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Impairment of Synaptic Plasticity by Cannabis, Δ^9-THC, and Synthetic Cannabinoids

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The ability of neurons to dynamically and flexibly encode synaptic inputs via short- and long-term plasticity is critical to an organism's ability to learn and adapt to the environment. Whereas synaptic plasticity may be encoded by pre- or postsynaptic mechanisms, current evidence suggests that optimization of learning requires both forms of plasticity. Endogenous cannabinoids (eCBs) play critical roles in modulating synaptic transmission via activation of cannabinoid CB1 receptors (CB1Rs) in many central nervous system (CNS) regions, and the eCB system has been implicated, either directly or indirectly, in several forms of synaptic plasticity. Because of this, perturbations within the eCB signaling system can lead to impairments in a variety of learned behaviors. One agent of altered eCB signaling is exposure to "exogenous cannabinoids" such as the primary psychoactive constituent of cannabis, Δ^9-THC, or illicit synthetic cannabinoids that in many cases have higher potency and efficacy than Δ^9-THC. Thus, by targeting the eCB system, these agonists can produce widespread impairment of synaptic plasticity by disrupting ongoing eCB function. Here, we review studies in which Δ^9-THC and synthetic cannabinoids impair synaptic plasticity in a variety of neuronal circuits and examine evidence that this contributes to their well-documented ability to disrupt cognition and behavior.

One definition of learning is that of a change in behavior or knowledge caused by experience.[1] In a broader sense, the definition of synaptic plasticity is similar; that is, a change in synaptic strength occurs in response to repetitive activity (experience). As synaptic plasticity is thought to represent a mechanism supporting learning and memory storage, this definition seems apt. Like short-term and long-term memory, synaptic plasticity can refer to changes that occur on either short or long time scales (Citri and Malenka 2008; Monday et al. 2018). Thus, short-term plasticity typically refers to synaptic processes that occur over more than hundreds of milliseconds (Abbott and Regehr 2004; Melis et al. 2004a; Regehr 2012), whereas long-term plasticity represents synaptic changes that persist for hours, days, months, or longer.

More formally, long-term potentiation (LTP) is a form of synaptic plasticity in which a long-lasting increase in excitatory transmission occurs following repetitive synaptic

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activity. LTP was initially described at hippocampal glutamatergic synapses in the pioneering studies of Timothy Bliss and Terje Lømo (Lømo 1971; Bliss and Lømo 1973), but was later described at many synapses throughout the central nervous system (CNS) (for review, see Nicoll 2017). Later, long-term depression (LTD), a long-lasting decrease in excitatory synaptic transmission following repeated synaptic activation, was described in the cerebellum (Ito et al. 1982). The scope of influence of LTD and LTP was later broadened to also include inhibitory synapses. It is now widely accepted that both LTP and LTD are ubiquitous mechanisms to modify the strength of communication among neurons throughout the CNS (Lynch et al. 1977; Sjöström et al. 2003; Ronesi and Lovinger 2005; Jörntell and Hansel 2006; Ito et al. 2014; Kim and Cho 2017), and a general consensus has emerged that LTP and LTD play roles in the acquisition (learning) and maintenance of memories (Whitlock et al. 2006; Johansen et al. 2010; Nabavi et al. 2014; Kim and Cho 2017; Abraham et al. 2019).

In contrast to long-term plasticity, short-term changes in synaptic transmission can also occur in response to pathway activation in the CNS. One well-known example of short-term plasticity is a brief increase or decrease in synaptic strength observed when the same synapse is repeatedly activated in rapid succession (typically within tens of milliseconds). This form of short-term plasticity is referred to as paired-pulse facilitation or paired-pulse inhibition, depending on the effect of the first synaptic activation on the second of the closely spaced pair (Zucker and Regehr 2002; Regehr 2012). Another example of short-term plasticity can be observed when a postsynaptic neuron of a synaptically coupled pair is depolarized, leading to the transient (typically 10–60 sec) inhibition of the synaptic response. This phenomenon is referred to as depolarization-induced suppression of inhibition (DSI) when observed at inhibitory synapses (Pitler and Alger 1994), or excitation (DSE) when seen at excitatory synapses (Kreitzer and Regehr 2001b).

Synaptic plasticity has historically been most intensively studied at glutamatergic and GABAergic synapses in the CNS. However, plasticity at these sites can also be dependent on, or modified by, an even wider array of neuromodulators, such as dopamine (DA) or serotonin, and lipids such as the endogenous cannabinoids (eCBs) (Otmakhova and Lisman 1996; Chevaleyre et al. 2006; Lovinger 2010; Palacios-Filardo and Mellor 2019). In this review, we focus on roles for the eCB system in contributing to synaptic plasticity within the CNS and how disruption of these processes by synthetic and plant-derived cannabinoids, such as Δ^9-THC, can lead to impairments in learned behavior.

