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Functional Relevance of Endocannabinoid-Dependent Synaptic Plasticity in the Central Nervous System

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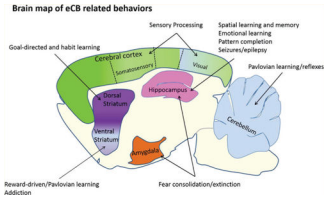
Abstract

The endocannabinoid (eCB) signaling system plays a key role in short-term and long-term synaptic plasticity in brain regions involved in various neural functions ranging from action selection to appetite control. This review will explore the role of eCBs in shaping neural circuit function to regulate behaviors. In particular, we will discuss the behavioral consequences of eCB mediated long-term synaptic plasticity in different brain regions. This review brings together evidence from in vitro and ex vivo studies and points out the need for more in vivo studies.

Graphical Abstract



Keywords

Arachidonoylethanolamine; 2-arachidonoylglycerol; cannabinoid receptors; depolarization-induced suppression of inhibition; depolarization-induced suppression of excitation; long-term depression; long-term potentiation

INTRODUCTION

Endogenous cannabinoids, also referred to as endocannabinoids (eCBs), are small lipid-derived signaling molecules found throughout the body, including the central and peripheral nervous systems.[1–4] In the brain, these signaling molecules differ from canonical vesicle-packaged neurotransmitters, such as glutamate and monoamine neuromodulators, such as dopamine. eCBs are directly synthesized from membrane phospholipids in response to

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neuronal activity.[5–7] These fatty acid derivatives cannot be packaged into vesicles, and there is no obvious mechanism for intracellular storage. Thus, their production is mainly thought to be “on-demand” and “use-dependent”.[5–7] In addition to the traditional “on-demand” synthesis of eCBs, there is evidence for presynthesized pools of eCBs that may be released in a stimulus specific manner.[8,9] It is not known how these eCB “pools” are maintained within a cell or released. In the nervous system, eCBs mainly modulate synaptic transmission via “retrograde signaling” in which postsynaptic release of the molecule leads to actions on presynaptic receptors.[10–12] There is evidence that eCBs can participate in direct receptor-mediated (nonretrograde) signaling, sometimes even in a receptor-independent manner.[13–16] Due to their transient and tightly regulated production, eCBs have the potential to quickly adjust the gain of incoming signals to modify circuit function and behavior.

There are two types of eCBs, arachidonoylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG), that differ in their biosynthesis/degradation pathways and affinity for binding to the cannabinoid type 1 and 2 receptors (CB1 and CB2).[2,17–21] 2-AG is the most abundant and efficacious eCB ligand, while AEA is a lower efficacy ligand. Differences in desensitization between the two eCBs lead to differential time course of responses to agonist application, but desensitization appears to be too slow to contribute to the time course of effects on synaptic transmission.[4,22,23] The duration of modulation by eCBs at synapses is most likely determined by enzymatic degradation and possibly by a poorly characterized reuptake mechanism.[24–29] AEA can also directly act on multiple ionic channels at low concentrations, presumably in its tonic signaling state.[13,30–33]

Both AEA and 2AG appear to be synthesized on the postsynaptic side of the synapse. Indeed, the enzyme that catalyzes 2-AG synthesis, diacylglycerol lipase (DAGL), is found in the postsynaptic structure of many neurons.[34–36] The main pathway for AEA synthesis in brain is not fully certain, but physiological studies support a postsynaptic role for synthesis and release.[37,38] The eCB degradation pathways are segregated across the synapse, with the AEA-catabolic enzyme fatty acid amide hydrolase (FAAH) localized mainly in postsynaptic structures and the 2-AG-degrading enzyme monoacylglycerol lipase (MGL) located mainly on the presynaptic side.[39,40] The differences in efficacy and the spatial segregation of the degradation pathways for the two eCBs support the hypothesis that AEA and 2-AG have differential functional roles in eCB mediated signaling in different brain regions or at different synapses within these brain regions (Figure 1).

