., 2001) and NAc LTD is blocked by CB₁ receptor antagonism and absent in CB₁ knockout mice (Hoffman et al., 2003; Robbe et al., 2002). However, in contrast to the dorsal striatum, NAc eCB-LTD is diminished by selective inhibition of group 1 mGluRs (specifically mGluR5), but not dopamine D₂ receptors (Robbe

et al., 2002). While it is clear that eCB-LTD occurs at glutamatergic synapses it is not yet established whether endocannabinoids mediate LTD at GABAergic synapses in the NAc.

3.2.3 Amygdala—Stimulation of afferent neurons in the BLA induces LTD of GABAergic neurotransmission that is abolished by CB₁ receptor antagonists and absent in CB₁ receptor (–/–) mice (Marsicano et al., 2002). Surprisingly, LTP is significantly enhanced in the BLA of CB₁ (–/–) mice though a lack of CB₁ antagonist effects on BLA LTP in wildtype mice suggests this may result from between-systems compensatory adaptations to life-long absence of CB₁ receptors. Several subsequent reports have confirmed the presence of eCB-LTD in the amygdala (Chevalleyre et al., 2007; Huang et al., 2003; Shin et al., 2010) and have determined that this process is reliant on mGluR1 receptor function (Azad et al., 2004). However, BLA eCB-LTD is insensitive to reductions in calcium, PLC activity and DAGL activity, which discounts a possible involvement of 2-AG signaling. eCB-LTD is significantly greater in FAAH (–/–) vs. wildtype mice and is sensitive to inhibition of adenylate cyclase and PKC pointing to an involvement of AEA. However, the effects of acute FAAH inhibition in wildtype mice and the involvement of CB₁ receptors in the potentiated eCB-LTD observed in FAAH (–/–) mice has not been evaluated, allowing the possibility that some portion of the eCB-LTD observed in the context of FAAH inhibition is mediated through a non-CB₁ mechanism such as TRPV1 receptors (Chavez et al., 2010; Grueter et al., 2010). In addition to these observations in BLA, recent evidence clearly demonstrates the existence of eCB-mediated DSE in cortical inputs to the lateral and central amygdala (Kamprath et al., 2011; Kodirov et al., 2009).

3.2.4 Hippocampus—Repetitive stimulation of glutamatergic pyramidal cells in the CA1 region of the hippocampus induces heterosynaptic depression at neighboring GABAergic inhibitory synapses, which is blocked by CB₁ receptor antagonists and absent in CB₁ receptor (–/–) mice (Chevalleyre and Castillo, 2003). Similar to the amygdala, hippocampal eCB-LTD is prevented by pharmacological inhibition of group I mGluRs but not by postsynaptic application of a Ca²⁺ chelator (Chevalleyre and Castillo, 2003). However, in contrast to the amygdala, hippocampal LTD is attenuated by pharmacological inhibition of DAGL, suggesting a role for 2-AG in this process (Chevalleyre and Castillo, 2003; Edwards et al., 2006). Consistent with this is evidence that high frequency stimulation of hippocampal slices results in selective increases in tissue 2-AG, but not AEA, content (Stella et al., 1997). Unique to the hippocampus are the findings that persistent upregulation of endocannabinoid signaling at GABAergic synapses facilitates subsequent LTP of excitatory glutamatergic synapses (Chevalleyre and Castillo, 2004; Zhu and Lovinger, 2007), and that this “metaplasticity” requires a transient rise in postsynaptic Ca²⁺ concentrations but not concurrent activation of mGluRs (Edwards et al., 2008).

3.2.5 Prefrontal cortex and Ventral tegmental area—CB₁ receptor activation suppresses excitatory inputs to layer 5 pyramidal cells in rodent PFC and repetitive stimulation in PFC can elicit LTD of excitatory transmission in this region (Lafourcade et al., 2007). This CB₁-dependent LTD is reliant on the activation of postsynaptic mGluR5 and PLC, requires a rise in postsynaptic Ca²⁺ concentrations, is enhanced following MAGL inhibition and attenuated following DAGL inhibition (Lafourcade et al., 2007). Together with evidence that PFC LTD is unaltered by FAAH inhibition (Lafourcade et al., 2007) these findings strongly implicate role for 2-AG in this process. Plasticity of inhibitory transmission in the PFC is also under eCB regulation (Chiu et al., 2010). However, in contrast to eCB-LTD of excitatory synapses, modulation of inhibitory transmission in the PFC is facilitated by dopamine D₂ receptor activation and independent of postsynaptic elevations in Ca²⁺ concentrations (Chiu et al., 2010). With respect to neurotransmission in the VTA, dopamine D₂ receptors are known to cooperate with group I mGluRs to induce

eCB-LTD of excitatory and inhibitory synaptic transmission, in a manner similar to eCB-mediated long-term plasticity in the striatum (Pan et al., 2008a). Indeed, activation of excitatory PFC inputs to VTA dopamine cells elicits 2-AG-mediated suppression of excitation *in vivo* (Melis et al., 2004), thereby decreasing the probability of burst firing of dopamine neurons. This form of eCB-mediated “fine-tuning” of dopamine transmission that connects limbic and motor systems might have a crucial role in information processing of reward-related stimuli under conditions of stress or drug dependence.