THE ENDOGENOUS CANNABINOID SYSTEM AND CANNABINOID LIGANDS

The discovery of a brain eCB system began with the identification of cannabinoid agonist binding sites and cloning of the cannabinoid CB1 receptor protein (CB1R) (Devane et al. 1988; Herkenham et al. 1990; Howlett et al. 1990; Matsuda et al. 1990). This was followed by identification of two endogenous agonists at these receptors, known as *N*-arachidonoylethanolamine ([AEA]; anandamide) (Devane et al. 1992) and 2-arachidonylglycerol (2-AG) (Stella et al. 1997). It was also at this time that enzymatic pathways were discovered that convert membrane-bound phospholipids into eCBs in response to a variety of cellular stimuli (Piomelli 2003; Bisogno et al. 2005). We now understand that the synthesis and catabolism of the eCBs are tightly regulated by specific enzymes that have been extensively reviewed elsewhere (Alger and Kim 2011; Di Marzo and Piscitelli 2015; Fowler et al. 2017). Before the discovery of the eCB system, the primary psychoactive constituent of cannabis, Δ^9-THC, was isolated from hashish (Gaoni and Mechoulam 1964) and later shown to bind to CB1Rs in the CNS (Herkenham et al. 1990). Additionally, many synthetic cannabinoids have been produced in both legitimate drug discovery programs and in illicit laboratories, and these compounds are typically selected because of their high potency and efficacy at CB1Rs compared with Δ^9-THC (Banister and Connor 2018). These properties of the illicit syn-

thetic cannabinoids likely contribute to their unwanted and medically serious side effects often observed clinically in humans (Adams et al. 2017; Hoffman et al. 2017). Studies conducted in many different brain regions now strongly support the idea that eCBs and exogenous cannabinoids, such as Δ^9-THC and synthetics, exert their effects in the brain by inhibiting neurotransmitter release through the activation of CB1Rs located on axon terminals (Stella et al. 1997; Katona et al. 1999; Szabo et al. 1999; Hoffman and Lupica 2000, 2001, 2013; Gerdeman and Lovinger 2001; Schlicker and Kathmann 2001), and this remains a central focus of cannabinoid research. Because the recreational use of synthetic cannabinoids and Δ^9-THC by humans has grown in popularity and because of their strong regulation of synaptic transmission, we focus on effects of these drugs on the eCB system in the context of its roles in synaptic plasticity in animal models. However, in general, brain-imaging studies in human cannabis users supports the idea that structural and functional changes are common and that these changes have clear behavioral and psychiatric consequences (Fischer et al. 2014; Volkow et al. 2014b; Broyd et al. 2016; Lupica et al. 2017; Bloomfield et al. 2019; Di Forti et al. 2019; Hwang and Lupica 2019).

ENDOCANNABINOID INVOLVEMENT IN SHORT-TERM PLASTICITY

The first demonstration that in situ eCB release could modulate synaptic transmission involved the phenomenon of DSI at hippocampal GABAergic synapses (Wilson and Nicoll 2001). Before this, DSI had been observed in both hippocampal pyramidal cells and cerebellar Purkinje neurons (Llano et al. 1991; Vincent et al. 1992; Pitler and Alger 1994), where it was shown that this short-term plasticity was blocked by calcium chelation within the postsynaptic cell body, indicating dependence on an intracellular rise in calcium (Llano et al. 1991; Pitler and Alger 1992). As additional experiments showed that the inhibition of the synaptic input occurred presynaptically, it was hypothesized that a messenger was released from the postsynaptic neuron following an increase in calcium caused by depolarization, and that this messenger acted retrogradely at the presynaptic axon terminal to somehow inhibit GABA release. The nature of this hypothesized retrograde messenger remained a mystery until it was shown that DSI could be blocked in hippocampal pyramidal neurons by the CB1R antagonist SR 141716A (rimonabant, Acomplia) (Wilson and Nicoll 2001), and that it was absent in mutant mice lacking the CB1R ($CB1R^{-/-}$) (Wilson et al. 2001; Ohno-Shosaku et al. 2002). These data, therefore, indicated that the retrograde messenger mediating DSI at these synapses was likely an eCB. Subsequent studies supported the idea that this eCB was 2-AG as pharmacological inhibition of its synthetic enzyme, diacylglycerol lipase (DAG), or inhibition of the catabolic enzyme monoacylglycerol lipase (MAGL) could bidirectionally modulate DSI (Makara et al. 2005; Tanimura et al. 2010). Similar findings of eCB-dependent DSI were soon extended to synapses in the cerebellum (Kreitzer and Regehr 2001a), and, later, DSE identified at several central glutamate synapses was also found to require an eCB (Kreitzer and Regehr 2001b; Ohno-Shosaku et al. 2002; Melis et al. 2004b). These studies firmly established a role for eCBs in mediating activity-dependent short-term plasticity throughout the CNS via retrograde signaling from postsynaptic to presynaptic neurons.

ENDOCANNABINOID INVOLVEMENT IN LONG-TERM PLASTICITY

The release of 2-AG after high-frequency activation of Schaffer collateral axons in the hippocampus and the ability of exogenously applied 2-AG to block hippocampal LTP provided the first indications that eCBs may participate in regulating long-term synaptic plasticity (Stella et al. 1997). Additional evidence also supported the idea that the short-term regulation of synaptic transmission by eCB-mediated DSI or DSE could interact with more conventional forms of long-term synaptic plasticity (Heifets and Castillo 2009). For example, when a weak stimulus that is insufficient to alone trigger LTP is paired

with the transient inhibition of GABA release caused by 2-AG-dependent DSI, LTP can be observed in hippocampal pyramidal cells (Carlson et al. 2002). Thus, short-term eCB-dependent suppression of GABA-mediated inhibition can gate long-term synaptic plasticity via this mechanism.