There are two modes of eCB signaling, tonic vs phasic, by which eCBs can regulate neurotransmitter release to affect network activity. In the hippocampus, AEA is thought to be the constitutive tonic eCB messenger, while 2-AG is considered the neuromodulatory phasic eCB messenger. However, it is yet to be determined if this pattern is observed in other brain regions. Indeed, it is likely that eCB signaling may not strictly adhere to one eCB type being tonic and the other phasic, but both AEA and 2-AG may switch between the different modes of signaling. Both eCBs can be produced in an activity dependent manner and may be differentially produced in different brain regions under different physiological conditions or pathophysiological states.[23,38,41–43] Further evidence to support this hypothesis comes from

experiments in which neuronal stimulation can selectively increase tissue levels of 2-AG but not AEA, even though both are present.[41,44,45]

As mentioned above, both eCBs bind to and activate CB1 and CB2 receptors. These are G-protein-coupled receptors (GPCRs) that upon activation signal through the $G\alpha_{i/o}$ family of heterotrimeric G-proteins.[1,46] CB1 receptors are abundantly expressed in the CNS in brain regions associated with learning and memory, such as hippocampus, striatum, amygdala, and prefrontal cortex[47,48] In these areas, CB1 receptors are highly expressed on glutamatergic and GABAergic (γ-aminobutyric acid) presynaptic terminals, made by both projection neurons and interneurons, making them ideally placed to fine-tune the regulation of synaptic efficacy and neuronal activity in response to incoming signals.[47,49,50]

The GABAergic interneurons that express CB1 in basolateral amygdala (BLA), hippocampus and neocortex are predominantly basket cells, but Schaffer collateral-associated interneurons in the CA1 hippocampal subfield also express CB1.[49,51,52] One common feature of these CB1-expressing interneurons in hippocampus and other cortical regions is that they express and presumably release the cholecystokinin (CCK) neuropeptide (Figure 1). It is interesting to note that excitation-secretion coupling in the presynaptic terminals of CCK-positive interneurons in BLA and hippocampus requires the N-type voltage-gated calcium channel ($Ca_V2.2$), and inhibition of this channel appears to be the predominant mechanism through which CB1 inhibits GABA release at these synapses.[53,54] The specificity of inhibition of release from this interneuron subtype appears to influence certain frequencies of activity within the hippocampus.[55] The observation that this inhibition is relieved when CCK-positive neurons fire at higher frequencies indicates that CB1 may have a high-pass filtering function within this microcircuit.[56] The functional implications of the specificity for synapses using N-type channels is not yet clear, but the channel subtype may contribute to the frequency-dependent effects of CB1 inhibition.

CB2 receptors are expressed mostly in the periphery,[3,47,57,58] with very little expression in the CNS.[59–61] The eCB system has been shown to be involved in both short and long-term decreases in synaptic transmission at glutamatergic and GABAergic synapses in many different brain regions.[12,62] This review will discuss the functional implications of eCB-mediated synaptic modifications in behaviors involving different brain regions (Figure 1), by giving an overview of in vitro and limited in vivo studies in an attempt to link physiology and behavior.

FUNCTIONAL ROLE OF ENDOCANNABINOID MEDIATED DSE AND DSI

Activation of presynaptic CB1 receptors by the release of postsynaptic eCBs often begins with increases in postsynaptic intracellular calcium and/or activation of $G\alpha q$-coupled GPCRs. The eCB release can suppress synaptic transmission transiently for a minute or less. One such form of short-term plasticity is called depolarization-induced suppression of inhibition (DSI) or excitation (DSE) and can be induced by a brief (seconds) postsynaptic depolarization.[5,63–70] This depolarization leads to increases in postsynaptic intracellular calcium via the activation of voltage-gated calcium channels to trigger eCB mobilization.[5,24,43,65,67,68] eCB mobilization can also be triggered by activation of $G\alpha q$-coupled GPCRs