3.2 TRPV1 mechanisms of endocannabinoid-mediated plasticity

As previously noted (see section 2) AEA is a potent agonist at TRPV1 receptors, which are non-selective ligand-gated cation channels. TRPV1 receptors are also potently activated by related lipid molecules including N-arachidonoyldopamine (NADA) and 12-(S)-HPETE (a lipoxygenase metabolite of arachidonic acid) (Kauer and Gibson, 2009). Although TRPV1 receptors were first identified and cloned in peripheral afferent fibers, several lines of evidence from immunohistochemical, *in situ* hybridization, RT-PCR and autoradiographic studies suggest these receptors are also expressed in brain (Kauer and Gibson, 2009). However, the existence and functional importance of TRPV1 receptors in the brain has been controversial due to substantial variance in estimates of TRPV1 density and distribution, reports of negative findings following TRPV1 manipulations of synaptic function (Benninger et al., 2008; Kofalvi et al., 2006) and recent evidence for a highly restricted TRPV1 distribution in the rodent, monkey and human brain (predominantly in primary sensory ganglia of the rostral midbrain and the posterior hypothalamus) (Cavanaugh et al., 2011). Despite this controversy, substantial data suggest that TRPV1 activation stimulates glutamate release (Bhaskaran and Smith, ; Marinelli et al., 2005; Musella et al., 2009; Shoudai et al.) and influences locomotion (Di Marzo et al., 2001), anxiety (Marsch et al., 2007; Micale et al., 2009; Rubino et al., 2008a) and stress responses (Li et al., 2008; Starowicz et al., 2008). Because each of these processes are involved in addiction, the influence of eCBs and related lipids at TRPV1 receptors is of relevance to the present topic.

Several forms of TRPV1-mediated synaptic plasticity have been described. Marsch and colleagues observed that LTP of EPSPs in the dorsal hippocampus is significantly reduced in TRPV1 knockout mice (Marsch et al., 2007) in direct contrast to the facilitation of LTP observed at these synapses in CB₁ knockout mice (Bohme et al., 2000). Subsequently the Kauer laboratory reported that TRPV1 receptor activation triggers LTD at excitatory synapses onto CA1 interneurons but not neighboring pyramidal cells in juvenile rats and mice (Gibson et al., 2008). Moreover, they observed that LTD is prevented by TRPV1 antagonists and is absent in TRPV1 knockout mice, suggesting that TRPV1 receptors are both necessary and sufficient for LTD of CA1 interneurons. The Di Marzo laboratory reported that TRPV1 stimulation suppresses fEPSPs in the superior colliculus (SC) of juvenile mice while TRPV1 antagonism prevents induction of LTD in this region (Maione et al., 2009). Correlation between the waning of TRPV1 labeling with the disappearance of SC LTD during the onset of adulthood provides further evidence for an important TRPV1 influence in this form of LTD (Maione et al., 2009). In contrast to these reports, Li and colleagues observed that TRPV1 stimulation facilitates LTP and inhibits LTD in the CA1 of juvenile rats (Li et al., 2008), though the reasons for these disparate observations remain unclear. Recent simultaneous reports from the Castillo and Malenka laboratories demonstrate that AEA activation of TRPV1 receptors induces LTD of excitatory transmission via induction of postsynaptic AMPAR endocytosis (Chavez et al., 2010; Grueter et al., 2010). Nearly identical evidence was gathered at excitatory synapses in the rat and mouse dentate gyrus (Chavez et al., 2010) and at medium spiny neurons in the core subregion of the mouse nucleus accumbens (Grueter et al., 2010). Because the nucleus accumbens observations were made in DRD2-EGFP mice certain caveats are merited

(Kramer et al., 2011), though the similarity of the nucleus accumbens profile to observations made in the dentate gyrus of C57BL/6 mice and Wistar rats (Chavez et al., 2010) suggest this form of plasticity may be widespread in rodent brain.

As described above, growing evidence suggests that eCBs and related lipids may influence synaptic plasticity through TRPV1 receptors in a manner that differs substantially from CB₁ receptor-mediated forms of plasticity. Although TRPV1 receptors may influence a variety of behaviors related to addiction there is presently a paucity of information about the effects of abused drugs on TRPV1-mediated cellular plasticity. One notable exception is the recent report from the Malenka lab demonstrating that a single exposure to cocaine prevents both mGluR-mediated eCB-LTD and TRPV1-LTD of NAc medium spiny neurons (Grueter et al., 2010). Their observation that TRPV1 knockout mice display enhanced behavioral sensitization to repeated cocaine administration provides important evidence of a TRPV1 influence in addiction-related behaviors (Grueter et al., 2010). Despite these initial observations, substantial work is clearly needed to characterize the effects of drug exposure on TRPV1-mediated synaptic plasticity and to elucidate the role of TRPV1 signaling mechanisms in addiction-related behaviors. Accordingly, the remainder of this review will focus on the effects of abused drugs on eCB-induced synaptic plasticity mediated through CB₁ receptors, followed by a consideration of the possible involvement of altered eCB-mediated synaptic plasticity in behaviors related to addiction.

4. Endocannabinoid synaptic plasticity and addiction-related behaviors

There is now substantial evidence that exposure to most drugs of abuse dysregulates synaptic plasticity in a variety of brain regions involved in the evolution of addiction (Hyman et al., 2006; Kalivas and O'Brien, 2008; Kauer and Malenka, 2007; Luscher and Huber, 2010; Luscher and Malenka, 2011; Van den Oever et al., 2010). For example, acute exposure to cocaine, morphine or nicotine induces transient loss of LTP at inhibitory GABAergic synapses in the VTA (Niehaus et al., 2010) consistent with prior reports demonstrating that these same drugs as well as ethanol affect inhibitory synaptic plasticity in this region (Liu et al., 2005; Melis et al., 2002; Nugent et al., 2007). In contrast, exposure to psychostimulants, opiates, ethanol and nicotine results in enhanced excitatory synaptic strength onto VTA dopamine neurons (Borgland et al., 2004; Faleiro et al., 2004; Saal et al., 2003; Ungless et al., 2001; White et al., 1995; Zhang et al., 1997). This tandem potentiation of excitatory transmission and loss of inhibitory LTP in VTA serves to heighten midbrain DA cell excitability, increasing dopaminergic signaling throughout the mesocorticolimbic system.