In contrast to the modification of long-term synaptic plasticity by short-term actions of eCBs within local hippocampal circuits, these signaling molecules are also known to play more direct roles (Heifets and Castillo 2009). For example, 2-AG-dependent LTD is observed at glutamatergic Schaffer collateral synapses, but not perforant path synapses, onto the same population of CA1 pyramidal neurons (Xu et al. 2010). Therefore, this eCB-dependent LTD likely reflects reliance on distinct molecular signaling pathways engaged by eCBs at these Schaffer collateral and lateral perforant path (LPP) synapses (Xu et al. 2010; Wang et al. 2018). Endocannabinoids also appear to be obligatory for low-frequency-evoked LTD at excitatory synapses in dorsal striatum (Gerdeman et al. 2002; Ronesi and Lovinger 2005), nucleus accumbens (NAc) (Robbe et al. 2002; Hoffman et al. 2003), prefrontal cortex (PFC) (Lafourcade et al. 2007; Lovelace et al. 2014; Martin et al. 2015), cerebellum (Safo and Regehr 2005), basolateral amygdala (BLA) (Huang et al. 2003), and ventral tegmental area (VTA) (Haj-Dahmane and Shen 2010; Labouèbe et al. 2013). Moreover, GABAergic synapses within the PFC (Chiu et al. 2010), amygdala (Marsicano et al. 2002), and VTA (Pan et al. 2008) also express eCB-dependent LTD. Another form of synaptic plasticity, known as spike-timing dependent plasticity (STDP), can produce either LTD (t-LTD), typically when a synaptic response follows a postsynaptic spike by tens of milliseconds, or LTP (t-LTP), when a synaptic response precedes a postsynaptic spike by tens of milliseconds (Caporale and Dan 2008). However, in the striatum, t-LTP can also be produced when an excitatory postsynaptic potential (EPSP) follows a postsynaptic spike (Fino et al. 2005) and evidence suggests that eCBs can bidirectionally modulate striatal STDP resulting in either t-LTP or t-LTD (Cui et al. 2015; Xu et al. 2018).

Endocannabinoids can also interact with astrocytes to facilitate long-term synaptic plasticity in the hippocampus. For example, t-LTD is observed at Schaffer collateral synapses in the juvenile mouse hippocampus when an action potential in a postsynaptic CA1 pyramidal cell is followed (18 msec) by a glutamate-mediated EPSP (Andrade-Talavera et al. 2016). This t-LTD depends on 2-AG release, 2-AG activation of CB1Rs on the astrocytes, and the release of D-serine from these glial cells (Andrade-Talavera et al. 2016). These investigators propose that D-serine acts at presynaptic *N*-methyl-D-aspartate (NMDA) receptors to induce t-LTD, suggesting that 2-AG can play a critical role in hippocampal synaptic plasticity by coordinating the release of astrocytic signaling molecules. In further support of this, astrocytic CB1Rs appear to regulate D-serine levels in adult animals, and this facilitates hippocampal LTP and object recognition memory (Robin et al. 2018). Endocannabinoids can also directly stimulate glutamate release from astrocytes, which can then activate metabotropic glutamate receptors (mGluRs) to transiently potentiate synaptic signaling at Schaffer collateral-CA1 synapses (Navarrete and Araque 2010). Collectively, these data support a role for astroglial CB1Rs and eCBs in regulating synaptic plasticity at hippocampal synapses, and additional evidence suggests that disruption of these processes following exposure to Δ^9-THC and synthetic cannabinoids can impair synaptic plasticity and working memory (Han et al. 2012).

In addition to these roles for eCBs in synaptic plasticity at excitatory synapse, 2-AG has been shown to promote a spatially localized form of LTD of hippocampal inhibitory GABAergic synapses known as I-LTD (Chevaleyre and Castillo 2003, 2004). Moreover, a functional role for I-LTD has been established by its ability to gate LTP at glutamate synapses within a restricted area defined by the spatial extent of 2-AG release and its suppression of GABAergic transmission (Chevaleyre and Castillo 2004).

In summary, given the involvement of synaptic plasticity in encoding a broad variety of adaptive learned behaviors (e.g., habit and motor learning, spatial learning, fear conditioning),

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and the ability of eCBs to regulate short- and long-term plasticity in many brain areas (Hilario et al. 2007; Gremel et al. 2016; Augustin and Lovinger 2018; Segev et al. 2018), it is clear that alterations within the eCB system caused by exposure to Δ^9-THC and synthetic cannabinoids have the potential to disrupt the coordinated activity that is necessary for these learned behaviors (Lupica and Hoffman 2018).