such as the muscarinic acetylcholine receptors and group 1 metabotropic glutamate receptors to induce short-term depression (STD) and can further enhance the magnitude and expression of DSI and DSE.[6,7,71] It is important to state that STD and DSI/DSE cooperatively interact and do not directly oppose each other. It is not clear which type of eCB is involved in short-term plasticity and whether the type of eCB varies with brain region. However, 2-AG appears to be the most likely candidate for involvement in DSI/DSE based on experiments showing that increased 2-AG signaling enhances these forms of plasticity.[72–74] Cell-type specific deletion of 2-AG signaling reduces the magnitude of DSI and DSE in striatum, supporting a role for this eCB in this brain region.[75] The transient suppression of synaptic transmission caused by STD or DSI/DSE may help to modulate neuronal activity by altering neuronal excitability and/or resetting neuronal responsiveness to incoming afferent information to influence behavior. To date, eCB mediated DSI/DSE has been observed in many brain regions, but it is best characterized in the hippocampus and cerebellum.[76–79] It is likely that DSI/DSE has distinct physiological and behavioral functions depending on the synapses and brain region in which it is expressed.

Despite the implication of DSI/DSE and STD in neuronal modulation that affects circuit function, little is known about the occurrence of these forms of short-term plasticity in vivo. In fact, there are questions concerning the physiological relevance, if any, of these forms of transient synaptic plasticity.[80] A computational model of presynaptic input firing predicts that the temporal summation of convergent inputs can produce a calcium dependent mobilization of eCB to result in DSI in vivo.[81] Melis and colleagues, demonstrated that a brief afferent stimulus train, mimicking firing rates in vivo, can induce an eCB-mediated STD in vitro and more importantly in vivo in the ventral tegmental area (VTA), a brain region involved in reward learning.[82] This dampening of neuronal activity could signal changes in reward information, thereby locally modulating neuronal activity to shape circuit function. Additionally, eCB mediated STD is augmented after a behavioral conditioning task, indicating that this can itself be modulated by changes in vivo as a result of environmental experience.[83,84] Although there is no definitive evidence that DSI/DSE suppresses synaptic transmission in vivo, the aforementioned results demonstrate that it is possible for STD, lasting a few seconds, to sculpt neuronal firing rates to affect neural function. It is likely that these transient changes can encode alterations in reward value in real time during a behavioral task. Additionally, the fast dynamic switch between activation and inhibition at different synapses or the interruption of ongoing activity may help in action selection during a behavioral task. It is well-known that these forms of eCB mediated synaptic plasticity constitute a widespread phenomenon in the CNS.[12,68] However, little research has been done to examine the contribution of eCB mediated shortterm plasticity to behavior. More research on identifying conditions and molecular mechanisms that promote STD in vivo is needed to fully understand the physiological and functional significance of eCB mediated transient synaptic plasticity.

FUNCTIONAL SIGNIFICANCE OF ENDOCANNABINOID MEDIATED LTD

In addition to eCBs mediating short-term synaptic plasticity, the eCB system can also produce longer-term changes in synaptic efficacy lasting hours to weeks that are referred to as long-term potentiation (LTP) and long-term depression (LTD). eCB-LTD is notably the

best characterized and widespread form of eCB mediated long-term synaptic plasticity and can occur at both glutamatergic and GABAergic synapses throughout the brain.[85–95] Endocannabinoid-dependent LTD can be induced by a transient increase in neuronal activity that leads to increases in calcium that result in the synthesis/release of eCBs from the postsynaptic cell to bind to presynaptic CB1 receptors.[85,96,97] Depending on the brain region, eCB-LTD can be altered by neuromodulators, such as dopamine, which can influence cAMP signaling to facilitate LTD.[42,90,98–101]