As previously detailed an important influence of eCB transmission on synaptic plasticity has been clearly established in several brain regions with known involvement in the etiology of drug addiction, including the NAc, VTA, PFC, dorsal striatum, hippocampus and amygdala. Accordingly, drug-induced disruption of these mechanisms may contribute to aberrations in learning, memory and affective state that propel addiction. Relatively few studies have directly evaluated drug-induced alterations in eCB-mediated plasticity and these are reviewed in the sections that follow.

4.1 Disruption of eCB-mediated synaptic plasticity by drugs of abuse

4.1.1 Δ^9 -THC—In 2003 the Lupica group reported that eCB-mediated LTD of excitatory signaling in the rat NAc is abolished following a 7 d treatment regimen with either Δ^9 -THC or the synthetic CB₁ receptor agonist WIN 55,212-2 (Hoffman et al., 2003). This effect was correlated with decreased sensitivity to the inhibitory effects of CB₁ receptor agonists at both excitatory and inhibitory synapses, and from this it was theorized that the cannabinoid-induced disruption of eCB-LTD results from a down regulation of CB₁ receptor function. In

the following year the Manzoni lab reported that a single exposure to $\Delta 9$ -THC abolishes eCB-mediated LTD of both excitatory and inhibitory transmission in the mouse NAc and hippocampus (Mato et al., 2004). DSI was also reduced in $\Delta 9$ -THC-treated animals and because this process is not reliant on mGluR activation a drug-related attenuation in mGluR function was discounted. The $\Delta 9$ -THC-induced reduction in LTD was determined to be transient (< 24 h) and CB₁ receptor dependent. While no alterations in CB₁ expression or G-protein coupling were evident $\Delta 9$ -THC-treated animals were tolerant to the inhibitory effects of CB₁ receptor agonists, consistent with the findings by Hoffman and colleagues (Hoffman et al., 2003). Subsequently the Manzoni group reported that LTD of NAc excitatory transmission is not altered following a 7 d regimen of $\Delta 9$ -THC treatment despite the presence of diminished CB₁ receptor G-protein coupling and tolerance to the inhibitory effects of CB₁ receptor agonists on excitatory transmission (Mato et al., 2005). This surprising preservation of LTD following repeated $\Delta 9$ -THC exposure was found to result from recruitment of mGluR2/3 mechanisms that were posited to compensate for reduced eCB influence resultant from desensitized CB₁ receptor function. The reasons for the differential effects of repeated $\Delta 9$ -THC exposure on NAc LTD reported by the Lupica and Manzoni labs are not clear, though several experimental factors distinguish these studies including nearly 7-fold differences in $\Delta 9$ -THC dose and the rodent species under study (Sprague Dawley rats vs. C57Bl/6 mice).

4.1.2 Cocaine—In 2004 the Manzoni group reported that eCB-LTD of evoked excitatory transmission is abolished in the mouse NAc 24 h after a single injection of a moderately high cocaine dose (20 mg/kg) (Fourgeaud et al., 2004) similar to previous reports of diminished mGluR-induced LTD in the NAc following a single cocaine exposure (Swanson et al., 2001). This effect was not associated with a reduction in CB₁ receptor function or generalized alteration in the plasticity of excitatory transmission in this region. However, a significant reduction in mGluR5 expression and influence was evident and it was theorized that the cocaine-induced abolition of eCB-LTD resulted from diminished mGluR5-mediated eCB production. These findings indicate that acute cocaine exposure results in heightened excitatory signaling in the mouse NAc (e.g. reduced LTD of excitation). In concert with this, repeated cocaine exposure results in reduced inhibition of rat VTA dopamine cells through facilitated induction of eCB-mediated LTD of GABAergic cells (Pan et al., 2008b). This effect of cocaine is reliant on dopamine D₂ and group I mGluR activation, and requires CB₁ receptor activation for the induction, but not maintenance of LTD. Inhibition of PLC or DAGL function attenuates this cocaine-related LTD induction, implicating a role for 2-AG in this process. Pretreatment with D₁, D₂, mGluR5, NMDA or CB₁ receptor antagonists prior to each daily cocaine injection blocks the reduction in GABAergic inhibition commonly observed in rat VTA following repeated cocaine treatment (Fourgeaud et al., 2004; Liu et al., 2005), suggesting that this consequence of repeated cocaine exposure involves the induction of eCB-mediated LTD of inhibitory transmission in the VTA. 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 bed nucleus of the stria terminalis (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 and Winder, 2009; Stewart, 2000). The

BNST extends a substantial projection to the VTA (Dong and Swanson, 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.

4.1.3 Alcohol—Acute and repeated alcohol exposure has also been shown to disrupt eCB-mediated synaptic plasticity. Short periods of low-frequency stimulation produce a CB₁-dependent long-lasting disinhibition (DLL) of striatal output neurons as a result of reduced synaptic strength at inhibitory synapses (Adermark and Lovinger, 2009). Acute exposure of striatal slices to moderate ethanol doses substantially reduces eCB-mediated DLL of neurons in the dorsolateral striatum (Clarke and Adermark, 2010). DLL is also significantly reduced in the dorsolateral striatum of rats that had voluntarily consumed pharmacologically-relevant amounts of ethanol for seven weeks (Adermark et al., 2011). Interestingly, both acute and chronic ethanol suppresses DLL induced by either the calcium channel activator FPL64176 or the CB₁ receptor agonist WIN 55,212-2 suggesting that ethanol affects DLL at a stage that is downstream from CB₁ receptor activation. Acute ethanol also reduces eCB-mediated LTD at inhibitory striatal synapses though no significant ethanol effects are evident on LTD of excitatory synapses (Clarke and Adermark, 2010). Because the dorsal striatum is involved in reward-guided learning and habitual behavior (Volkow et al., 2007; Yin et al., 2008) it is possible that ethanol-induced interference in eCB-LTD contributes to maladaptive habitual behavior associated with addiction.