Dysregulation of Synaptic Plasticity by Exogenous Cannabinoids

As described above, the eCB system is involved either directly or indirectly in several forms of synaptic plasticity throughout the CNS. Therefore, it is perhaps unsurprising that the phytocannabinoid Δ^9-THC or synthetic cannabinoids can profoundly interact with the mechanisms supporting synaptic plasticity. Whereas the full consequences of exogenous cannabinoid exposure and its effects on synaptic plasticity are incompletely understood, current evidence strongly supports the claim that the eCB system is altered by exogenous cannabinoids, and this has clear implications for human behavior in cannabis use disorder (Volkow et al. 2014a; Hasin 2018) as well as in other cognitive impairments and adverse outcomes associated with use of cannabis and synthetic cannabinoids (Every-Palmer 2011; Bassir Nia et al. 2016). Indeed, the available evidence suggests that dysregulation of synaptic plasticity following acute or long-term exposure to exogeneous cannabinoids is likely to have widespread effects on information processing, cognition, memory, emotion, and personality (Lupica and Hoffman 2018). Below, we highlight findings in which changes in synaptic plasticity across several brain areas have been assessed following acute or repeated cannabinoid exposure and attempt to place this in behavioral context.

DORSAL STRIATUM AND VENTRAL STRIATUM (NUCLEUS ACCUMBENS)

The striatum is a functionally heterogeneous brain structure thought to be involved in motivation, motor learning, habit formation, reward, and drug addiction. Moreover, recent studies show that both LTP and LTD are critical to these behavioral roles of the striatum and that eCBs are involved in several forms of striatal long-term plasticity (Gremel et al. 2016; Perrin and Venance 2019). As mentioned above, LTD of glutamatergic afferents to medium spiny neurons in dorsal and ventral striatum has been described, and several studies show that this requires 2-AG (for review, see Perrin and Venance 2019). Because this form of plasticity is critical for both dorsal and ventral striatal function, it is likely that disruption of eCB signaling will alter behavioral output that broadly relies on striatal circuits. In this regard, both acute and chronic in vivo exposure to Δ^9-THC can impair eCB-dependent LTD in the NAc (ventral striatum), and this is associated with desensitization of CB1Rs (Hoffman et al. 2003; Mato et al. 2004). Moreover, long-term treatment with Δ^9-THC can shift goal-directed responding to habitual responding (also known as perseveration) during reinforcer devaluation in mice, a behavior that is dependent on intact dorsal striatal function (Nazzaro et al. 2012). This behavioral impairment was also associated with the loss of eCB-dependent LTD in the striatum, and both the behavior and LTD were rescued by an inhibitor of small-conductance, calcium-activated, potassium channels (S_K channels), which has been shown to facilitate 2-AG function (Riegel and Lupica 2004; Nazzaro et al. 2012). More recently, self-administration of Δ^9-THC combined with the phytocannabinoid cannabidiol (CBD) in rats was associated with a loss of NMDA receptor–dependent LTD in the NAc core (Neuhofer et al. 2019). In this case, LTD was restored in rats extinguished from Δ^9-THC + CBD self-administration when cues previously associated with the drugs were presented, leading to renewed drug seeking, or by a positive allosteric modulator of CB1Rs (Neuhofer et al. 2019). Together, these findings suggest that long-term exposure to exogenous cannabinoids can disrupt both synaptic plasticity and striatal-dependent behavior, and that enhancement of eCB signaling can rescue the synaptic and behavioral deficits.

Exogenous cannabinoid exposure also appears to differentially affect distinct NAc affer-

ents as shown in a study from our laboratory in which optogenetics was used to selectively activate several discrete glutamatergic afferents to the ventral striatal shell region (NAcs). We found that repeated in vivo exposure to Δ^9-THC produced an imbalance in the strength of these connections such that the influence of both ventral hippocampal and BLA inputs on NAc medium spiny neurons was increased, whereas those from medial PFC were greatly diminished (Hwang and Lupica 2019). Moreover, LTD, produced by a brief application of a type-I mGluR agonist, was eliminated at PFC and ventral hippocampal NAc inputs by long-term Δ^9-THC, whereas LTD at BLA inputs was unaltered (Hwang and Lupica 2019). These findings suggest that Δ^9-THC exposure can cause an imbalance in the excitatory synaptic control of ventral striatal output and, given the established role for mGluR-Is in facilitating eCB release and LTD in the NAc and dorsal striatum (Gerdeman et al. 2002; Robbe et al. 2002; Kreitzer and Malenka 2005), imply that the influence of eCB-dependent plasticity on these pathways is lost. Thus, not only is the excitatory influence of the ventral hippocampus on the NAcs greatly enhanced following long-term Δ^9-THC exposure, but it is also refractory to potential inhibitory control by LTD.