eCB LTD can also occur in response to activation of metabotropic receptors, such as metabotropic glutamate type 5 (mGluR5) and serotonin type 2 (5-HT_2) GPCRs that stimulate diacylglycerol formation leading to increased 2-AG production, and produce increased calcium release from intracellular stores to participate in mobilizing eCBs.[6,71,90,102] LTD initiated by eCB activation of CB1 receptors persists long after CB1 receptor activation has ended.[86,88,103–105] It is still unclear whether the same type of eCB (2-AG vs AEA) is involved in mediating the long-term changes in synaptic plasticity resulting from transient increases of afferent neuronal activity and those induced by postsynaptic activation of metabotropic receptors. AEA has been implicated as the eCB signaling molecule mediating eCB-LTD in the dorsal striatum (DS).[38,106] Ade and Lovinger showed that during development, there is a switch from LTP to eCB-LTD.[38] More interestingly, this switch in synaptic plasticity is accompanied by a developmental increase in AEA production levels.[38] Also, it is not known how CB1 receptor activation can differentially mediate both short-term and long-term changes in synaptic plasticity. Chevaleyre and colleagues demonstrated that cAMP/PKA signaling and Rim 1α function downstream of CB1 receptor activation are needed for eCB-LTD and not STD.[103] However, more research identifying the intracellular signaling components downstream of CB1 receptor activation is needed to fully understand the mechanistic difference between CB1 receptor-mediated STD and LTD. Long-term changes in synaptic plasticity at corticostriatal synapses are postulated to contribute to mechanisms of action control, such as skill and instrumental learning (Figure 1). In fact, aberrant corticostriatal synaptic plasticity has been implicated in numerous movement disorders, including Parkinson's and Huntington's diseases.[98,107–109]

GOAL-DIRECTED/HABITUAL BEHAVIORS

Prefrontal Cortex-Striatal eCB-LTD.

The prefrontal cortex (PFC) refers to cortical subregions that sit at the anterior of the frontal cortex. These cortices send glutamatergic afferents to a variety of subcortical regions including BLA, other allocortical and neocortical areas, nucleus accumbens (NAc) and dorsomedial striatum (DMS).[110,111] The prefrontal cortices are generally thought to have roles in such advanced cognitive functions as cognitive and behavioral flexibility, decision making, executive function, and perhaps even consciousness.[112–115] However, more specific functions of these cortices and their projections include roles in reversal learning and extinction of fear conditioning.[116–118] There are ongoing debates as to whether rodents possess true prefrontal cortical areas, but it is clear that many regions of mouse and rat frontal cortex have connectivity similar to that of primate PFC, and there is some evidence that the functions of these areas within cortical-subcortical circuits are similar across

species. For the purposes of this review, we will focus on eCB actions on neurons that are part of 3 PFC regions where these neuromodulatory actions are well characterized, the infralimbic and prelimbic medial prefrontal areas (ILC, PLC respectively, often referred to as mPFC when not explicitly differentiated) and the orbitofrontal cortex (OFC). The CB1 receptor has been localized to neurons in the PFC, with especially prominent mRNA expression in ILC, PLC, and OFC (Allen Brain Atlas; http://www.brain-map.org/).[49,119,120] Receptors have been localized to presynaptic terminals of both GABAergic and glutamatergic neurons within these PFC subregions,[121,122] and the receptor is also present on terminals of glutamatergic neurons that project from PFC to subcortical regions (Figure 1).[123–125] Thus, the eCB signaling system is well positioned to influence processing within PFC as well as PFC communication and control of other brain regions.