4.2 CB₁ receptor involvement in the evolution of addiction-related behavior

Substantial evidence implicates cannabinoid CB₁ receptors and their endogenous ligands in the motivational effects of most classes of abused substances (for thorough reviews see (Lopez-Moreno et al., 2008; Lopez-Moreno et al., 2010; Moreira and Lutz, 2008; Parolaro and Rubino, 2008; Serrano and Parsons, 2011; Wiskerke et al., 2008)). A growing literature also demonstrates a role for CB₁ receptors in the etiology of behaviors that evolve over the course of long-term drug exposure such as behavioral sensitization, altered learning and memory (extinction learning and relapse to drug-seeking), enhanced stress responsivity and abnormal affective control. These behavioral alterations likely result in part from dysregulated signaling plasticity (Berke and Hyman, 2000; Gerdeman and Lovinger, 2003), and as such these findings are discussed in following sections.

4.2.1 Behavioral Sensitization—Behavioral sensitization refers to an amplified behavioral and neurochemical response elicited by drug challenge following a history of repeated drug exposure, and is considered to be the consequence of drug-induced neuroadaptive changes in a circuit involving dopaminergic and glutamatergic interconnections between the VTA, NAc, PFC and amygdala (Vanderschuren and Kalivas, 2000). Several conceptualizations posit that sensitization induces a persistent hyper-responsiveness of brain motivational circuitry to drugs and drug-associated stimuli (Robinson and Berridge, 1993, 2008; Vanderschuren and Pierce, 2010; Wise and Bozarth, 1987). The involvement of the endocannabinoid system (ECS) in behavioral sensitization remains inconclusive. For example, while some studies report attenuated behavioral sensitization following a single exposure to cocaine or amphetamine in CB₁ receptor knockout mice or wildtype mice pretreated with a CB₁ receptor antagonist (Corbille et al., 2007) other studies report unaltered sensitization to repeated cocaine exposure in CB₁ receptor knockout mice (Martin et al., 2000) or wild type mice given CB₁ antagonist pretreatment cocaine (Filip et al., 2006; Gerdeman et al., 2008; Lesscher et al., 2005). These discrepant findings may suggest that a CB₁ receptor influence on the induction of psychostimulant sensitization is masked over the course of repeated drug exposure. Additional work has demonstrated that behavioral sensitization to repeated amphetamine is

absent in CB₁ (–/–) mice but is enhanced in wildtype mice given CB₁ receptor antagonist pretreatment prior to each amphetamine exposure (Thiemann et al., 2008). This disparity may point toward developmental compensations to life-long CB₁ receptor absence in the knockout animals or off-target pharmacological effects of SR141716A. A differential influence of CB₁ receptors in the induction versus expression of morphine sensitization has been reported wherein CB₁ receptor antagonism blocks the expression of previously established sensitization but does not modify the induction of sensitization produced by repeated morphine (Vigano et al., 2004). A CB₁ influence on behavioral sensitization may also be context-dependent, as SR141716A diminishes expression of cocaine sensitization in environments previously paired with cocaine delivery, but not in novel environments unassociated with cocaine (Gerdeman et al., 2008). A preferential CB₁ receptor influence in regulating drug-related behaviors in drug-paired environments is consistent with substantial evidence implicating eCB mechanisms in the reinstatement of drug-seeking behavior.

4.2.2 Learning & memory: extinction learning and drug-seeking behavior—

Drug intake produces powerful interoreceptive effects and memory of these effects increases the likelihood of continued drug use. Over time these interoreceptive effects become associated with environmental cues to the point where these drug-associated cues alone can induce craving and thereby propel continued drug use. This form of drug-related memory is also causal in relapse to drug use following periods of abstinence (Carter and Tiffany, 1999; Leshner, 1997; McLellan et al., 2000; O'Brien et al., 1998; O'Brien et al., 1992; O'Brien and McLellan, 1996).

The ECS is well known to play a prominent role in learning and memory processes (Hashimoto et al., 2007; Heifets and Castillo, 2009; Marsicano and Lafenetre, 2009; Zhu, 2006) and because eCB signaling is disrupted by most drugs of abuse (Serrano and Parsons, 2011) a role for the ECS in the learning and memory components of addiction may be hypothesized. CB₁ receptors play an important role in the conditioning effects produced by ethanol (Houchi et al., 2005; Hungund et al., 2003; Thanos et al., 2005; Wang et al., 2003), opiates ((Chaperon et al., 1998; Martin et al., 2000; Navarro et al., 2001; Singh et al., 2004) but see (Rice et al., 2002)), and nicotine (Castane et al., 2002; Forget et al., 2006; Forget et al., 2005; Le Foll and Goldberg, 2004; Merritt et al., 2008), though a lesser CB₁ receptor influence is reported for the conditioning effects of psychostimulants (Houchi et al., 2005; Martin et al., 2000). While these effects are generally interpreted in the context of drug reward, a CB₁ receptor contribution to the associative learning aspects of drug exposure is also likely. This may be particularly evident from growing evidence implicating CB₁ receptors in the reinstatement of extinguished drug-seeking behavior (a model of relapse, see 4.2.2.2). Moreover, as described below CB₁ receptors have been implicated in memory extinction and as such dysregulation of eCB signaling could contribute to a persistent reactivity to drug-related memories that characterizes addiction.