The changes in striatal excitatory transmission and capacity for LTD have also been shown to be accompanied by structural changes in medium spiny neuron anatomy. Thus, repeated experimenter-delivered Δ^9-THC causes an increase in both dendritic length and the number of dendritic spines (spine density) (Kolb et al. 2006, 2018) as well as an increase in spine density in the dorsal striatum (Fernández-Cabrera et al. 2018). However, another study showed that there was a decrease in the density of dendritic spines in NAc medium spiny neurons after extinction from Δ^9-THC + CBD self-administration, and this was associated with a loss of LTD (Spencer et al. 2018). The most obvious differences among these studies that may account for the discrepancies in anatomical data are the use of contingent self-administration of Δ^9-THC versus noncontingent exposure as well as the use of Δ^9-THC + CBD versus Δ^9-THC alone. Reconciliation of these disparate findings represents an important direction for future studies. However, despite these differences, these studies show that long-term exposure to Δ^9-THC can cause profound changes in synaptic function in dorsal and ventral striatum that parallel changes in behavior, which relies on the integrity of the eCB system. Interestingly, other drugs that have high abuse liability, including opiates, psychostimulants, and ethanol, also impair striatal LTD (Moussawi et al. 2009; Kasanetz et al. 2010; Pierce and Wolf 2013; Shen and Kalivas 2013; Spiga et al. 2014) and this has been linked to habitual drug seeking in a rat cocaine self-administration study (Kasanetz et al. 2010). In several of these studies, the physiological and behavioral alterations have also been associated with structural changes in medium spiny neuron morphology, suggesting that both pre- and postsynaptic components of synaptic transmission can be affected by exposure to abused drugs, including cannabinoids.

HIPPOCAMPUS

Schaffer Collateral-CA1 Synapses

As described above, the eCB system can regulate hippocampal function and CB1Rs are located on both GABAergic and glutamatergic axon terminals in this brain structure (Katona et al. 1999, 2006; Hoffman and Lupica 2000; Dinh et al. 2002; Mátyás et al. 2008). The participation of eCBs in facilitating LTP, either through suppression of GABAergic transmission (Carlson et al. 2002; Chevaleyre and Castillo 2004) or through the promotion of astroglial signaling (Gomez-Gonzalo et al. 2015; Robin et al. 2018), suggests that Δ^9-THC or synthetic cannabinoids can disrupt synaptic plasticity through a variety of mechanisms. Experiments in our laboratory showed that repeated in vivo exposure to Δ^9-THC blocked LTP at Schaffer collateral-CA1 synapses (Hoffman et al. 2007). The LTP disruption required at least 3 days of Δ^9-THC exposure, was only partially reversed 14 days after Δ^9-THC withdrawal, and required CB1Rs, as the LTP impairment by Δ^9-THC was prevented by a CB1R antagonist (Hoffman et al.

2007). This partial recovery of LTP at 2 weeks of withdrawal from Δ^9-THC correlates with the incomplete recovery of CB1R binding in the hippocampus (Hirvonen et al. 2012), as well as the time course of hippocampal-dependent memory impairments following Δ^9-THC withdrawal in humans (Bolla et al. 2002). The observation that long-term Δ^9-THC prevents LTP is also generally consistent with the ability of a variety of synthetic cannabinoid agonists to disrupt hippocampal synaptic plasticity (Hill et al. 2004; Fan et al. 2010; Basavarajappa and Subbanna 2014; Hoffman et al. 2017).

Although the Δ^9-THC-induced impairment in hippocampal LTP could result from its actions at CB1Rs located on either glutamatergic or GABAergic terminals, the genetic deletion of these receptors from only GABAergic neurons reduces LTP, whereas their deletion on glutamatergic neurons enhances LTP (Monory et al. 2015). Using a similar selective CB1R deletion strategy, it was also shown that the memory impairment caused by acute Δ^9-THC was absent when CB1Rs were deleted on GABAergic terminals, where these receptors are more abundantly expressed (Puighermanal et al. 2009, 2013). Consistent with these results, long-term Δ^9-THC exposure appears to preferentially reduce CB1R sensitivity to agonists on GABAergic but not glutamatergic axon terminals in the hippocampus (Hoffman et al. 2007), and CB1R protein expression on GABA neuron axon terminals is strongly reduced following this treatment (Dudok et al. 2015). Therefore, and somewhat paradoxically, these studies seem to imply that long-term Δ^9-THC exposure has a larger impact on CB1Rs on GABAergic axon terminals than on glutamatergic terminals, and that these Δ^9-THC-induced alterations contribute to deficits in LTP generated at glutamate synapses (Carlson et al. 2002; Chevaleyre and Castillo 2004). We speculate that this may reflect changes in an ongoing modulatory role of eCBs on GABAergic synaptic transmission that interacts with synaptic glutamatergic processes, such as the facilitation of glutamatergic LTP by DSI (Carlson et al. 2002). In support of this idea, treatment of hippocampal autaptic cultures with Δ^9-THC for 19 hours eliminates DSI (Straiker and Mackie 2005), suggesting that this ongoing short-term suppression of GABAergic inhibition and its ability to facilitate LTP might also be lost following long-term Δ^9-THC exposure. As described above, I-LTD of GABAergic synaptic transmission in the hippocampus can suppress inhibition within restricted regions of CA1 pyramidal neuron dendrites to facilitate LTP induction at glutamatergic synapses within this sphere of I-LTD influence (Chevaleyre and Castillo 2004). As this form of 2-AG-dependent plasticity is strongly reduced following a single in vivo exposure to Δ^9-THC (Mato et al. 2004), it is likely that long-term Δ^9-THC would similarly impair this process. Therefore, these studies suggest ways in which reductions in eCB-dependent regulation of GABAergic synapses caused by Δ^9-THC exposure can lead to impaired plasticity at glutamatergic synapses in the hippocampus.