Some of the initial evidence for eCB and CB1 receptormediated synaptic plasticity came from electrophysiological experiments in medial PFC slices. The work of Crepel and colleagues showed that a CB1 receptor agonist inhibited glutamatergic transmission at synapses onto layer V PLC projection neurons via an apparent presynaptic mechanism.[126] A CB1 receptor inverse agonist increased glutamatergic transmission, revealing some of the first evidence for tonic receptor activity that depresses transmitter release. These investigators also found that activation of CB1 receptors increased the proportion of neurons showing HFS-induced LTD, while receptor antagonism favored LTP. In hindsight, these data clearly presage the discovery of eCB-LTD a few years later, although at the time these investigators did not distinguish between a modulatory role for eCBs and CB1 and a central role in the LTD induction mechanism. Subsequent studies have examined eCB-LTD at other synapses in the PFC, as well as the roles of eCBs, CB1 and LTD in a variety of PFC functions. At inhibitory synapses onto layer V PFC pyramidal neurons, eCBs contribute to LTD of inhibitory synapses (iLTD) that requires activation of a group I mGluR and is modulated by dopamine via dopamine D2 receptors (D2Rs).[127] This dopaminergic modulation is intriguing as the CB1 and D2Rs are situated in close proximity to one another on the GABAergic terminals that show eCB-mediated plasticity. The GABAergic neuronal subtypes that express these receptors are not yet clear, but it is probable that these neurons include those that make perisomatic synapses and are similar to CB1-receptor expressing basket cells in other cortical regions.

Endocannabinoids and CB1 receptors expressed by OFC projection neurons appear to have important roles in stimulus-response (S-R) or “habit learning” (Figure 1).[125] Experiments in the Costa laboratory first found a role for eCBs/CB1 receptors in this type of learning.[128] Further investigation of this role revealed that knocking out CB1 receptors in mouse OFC neurons prevented S-R learning, and this effect was also observed when the knockout was restricted to glutamatergic projection neurons.[125] Using a retrograde viral-based strategy in the latter experiments, these investigators also showed that CB1 receptors inhibit glutamatergic synapses from OFC projection neurons onto medium spiny neurons (MSNs) in the DMS, and that this modulation was lost in the projection neuron-specific CB1 receptor KO condition. These findings provide some of the most direct evidence of an effect of CB1 on a specific corticostriatal synapse. Mimicking the effect of presynaptic CB1 with Gi/o-DREADD expression/activation at OFC-DMS synapses fostered S-R learning, including experiments in which the DREADD agonist was applied locally within DMS. It is

postulated that presynaptic suppression of OFC inputs fosters S-R learning, most likely by inhibition of OFC-derived information about outcome value status that normally supports competing action-outcome or “goal-directed” instrumental performance.

It must be noted that CB1 receptors on OFC-DMS presynaptic terminals may not be the only such receptors involved in S-R learning. Examination of the mechanisms underlying promotion of S-R learning after chronic Δ9-tetrahydrocannabinol (THC) treatment indicated that receptors and eCB-LTD in the dorsolateral striatum also have important roles in this learning process.[129] This study puts forth the hypothesis that bidirectional synaptic plasticity, allowing for synaptic flexibility, is important for selecting the appropriate goal-directed or habitual behaviors. Thus, there may be several cellular and brain regional loci at which the eCB/CB1 system contributes to instrumental learning and environmental and drug effects on this learning.

There is a growing literature describing effects of drugs of abuse and other environmental manipulations of eCB synaptic actions in the PFC, as well as on goal-directed behaviors (Figure 1). Exposing rats to repeated in vivo THC administration in adult mouse leads to a loss of eCB-LTD at glutamatergic synapses between PFC and NAc.[105] The loss of eCB-LTD is also observed following exposure to THC during adolescence in female rats, and this is accompanied by altered maturation of several molecules involved in eCB signaling and other forms of synaptic plasticity.[130] Many of these changes persist into adulthood. Adolescent exposure to CB1 receptor agonist also produces lasting impairment in other aspects of PFC function, and the performance of cognitive tasks that involve the PFC.[131–134] In vivo exposure to cocaine impairs eCB-LTD at glutamatergic synapse in PLC,[135] and even a single in vivo injection of this drug can impair induction of eCB-LTD at PFC synapses in the NAc.[136] Endocannabinoid actions in the PFC may also have roles in psychiatric disorders.[137–139] Drugs of abuse interfere with bidirectional plasticity at certain synapses, resulting in the inability to properly update normal patterns of plasticity (i.e., LTD and LTP) in key circuits in response to incoming sensory stimuli (Figure 1). More detailed reviews on the role of eCBs in addiction and addiction-related behaviors can be found elsewhere.[140–142]

Prefrontal Cortex-Striatal eCB Modulated DA Release.