4.2.2.1 Extinction learning: The potent motivational effects of drug-related cues create substantial difficulties during periods of attempted drug abstinence. Accordingly there has been considerable interest in developing interventions to reduce the potency of these cues for eliciting craving and relapse. One approach for lessening the motivational impact of conditioned cues is through extinction, through which a subject learns that a drug-associated cue no longer has predictive value. Extinction typically requires repeated presentation of the conditioned cue without delivery of the expected outcome and this progressively devalues the motivational impact of the cue. Extinction is not simply a “forgetting” of conditioned behavior, but instead is an active learning process that overrides the original association memory (Bouton, 2004). The use of extinction therapy for addiction has thus far been ineffective in reducing relapse in both humans (Conklin and Tiffany, 2002) and rodents

(Crombag and Shaham, 2002; Weiss et al., 2001), and it is conceivable that these negative findings result from drug-related disruption of extinction learning mechanisms.

Several studies have demonstrated an important eCB influence in memory extinction. Marsicano and colleagues observed that while CB₁ deficient mice exhibit normal acquisition and consolidation of fear conditioning, extinction of fear memory is strongly impaired in these animals (Marsicano et al., 2002). An important role for CB₁ receptors in the extinction of contextual fear memory (Suzuki et al., 2004), and fear potentiated startle (Chhatwal et al., 2005; Chhatwal et al., 2006) has also been shown. The Lichtman laboratory has reported that CB₁ deficient and SR141716A-treated wildtype mice exhibit impaired extinction learning in the Morris water maze and passive avoidance tasks that are each conducted in an aversive, mildly stressful context (Niyuhire et al., 2007; Varvel et al., 2005; Varvel and Lichtman, 2002). Similar findings have been made using the CB₁ receptor antagonist SR147778 in rats (Pamplona et al., 2008; Pamplona et al., 2006). In contrast to these findings, CB₁ receptor inactivation does not alter the extinction of behaviors maintained by appetitive, non-aversive memories (Holter et al., 2005; Niyuhire et al., 2007).

Collectively these findings suggest that disruption of eCB and/or CB₁ receptor mechanisms confers deficient extinction of aversive memories. Because aversive memory may be involved in relapse to drug taking behavior (Kaplan et al., 2011; Quirk and Gehlert, 2003; Stewart and Kushner, 2001) dysregulated eCB signaling following long-term drug exposure may contribute to the limited efficacy of extinction therapy for addiction (Conklin and Tiffany, 2002; Crombag and Shaham, 2002; Weiss et al., 2001). Accordingly, therapeutic approaches that restore proper eCB function may enhance the utility of extinction therapy for prolonging drug abstinence.

4.2.2.2 Drug-seeking (relapse): Recently developed animal models of drug seeking (See, 2005; Shaham et al., 2000; Shalev et al., 2002; Stewart, 2000; Weiss, 2005) have demonstrated an important influence of cannabinoid signaling in the re-initiation of drug-seeking and -taking behaviors. For example, direct acting CB₁ receptor agonists such as Δ^9 -THC, HU-210, WIN 55,212-2, and CP 55,940 reinstate extinguished drug-seeking behavior for cannabinoids (Justinova et al., 2008; Spano et al., 2004), opioids (De Vries et al., 2003; Fattore et al., 2005a; Fattore et al., 2003), ethanol (Lopez-Moreno et al., 2004; McGregor et al., 2005), nicotine (Biala and Budzynska, 2008) and cocaine (De Vries et al., 2001).

In contrast, CB₁ receptor antagonism attenuates drug-seeking behavior associated with a variety of abused substances. SR141716A significantly reduces operant responding for a conditioned cue paired with Δ^9 -THC self-administration in squirrel monkeys (Justinova et al., 2008) and blocks the reinstatement of heroin-seeking behavior in rats (De Vries et al., 2003; Fattore et al., 2003; Fattore et al., 2005b). A specific influence of CB₁ receptors in the PFC and shell of the NAc, but not BLA has been demonstrated for heroin-seeking behavior in rats (Alvarez-Jaimes et al., 2008), consistent with the known involvement of these structures in the expression of goal-directed behaviors in response to stimuli predicting drug availability (Kalivas and Volkow, 2005).

CB₁ receptor antagonism also attenuates ethanol-seeking behavior. SR141716A reduces reinstatement of ethanol-seeking behavior triggered by an ethanol-paired odor cue (Cippitelli et al., 2005; Economidou et al., 2006). Moreover, both SR141716A and the similar CB₁ receptor antagonist SR147778 reduce excessive ethanol intake observed following periods of abstinence (an animal model of relapse-like alcohol consumption) (Gessa et al., 2005; Serra et al., 2002). In contrast, administration of the CB₁ receptor agonist WIN 55,212-2 during alcohol abstinence increases post-abstinence elevations in alcohol consumption for up to 2 weeks after deprivation (Alen et al., 2008; Lopez-Moreno et

al., 2004). These observations suggest that CB₁ receptors exert a facilitory influence on post-abstinence increases in alcohol consumption.

CB₁ receptor antagonism also reduces the reinstatement of nicotine-seeking behavior induced either by presentation of discrete drug-paired cues (Cohen et al., 2005; De Vries et al., 2005) or exposure to environments previously paired with nicotine self-administration (Diergaarde et al., 2008). Similar to the work on heroin-seeking behavior described above, bilateral SR141716A infusions into the NAc shell, PFC and BLA dose-dependently reduce cue-induced nicotine-seeking behavior (Kodas et al., 2007).

Although CB₁ receptor antagonism produces subtle and inconsistent effects on psychostimulant self-administration as compared with other drugs of abuse (Serrano and Parsons, 2011), substantial evidence indicates a strong CB₁ receptor influence in the reinstatement of psychostimulant-seeking behavior. In fact, the first evidence of a CB₁ receptor involvement in drug-seeking behavior was gathered using a model of cocaine-seeking behavior (De Vries et al., 2001). In this study De Vries and colleagues observed that SR141716A dose-dependently attenuates both cocaine-primed and cue-induced reinstatement of cocaine-seeking behavior in rats. These findings were subsequently replicated by others using higher SR141716A doses (Filip et al., 2006) and the more selective CB₁ receptor antagonist AM251 (Xi et al., 2006). Both drug priming- and cue-induced reinstatement of methamphetamine-seeking behavior are also reduced by SR141716A (Anggadiredja et al., 2004) though similar effects were not observed with AM251 (Boctor et al., 2007).