In addition to its ability to block LTP, Δ^9-THC can also induce LTD at CA3 to CA1 pyramidal cell Schaffer collateral synapses in vivo (Han et al. 2012). Interestingly, this effect of Δ^9-THC appears to result from activation of CB1Rs located on astrocytes (Navarrete and Araque 2010), the subsequent activation of postsynaptic NMDA receptors, and the internalization of AMPA receptors (AMPARs) (Han et al. 2012). A similar astroglial-dependent LTD was observed following treatment with JZL-184, an inhibitor of MAGL, the enzyme necessary for 2-AG degradation, thereby implicating this eCB (Wang et al. 2017). More recently, activation of astroglial CB1Rs was shown to enhance D-serine release, thereby facilitating NMDA function, enhancing hippocampal LTP, and improving novel object recognition memory (Robin et al. 2018). Together, these data suggest that CB1R activation by exogenous cannabinoid ligands can bidirectionally modulate CA3 to CA1 hippocampal synaptic plasticity via CB1Rs located on neurons and glial cells. The effects of repeated cannabinoid exposure on astroglial signaling remains an intriguing area for future investigations.

Similar to the striatum, the changes in hippocampal synaptic plasticity caused by long-term exogenous cannabinoid exposure parallel

alterations in dendritic structure and morphology. Reductions in spine density are reported in both dentate granule cells (Rubino et al. 2009) and CA1 pyramidal neurons (Chen et al. 2013) following repeated Δ^9-THC treatment. More recently, it has also been suggested that chronic activation of CB2 receptors may play a role in regulating hippocampal synaptic morphology and synaptic plasticity (Kim and Li 2015; Li and Kim 2016), and chronic exposure to CB2 agonists increases spine density in cultured hippocampal neurons (Kim and Li 2015). However, it should be noted that nearly all reported effects of Δ^9-THC and other synthetic cannabinoids on a variety of hippocampal-dependent behaviors and synaptic plasticity are blocked by selective CB1 antagonists, and are absent in mutant mice lacking CB1Rs (Varvel et al. 2001; Varvel and Lichtman 2002; Hoffman et al. 2007; Heifets et al. 2008; Wise et al. 2009; Hebert-Chatelain et al. 2016). Thus, any contribution of non-CB1 receptors to the effects of exogenous agonists must be carefully evaluated with this caveat in mind.

Other Hippocampal Synapses

The LPP connects entorhinal cortical neurons to those in the dentate gyrus of the hippocampus, as well as to other hippocampal subfields (Witter 1993, 2007). There is evidence that eCB activation of CB1Rs is involved in promoting LTP in this pathway, which is implicated in spatial and episodic memory as well as learning (Wilson et al. 2013; Wang et al. 2016). The role of eCBs in facilitating LTP in this pathway appears to reflect a direct effect on reorganization of the actin cytoskeleton in presynaptic LPP terminals. Thus, latrunculin-A (lat-A), an inhibitor of actin filament polymerization, impaired eCB-dependent LTP (Wang et al. 2016). In addition, an odor-based learning task that is dependent on LPP function was blocked by the CB1R antagonist AM251 and enhanced by an inhibitor of 2-AG degradation (Wang et al. 2016). In a subsequent study, these investigators found learning-induced increases in the presynaptic LPP expression of pROCK, a protein involved in actin stabilization (Wang et al. 2018). More importantly, these observed increases in protein expression at LPP terminals were prevented by prior treatment of the animals with AM251. Thus, it appears that eCBs are necessary for promoting plasticity and learning in this circuit. Because reductions in spine density are observed in the dentate gyrus following chronic Δ^9-THC (Rubino et al. 2009), it is possible that these changes reflect disruptions to ongoing eCB activity within this pathway. Together, these intriguing findings show that the LPP may be a critical site for cannabinoids involvement in hippocampal-dependent learning and memory, and these hippocampal afferents represent an important subject for additional research on memory impairments caused by exogenous cannabinoids.

VENTRAL TEGMENTAL AREA

The VTA is a central component of the brain's reward system that contains DA neurons that project to forebrain areas. These cells also receive inputs from a large number of brain regions and integrate information from both glutamatergic and GABAergic afferents (Björklund and Dunnett 2007; Geisler et al. 2007). It is now well-established that VTA DA neurons release eCBs, and that these lipid mediators strongly regulate synaptic inputs to DA neurons (Melis et al. 2004b; Riegel and Lupica 2004; Wang and Lupica 2014). Thus, 2-AG released from DA neurons inhibits both GABAergic and glutamatergic inputs to these cells (Haj-Dahmane and Shen 2010; Melis et al. 2014; Wang et al. 2015) and can also limit LTP of glutamatergic afferents (Kortleven et al. 2011). The importance of eCB signaling within the VTA for regulating both rewarding and aversive behaviors has also been established (Oleson et al. 2012; Wenzel et al. 2018). Exposure to exogenous cannabinoids also alters eCB control of synaptic function in the VTA. For example, our laboratory has shown that a single exposure to Δ^9-THC can trigger LTD of glutamatergic pedunculopontine nucleus (PPN) inputs to VTA DA neurons, and that this is mediated by insertion of GluA2 subunit-containing AMPARs at these synapses (Good and Lupica 2010). Moreover, this effect