Recently it has been shown that CB1 receptors on terminals of mPFC-NAc projections modulate cholinergically driven DA release in vitro and in vivo.[143] This eCB-mPFC modulation of DA signaling can be mediated by either 2-AG or AEA This study also provided evidence that “on-demand” activation of 2-AG-CB1 receptor signaling suppresses DA release under conditions where this release is driven by brief bursts of stimulation of NAc cholinergic interneurons. The cellular source of the 2-AG produced by this stimulation is not yet clear. The NAc is perfectly positioned to integrate excitatory signals from PFC, hippocampus, and amygdala, as well as dopaminergic signals from VTA to affect downstream output circuitry to control motivated goal-directed behavior.[144–146] Indeed, eCBs and CB1 receptors in mPFC and NAc can modulate goal directed behavior in a drug reinstatement paradigm.[147] It is believed that maladaptive long-term changes at these inputs contribute to addictive behaviors.[148,149] Previously it has been shown that mPFC-NAc terminal activation can promote self-stimulation,[150] indicating a role for this projection in

reward-driven behavior. Recently published data have extended these findings by demonstrating that CB1 receptor modulation of mPFC-NAc afferents can alter this self-stimulation.[143] Mateo and colleagues showed that 2AG signaling via CB1 receptor activation reduces mPFC-NAc self-stimulation in an instrumental task.[143] One possible mechanism is that activation of CB1 receptors located on mPFC-NAc terminals decreases glutamate release either through STD or LTD, thereby decreasing cholinergically driven DA release in the NAc to modulate reward-driven instrumental responding. Given that mPFC-NAc self-stimulation responding is elevated on the first day of training, eCB-LTD may not be needed for the initial goal-directed learning process, but may be needed for the maintenance of mPFC-NAc responding. The role of habit processes in this self-stimulation paradigm is not yet known, but 2-AG and CB1 receptors could also play a role in the development of habitual responding.

Parkinson's Disease: Corticostriatal eCB-LTD.

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized by profound motor dysfunction[151–153]arising from the gradual loss of DA neurons in substantia nigra pars compacta (SNc) that project to the DS, an area important for movement control, goal directed and habitual behaviors.[154,155] The loss of DA receptor activation leads to changes in corticostriatal plasticity that affect basal ganglia network function.[108,156] Specifically, corticostriatal LTD is lost after in vivo DA depletion when measured in vitro[98,157,158] or *in vivo*.[159] This form of LTD is dependent on eCB signaling[85,99,108] and DA-D2R activation[98,99,157,158,160] The site of the DA-D2Rs involved in this LTD is still under debate. Some pharmacological studies have implicated striatal cholinergic interneurons,[99,160] while others have implicated DA-D2R-containing MSNs.[101,156,161] Nonetheless, DA-D2R activation enhances AEA eCB release in striatum,[42] and AEA has been postulated as the eCB signaling molecule involved in corticostriatal LTD.[38,106,108] Flowever, a role for 2-AG in striatal LTD has not been ruled out by any means. Other neurotransmitters and receptors, including the A2A adenosine receptor,[160,161] have also been implicated in the modulation of striatal eCB-LTD, but the precise mechanism of action of these receptors remains unclear.

Following DA depletion, there is an enhancement of eCB levels[162,163] that is associated with the inhibition of movement.[163] Both corticostriatal LTD and the effects of DA depletion on movement can be restored by DA receptor activation and the enhancement of eCB signaling.[42,108,156,158,164,90] This tightly orchestrated activation of DA receptors and the appropriate levels of eCB signaling are necessary for the expression of corticostriatal LTD[160] and proper voluntary movement.[108] Although the loss eCB-LTD has been the central focus of corticostriatal dysfunction following DA-depletion, there are also alterations in the expression and induction of LTP. Depending on the degree of DA depletion, corticostriatal LTP is lost[158,165] or aberrant LTP can be induced using stimulation paradigms that normally induce eCB-LTD.[98,108,156] More interestingly, bidirectional plasticity at corticostriatal synapses is lost, leaving only unidirectional changes in corticostriatal efficacy following DA depletion.[156,166] These findings suggest that the DA depletioninduced loss of synaptic flexibility contributes to the motor deficits in PD and bidirectional synaptic modification is critical for proper movement control.