Thus, substantial evidence implicates CB₁ receptor signaling in drug-seeking behavior for a variety of abused substances that differ substantially in pharmacodynamic mechanism including cannabinoids, opioids, alcohol, nicotine and psychostimulants. It is also notable that CB₁ receptor antagonism blocks cue- and “priming”-induced reinstatement of seeking behavior for non-drug rewards such as sucrose and corn oil ((De Vries et al., 2005; Ward et al., 2009) but see (Xi et al., 2006)). Collectively these findings suggest a general role for CB₁ receptors in the modulation of conditioned reward. These observations have been forwarded as support for an eCB involvement in relapse-like behavior, though caveats regarding the inverse agonist properties of many CB₁ receptor antagonists weaken these conclusions (MacLennan et al., 1998; Pan et al., 1998).

To more directly address this issue recent studies have begun evaluating the effect of eCB clearance inhibitors on drug-seeking behavior. Neither cue- nor stress-induced reinstatement of ethanol-seeking behavior are altered following treatment with the FAAH inhibitor URB597 or the eCB reuptake inhibitor AM404 (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). Similarly, both URB597 and the non-selective FAAH inhibitor PMSF significantly attenuate both priming- and cue-induced cocaine-seeking behavior (Adamczyk et al., 2009). These observations are somewhat surprising given that CB₁ receptor stimulation has been shown to enhance drug-seeking and FAAH inhibition is expected to produce substantial increases in brain AEA levels. However, in addition to AEA FAAH hydrolyzes a large number of fatty acid moieties (Ahn et al., 2008) and it is conceivable that the effects of FAAH inhibition on drug-seeking are mediated through some lipid signaling molecule other than AEA. Moreover, it should be borne in mind that AEA potently activates non-CB₁ receptor signaling mechanisms such as TRPV1 receptors that are known to mediate behavioral effects that are sometimes opposite to those produced by CB₁ receptor activation (Micale et al., 2009; Santos et al., 2008; Terzian et al., 2009).

4.2.3 Stress responsivity—A substantial clinical and preclinical literature indicates that various forms of stress are involved in the etiology and maintenance of drug dependence. In humans 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 and Guerin, 1996; Koob and Kreek, 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 and Le Moal, 1998; Rouge-Pont et al., 1998; Rouge-Pont et al., 1995; Tidey and Miczek, 1997). Long-term drug use is theorized to result in an allostatic shift in reward state characterized by increased influence of CNS stress systems and chronic dysregulation of the HPA axis that serves to propel an escalation of drug consumption (Koob and Kreek, 2007; Koob and Le Moal, 1997; Le Moal, 2009).

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). Several rodent studies have shown that stress-induced glucocorticoid secretion increases eCB production in the amygdala, hippocampus, PFC, paraventricular nucleus (and other regions of the hypothalamus) and periaqueductal grey (Di et al., 2003; Di et al., 2005; Di et al., 2009; Hill et al., 2010; Hohmann et al., 2005; Malcher-Lopes et al., 2006; Patel et al., 2005a; Patel et al., 2004). Similarly, social stress has been shown to rapidly increase circulating levels of 2-AG in humans (Hill and McEwen, 2009). There is a strong CB₁ receptor presence in these and other brain regions involved in regulating stress responsivity (including midbrain monoaminergic nuclei such as the locus coeruleus and dorsal raphe) and substantial evidence demonstrates that eCB signaling through these receptors provides an inhibitory feedback influence that constrains stress-induced HPA axis activation and resultant increases in glucocorticoid secretion (Barna et al., 2004; Cota et al., 2007; Di et al., 2003; Haller et al., 2004; Manzanares et al., 1999; Patel et al., 2004; Uriguen et al., 2004; Valverde, 2006; Wade et al., 2006). In contrast, several studies have observed stress-induced reductions in AEA content in the amygdala, PFC and hippocampus (Hill et al., 2008a; Hill et al., 2009; Patel et al., 2005b; Rademacher et al., 2008). Based on the hypothesis that eCBs exert a tonic steady-state regulation of HPA activity it is theorized that stress-induced reductions in AEA allow enhanced HPA axis activation and subsequent expression of stress responses (Patel et al., 2004). 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 this regard, it is conceivable that altered eCB-mediated plasticity induced by long-term drug exposure contributes to the persistent dysregulation of HPA axis function and increased sensitivity to stress associated with addiction (Koob and Kreek, 2007; Koob and Le Moal, 1997; Le Moal, 2009). Because strong evidence implicates stress exposure in the development of addiction (Goeders, 2002; Goeders and Guerin, 1996; Jose et al., 2000; Koob and Kreek, 2007; Lynch et al., 1999; Richman et al., 1996; Rospenda et al., 2000; Vengeliene et al., 2003) it is notable that stress can alter eCB-mediated plasticity in addiction-related brain regions. For example, prolonged exposure to unpredictable stress impairs eCB-mediated DSI, LTD and fEPSPs in the NAc through an attenuation of CB₁ receptor function (Wang et al., 2010). Repeated episodes of restraint stress result in attenuated eCB-mediated DSE and DSI in the rat PVN (Wamsteeker et al., 2010) and increased 2-AG-mediated DSI in the mouse BLA (Patel et al., 2009). Similarly, establishment of conditioned fear increases the efficacy of DSE and DSI in the central nucleus of the amygdala (Kamprath et al., 2011).