of Δ^9-THC is distinct from the actions of cocaine, which more globally affected plasticity at both PPN inputs, as well as at glutamatergic inputs to VTA DA neurons arising from other brain areas such as the PFC (Good and Lupica 2009, 2010; Xiao et al. 2018). In contrast, a subsequent study showed that long-term exposure to Δ^9-THC or the synthetic cannabinoid agonist HU-210 resulted in a loss of cell surface expression of GluA2 subunit-containing AMPARs and the potentiation of glutamate synapses arising from unidentified afferents (Liu et al. 2010). These investigators also showed that the potentiation of these synapses caused by long-term cannabinoid exposure could be subsequently weakened by low-frequency activation of these glutamatergic afferents, thus resulting in a form of LTD or "depotentiation" at these synapses onto VTA DA neurons (Liu et al. 2010). This form of LTD was blocked by a TAT-GluA2 peptide that prevents receptor endocytosis, suggesting that it was mediated by AMPAR internalization (Brebner et al. 2005; Liu et al. 2010). Thus, although acute Δ^9-THC exposure appears to selectively alter synaptic plasticity at a subcortical input to VTA DA neurons (Good and Lupica 2010), long-term exposure to the drug may result in changes in synaptic plasticity at a wider range of VTA DA neuron afferents (Liu et al. 2010).

In addition to literature describing synaptic plasticity in VTA DA neurons and its alteration by exposure to exogenous cannabinoids, a more recent study has shown that 2-AG-dependent LTD occurs at glutamate inputs to VTA GABAergic neurons, and that it can be occluded by acute Δ^9-THC exposure in vitro (Friend et al. 2017). This form of LTD in VTA GABA neurons was not affected by a single in vivo exposure to Δ^9-THC, but was absent after 7–10 days exposure to the drug (Friend et al. 2017). Together, the above studies suggest that a single exposure to Δ^9-THC can alter synaptic plasticity at PPN glutamate synapses onto VTA DA neurons, and that long-term exposure to either Δ^9-THC or synthetic cannabinoid agonists can disrupt synaptic plasticity at undefined glutamatergic inputs to both GABAergic and DAergic neurons within the VTA.

Emerging evidence also shows that eCB-dependent synaptic plasticity in the VTA is modified by abused drugs and that this may be involved in some aspects of drug use and psychiatric disorders (Wenzel and Cheer 2018). Studies from our laboratory have shown that cocaine stimulates synthesis and release of 2-AG from DA neurons, that this can increase DA neuron excitability and DA release in the NAc, and that this is mediated by CB1Rs located on DA neuron GABA afferents (Wang et al. 2015; Nakamura et al. 2019). The cocaine-induced enhancement of 2-AG function has also been shown to cause CB1R-dependent I-LTD of GABAergic synapses on these DA neurons (Pan et al. 2008). Therefore, these data imply that the ability of cocaine to increase forebrain levels of DA may be mediated, in part, by its stimulation of eCB function in the VTA. This, together with our understanding of the importance of midbrain DA systems for addiction and psychiatric disorders, indicates that the eCB system is likely to have an important role in these phenomena, and that additional investigations of the effects of long-term exposure to cannabinoids on the effects of cocaine should be a priority for future studies. More generally, however, given the critical role for VTA neurons in processing salient environmental stimuli and their involvement in reward and appetitive-based learning (Flagel et al. 2011; Brown et al. 2012; Wenzel et al. 2015), it is likely that the changes in synaptic plasticity produced by cannabinoid exposure will strongly influence these critical behavioral roles for VTA function.

BASOLATERAL AMYGDALA

The BLA is involved in processing fear and anxiety (Correia et al. 2016; Davis et al. 2017; Ressler and Maren 2019), and there is strong evidence that LTP within the BLA underlies the expression of fear conditioning (Nabavi et al. 2014; Kim and Cho 2017). Within the BLA, CB1Rs are expressed on GABAergic (Katona et al. 2001) and glutamatergic afferents (Azad et al. 2003) that converge to control BLA pyramidal cell output to cortical and subcortical brain areas (Pistis et al. 2004; Jones et al. 2010).

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Low-frequency stimulation of the BLA results in eCB-dependent LTD of inhibitory inputs to BLA principal neurons (Marsicano et al. 2002; Azad et al. 2004), which strengthens subsequent excitatory inputs to promote LTP (Azad et al. 2004). Strengthening BLA outputs to the medial PFC is likely to play a critical role in processing the emotional response to aversive stimuli (Laviolette et al. 2005; Tan et al. 2010). BLA eCB release is enhanced when a conditioned auditory stimulus is presented during extinction of fear conditioning, and CB1 antagonists impair this extinction (Marsicano et al. 2002). Thus, it has been proposed that eCBs within the BLA regulate extinction of fear conditioning, an observation that has clear relevance to posttraumatic stress disorders in humans. A further link between stress and eCB signaling within the BLA has been described by Di and colleagues (Di et al. 2016). These investigators showed that glucocorticoids promote endocannabinoid-mediated inhibition of GABAergic inputs to BLA neurons and that intra-BLA infusions of a CB1 antagonist or an inhibitor of 2-AG synthesis prevents the anxiety-like behaviors observed following restraint stress (Di et al. 2016). Such findings are consistent with earlier studies showing a role for eCBs within the BLA mediating both memory consolidation and its enhancement by glucocorticoids and link the brain's stress response to BLA eCB action (Campolongo et al. 2009; Morena et al. 2014). More recently, restraint stress was shown to decrease anandamide levels in the BLA, leading to enhanced glutamatergic transmission onto BLA principal cells (Yasmin et al. 2020). These effects were prevented in animals receiving a fatty acid amide hydrolase (FAAH) inhibitor before the restraint stress. Moreover, the same acute stress caused a delayed (10 days) increase in BLA pyramidal cell spine density that was also prevented by the FAAH inhibitor (Yasmin et al. 2020). Interestingly, 2-AG levels in the BLA were enhanced and GABAergic transmission reduced by the same stress procedure. Thus, stress may produce divergent actions on GABAergic and glutamatergic signaling through alterations in different eCBs.

Despite the extensive literature implicating the eCB system in regulating fear and anxiety, and the fact that many of the symptoms of cannabinoid use disorder involve changes in these behaviors (Crippa et al. 2009), the effects of chronic cannabinoid exposure on BLA synaptic plasticity remains relatively unexplored. Studies that have examined this have shown that chronic treatment of adolescent animals with either Δ^9-THC or synthetic cannabinoids can impair fear conditioning in adulthood (Gleason et al. 2012; Tomas-Roig et al. 2017). Additionally, another more recent study found that fear memory processing was impaired only when Δ^9-THC exposure was paired with a stressful experience (Saravia et al. 2019). It is intriguing that these behavioral effects were accompanied by increases in the density of immature dendritic spines in the BLA (Saravia et al. 2019) because such structural changes often accompany alterations in synaptic plasticity. Indeed, recent evidence suggests that eCBs participate directly in the delayed structural changes observed in BLA neurons following stress (Yasmin et al. 2020). Finally, work from our laboratory shows that the strength of glutamatergic BLA afferents to the NAc is more than doubled following repeated Δ^9-THC (Hwang and Lupica 2019). As this pathway is also implicated in conditioned drug-seeking behavior and the encoding of emotional valence (Everitt and Robbins 2005), it is possible that long-term cannabinoid exposure may increase the emotional salience of drug-paired environmental cues. Thus, functional studies on modifications in eCB signaling within the BLA and their contributions to altered synaptic plasticity following exposure to cannabinoid drugs remains a critical direction for future studies.

SUMMARY AND CONCLUSIONS

Cellular and behavioral research over the past 50 years indicates that diverse and ubiquitous mechanisms are present to alter the strength of synaptic connections across a wide range of temporal domains and brain regions. Because the mechanisms supporting this synaptic plasticity generally require repeated pathway activation, there are ostensible parallels between this cellular phenomenon and behavioral manifestations of learning and memory. Moreover, there is now

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direct evidence that synaptic plasticity can underlie changes in brain circuit function resulting from experience. This evidence is particularly strong in circuits within the striatum, the amygdala, and the hippocampus, in which plasticity regulates learning of habits, fear, and context, respectively. Because the eCB system is ubiquitously expressed in the CNS (Herkenham et al. 1990) and because it is involved in widespread control of synaptic function, it can either directly mediate or modulate synaptic plasticity in many brain regions. This regulation of synaptic function requires the synthesis and release of eCBs that then activate cannabinoid receptors, with CB1Rs having the most supporting evidence to date. Because of this, CB1Rs are critical for eCB system function and changes in their activation, coupling to downstream effectors, or availability can bias the contributions that the eCB system makes to the regulation of neural activity, plasticity, and learned behavior. As we describe here, extensive evidence shows that exposure to Δ^9-THC or to synthetic cannabinoids can impair synaptic plasticity in many brain areas, either directly or indirectly. Experimental approaches investigating the cause of these impairments generally point to CB1R desensitization or internalization as a primary cause (Hoffman et al. 2003, 2007; Sim-Selley 2003; Mato et al. 2004; Schlosburg et al. 2010; Nazzaro et al. 2012; Dudok et al. 2015; Goodman and Packard 2015). Thus, the evidence strongly suggests that long-term, or in some cases, single exposure to Δ^9-THC or synthetic cannabinoids can disrupt eCB-supported synaptic plasticity and its influence on behavior via alterations in CB1R function or expression. There is also evidence that the loss of ongoing eCB function can lead to more widespread "rewiring" of brain circuits, such as that seen in the NAc, hippocampus, and VTA after Δ^9-THC exposure (Hoffman et al. 2007; Good and Lupica 2010; Hwang and Lupica 2019). Collectively, these changes can produce deficits in learning and memory or, in some cases, deficits in "unlearning" or extinction of learned associations such as those observed in fear conditioning. Although much has been learned as to the influence of the eCB system on synaptic plasticity and behavior, additional research is needed to define the temporal limits of the effects of exogenous cannabinoids on synaptic plasticity in adult organisms, as well as on the effects of these drugs on brain development that may more permanently alter the functions of brain circuits dependent on intact eCB system function.

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