4.2.4 Affective control—Withdrawal is a critical component of most definitions of drug dependence. In addition to transient somatic symptoms withdrawal from most drugs of abuse is characterized by increased negative affective symptoms such as anxiety and depression (Alling et al., 1982; Carmody, 1992; Coffey et al., 2000; Janiri et al., 2005; Nunes and Levin, 2004; Nunes et al., 2004; Voltaire-Carlsson et al., 1996). These negative affective states can persist for months and in some cases years during protracted abstinence and the severity of these symptoms is hypothesized to be closely associated with susceptibility to relapse (Annis et al., 1998; Miller and Harris, 2000). Accordingly there has been substantial interest in the characterization of the neural mechanisms contributing to withdrawal-related affective dysregulation with the aim of identifying viable treatment targets for the prolongation of abstinence. Moreover, the prevalent comorbidity between affective disorders and substance use disorders has led to the suggestion that affective dysregulation is an antecedent to addiction (Bruijnzeel et al., 2004; Castle, 2008; Conway et al., 2006; Pani et al., 2010; Schuckit, 2006), providing further impetus for understanding the neurobiological intersection between affective state and addiction.

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 levels (Serrano and Parsons, 2011) and eCB-mediated synaptic regulation it is conceivable that dysregulated eCB function contributes to affective disturbances associated with drug dependence and protracted withdrawal.

4.2.4.1 Anxiety: It has long been recognized that CB receptor agonists produce bimodal effects on anxiety, with low doses having anxiolytic effects and high doses having anxiogenic effects in both humans (Ashton, 2001; Dannon et al., 2004; Hall and Solowij, 1998; Tournier et al., 2003) and rodents (Viveros et al., 2005). There is also considerable evidence that the ECS plays a role in modulating anxiety-related responses. Elevation of 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 and marble burying 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; Kinsey et al., 2011; Micale et al., 2009; Moise et al., 2008; Moreira et al., 2008; Naderi et al., 2008; Naidu et al., 2007; Patel and Hillard, 2006; Rutkowska et al., 2006; Scherma et al., 2008a). Of particular interest, 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 CB₁ receptor agonists, eCB clearance inhibitors do not appear to produce dramatic bi-phasic effects on anxiety-like behavior but appear to only produce anxiolytic-like behavioral effects.

Reductions in CB₁ receptor signaling tend to produce anxiogenic-like behavioral effects. CB₁ (–/–) mice display anxiety-like behaviors in a variety of tests including the elevated plus-maze, light/dark transfer box and social interaction test (Haller et al., 2002; Martin et al., 2002; Uriguen et al., 2004) and these effects are most evident under conditions of high stress (Haller et al., 2002). Pharmacologic inhibition of CB₁ receptor signaling also produces anxiety-like behavioral effects (Arevalo et al., 2001; McGregor et al., 1996; Navarro et al., 1997) and both genetic and pharmacological CB₁ receptor activation is associated with heightened sensitivity to stress-induced HPA axis activation and Fos expression in anxiety-related structures (Patel et al., 2005a; Uriguen et al., 2004).

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. As previously discussed disruption of CB₁ receptor signaling impairs the extinction of aversive memories (Cannich et al., 2004; Chhatwal et al., 2005; Chhatwal et al., 2009; Chhatwal et al., 2006; 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, CB₁ receptor activation either through direct pharmacologic stimulation or via 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).

Collectively these findings implicate the ECS 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. This process is mediated in part through eCB-mediated synaptic plasticity in amygdalar nuclei (Kamprath et al., 2011; Lafenetre et al., 2007; Viveros et al., 2007) and as such drug-induced disruption of eCB-mediated plasticity may contribute to increased anxiety associated with protracted drug abstinence.

4.2.4.2 Depression: Deficiencies in CB₁ receptor signaling appear to produce depressive-like symptoms in rodents and humans. CB₁ (–/–) 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, CB₁ (–/–) mice display a heightened HPA axis response to stress (Uruguén et al., 2004), in line with one of the most consistent findings in major depressive disorder. Although acute CB₁ receptor antagonist administration produces antidepressant-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 CB₁ 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., 2008b). 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 CB₁ receptor antagonist Taranabant (Aronne et al., 2010). Recent evidence also suggests that a single nucleotide polymorphism (SNP) in the CB₁ receptor gene (rs7766029) is highly associated with increased symptoms of depression following recent negative life events (Juhász et al., 2009), and a different CB₁ 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., 2008b). All of these data support the hypothesis that impaired CB₁ receptor signaling leads to depression-like symptomatology.

In general, enhancement of CB₁ receptor signaling produces antidepressant-like behavioral effects. Systemic administration of direct CB₁ receptor agonists reverses behavioral despair in the forced swim test under both acute (Adamczyk et al., 2008; Bambico et al., 2007; Hill and Gorzalka, 2005; Rutkowska and Jachimczuk, 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 and Gorzalka, 2005; McLaughlin et al., 2007; Naidu et al.,

2007; Rademacher and Hillard, 2007). FAAH ($-/-$) 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 CB₁ 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 and Hen, 2007; Perera et al., 2008).

5. Summary and concluding remarks

Endocannabinoid signaling through CB₁ receptors mediates both short- and long-term forms of synaptic plasticity in brain regions involved in the etiology of addiction including the NAc, VTA, PFC, amygdala, hippocampus and dorsal striatum. A growing literature demonstrates that eCB-mediated synaptic plasticity is disrupted following exposure to a variety of drugs of abuse including alcohol, cocaine and Δ^9 -THC. Exposure to these drugs generally leads to a transient loss of eCB-LTD at both inhibitory and excitatory synapses, though increased eCB-LTD of inhibitory synapses in the VTA is evident following cocaine exposure. Drug-induced disruption of eCB-mediated synaptic plasticity may contribute to heightened behavioral and neurochemical responses to drug exposure, decreased extinction of drug-related memories and increased cue-induced drug craving, stress responsivity, anxiety and depression. Accordingly, therapeutic approaches aimed at restoring normal eCB signaling may have clinical benefit for the treatment of addiction. The use of exogenous CB₁ receptor agonists for this purpose would likely be problematic as these compounds may induce drug craving, increase relapse and exacerbate withdrawal-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, do not increase drug-seeking behavior and do not produce anxiety- or depressive-like behavior. Importantly, because eCBs are generally produced on an “as needed” basis the inhibition of eCB clearance may enhance or prolong eCB signaling in a region-specific manner according to regionally distinct stimulus-induced eCB production (e.g. following stress, presentation of conditioned cues, etc.). This may be a substantial advantage over the widespread CB₁ receptor activation produced following administration of exogenous CB₁ receptor agonists. Although several studies have characterized the behavioral effects of FAAH inhibition, there is presently little knowledge of the behavioral effects of MAGL inhibition. Work in this area will be greatly facilitated by the recent development of selective and efficacious MAGL inhibitors (e.g. (Long et al., 2009)). An important caveat in this regard is recent evidence that long-term high dose administration of the MAGL inhibitor JZL184 downregulates CB₁ receptor expression and function and results in symptoms of physical dependence (Schlosburg et al., 2010). Although such effects may present a major limitation for the clinical use of this compound, 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., 2009; Kinsey et al., 2011; Schlosburg et al., 2009). It is unclear whether repeated treatment with low, behaviorally efficacious JZL184 doses also dysregulates CB₁ receptor signaling. It is also worth noting that chronic FAAH inhibition or deletion does not alter CB₁ receptor expression or function (Schlosburg et al., 2010) and as such therapies targeting FAAH may be less prone to adverse effects on central cannabinoid signaling. However, further characterization of the effects of long-term moderate eCB clearance inhibition is clearly needed to evaluate the potential benefits or problems associated with the clinical application of this therapeutic approach. Finally, while a CB₁ receptor involvement in synaptic plasticity and addiction-related behaviors is increasingly defined, further work is needed to characterize the relative influence of non-CB₁ receptor-

mediated eCB signaling mechanisms on these processes (e.g. CB₂, GPR55 and TRPV₁ receptors).

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Highlights

- We describe endocannabinoid-mediated synaptic plasticity in the brain.
- Evidence for drug-induced disruption of this synaptic plasticity is then presented.
- Implications of altered synaptic plasticity in the context of addiction is discussed.

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 DAGL α and DAGL β . 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

Regional eCB-mediated long-term plasticity

Brain Region	Receptors Involved	Synapse
Dorsal Striatum	Group I mGluR Dopamine D ₂	Glutamate, GABA
Nucleus Accumbens	Group I mGluR (mGluR5) TRPV1	Glutamate
Amygdala	Group I mGluR	GABA
Hippocampus	Group I mGluR TRPV1	Glutamate, GABA
Prefrontal Cortex	Group I mGluR (mGluR5) Dopamine D ₂	Glutamate, GABA
Ventral Tegmental Area	Group I mGluR Dopamine D ₂	Glutamate, GABA

See text for references

Table 2 Δ 9-THC induced alterations in eCB-mediated plasticity

Dosing	Species	Brain Region	Effect	Reference
10 mg/kg 1x/day for 7 days	Rat	Nucleus Accumbens	Abolished eCB-LTD of excitatory transmission	Hoffman et al., 2003
3 mg/kg 1x	Mouse	Nucleus Accumbens	Abolished eCB-LTD of excitatory transmission	Mato et al., 2004
3 mg/kg 1x/day for 7 days	Mouse	Nucleus Accumbens	No change in eCB-LTD of excitatory transmission	Mato et al., 2005
3 mg/kg 1x	Mouse	Hippocampus (CA1)	Abolished eCB-LTD of inhibitory transmission	Mato et al., 2004
3 mg/kg 1x	Mouse	Hippocampus (CA1)	Reduced DSI	Mato et al., 2004

Table 3

Cocaine-induced alterations in eCB-mediated plasticity

Dosing	Species	Brain Region	Effect	Reference
20 mg/kg 1x	Mouse	Nucleus Accumbens	Abolished eCB-LTD of excitatory transmission	Fourgeaud et al., 2004
15 mg/kg 1x/day for 5 – 7 days	Rat	Ventral Tegmental Area	Enhanced eCB-LTD of inhibitory transmission	Pan et al., 2008
0.3 mg/kg/infusion, self-administration (3h/day for 10 days)	Mouse	Bed Nucleus of the Stria Terminalis	Attenuated mGluR5-dependent LTD of excitatory transmission	Grueter et al., 2006
20 mg/kg 1x/day for 10 days	Mouse	Bed Nucleus of the Stria Terminalis	Abolished mGluR5-dependent LTD of excitatory transmission	Grueter et al., 2006
20 mg/kg 1x	Mouse	Bed Nucleus of the Stria Terminalis	No effect	Grueter et al., 2006

Table 4

Ethanol-induced alterations in eCB-mediated plasticity

Dosing	Species	Brain Region	Effect	Reference
20 – 50 mM EtOH brain slice superfusion	Rat	Dorsolateral Striatum	Abolished eCB-dependent DLL of inhibitory transmission	Clarke and Adermark, 2010
20 – 50 mM EtOH brain slice superfusion	Rat	Dorsolateral Striatum	Reduced eCB-LTD of inhibitory transmission	Clarke and Adermark, 2010
3.4 g/kg/day self-administration (21 days)	Rat	Dorsolateral Striatum	Abolished eCB-dependent DLL of inhibitory transmission	Adermark et al., 2011