GABAergic-STRIATAL eCB MEDIATED LONG-LASTING DISINHIBITION

Disinhibition is a mechanism through which eCB activation of CB1 receptors can induce a long-lasting increase in glutamatergic activation of striatal neurons. Low-moderate frequency intrastriatal electrical stimulation induces a longlasting decrease in GABAergic transmission at synapses onto MSNs.[95,167,168] When the synaptically driven massed firing of striatal neurons is measured in field potential recordings (i.e., the population spike, PS, driven by synaptic activation), this low-moderate-frequency stimulation induces a long-lasting increase in PS amplitude that persists after the stimulus protocol. This increase is not observed when $GABA_a$ receptors are blocked, indicating a role for fast inhibitory synaptic transmission in this form of plasticity. Thus, this synaptic change has been termed long-lasting disinhibition (DLL; Figure 1).[167] Antagonists of CB1 receptors block this DLL, and the underlying LTD of GABAergic synaptic transmission is prevented by knocking out CB1 receptors in striatal MSNs and fast-spiking GABAergic interneurons.[168] Two forms of eCB-LTD have been observed at GABAergic synapses onto striatal MSNs.[168] Differences in postsynaptic membrane potential, eCB subtype, and presynaptic neuronal subtype determine which type of iLTD is expressed.[168] Thus, there may be circumstances where the underlying eCB-mediated processes contributing to DLL differ, and it remains to be determined when these different forms of plasticity might occur in vivo.

Exposure to ethanol (EtOH) alters DLL induction and expression. In rats that consumed EtOH intermittently for 7 weeks DLL can no longer be induced by moderate-frequency electrical stimulation.[167] The ability of a CB1 receptor agonist to produce disinhibition was also impaired in striatum from these EtOH-consuming rats. The role in EtOH-related behaviors of CB1 receptors on different striatal GABAergic neurons and the iLTD and DLL processes needs to be explored.

ASSOCIATIVE MEMORY FORMATION

Medial Prefrontal Cortex-Amygdala eCB-LTD.

The role of eCBs/CB1 on mPFC-amygdala projections in synaptic plasticity and learning and memory has also been examined (Figure 1). It is well-known that glutamatergic projections from mPFC to the BLA influence the extinction of aversive memories.[118,169–171] The hippocampus also plays a role in the associative processing in fear conditioning paradigms.[172] The CB1 receptors in mPFC itself also appear to have roles in fear consolidation and extinction, and activation of these receptors can impair retrieval of these memories in the fearpotentiated startle paradigm.[173] Several studies have implicated AEA signaling in the extinction of aversive memories.[174–177] Disruption of eCB/CB1 receptor signaling is selective for the extinction of aversive memories because extinction of non-aversive memories in an appetitive behavioral paradigm is not impaired by CB1 antagonism.[178] The extinction of fear memories or relearning of “new” memories that overrides the previous “old” memories may be mediated by eCB-LTD signaling. In the amygdala, eCB-LTD has been reported at both the inhibitory and excitatory terminals.[123,179–181] Emerging evidence suggests that DSI is not the mechanism through which eCBs and CB1 receptor participate in fear memory extinction. Réintroduction of CB1 receptors in forebrain GABAergic neurons in mice that lack CB1 receptors restored DSI in the hippocampus and

amygdala, but did not restore fear extinction.[182] The authors report only “marginally” improved extinction of fear conditioning after the genetic restoration of CB1 receptors. One possible mechanism is that CB1 receptor activation results in eCB-LTD at the inhibitory synapses that may result in the disinhibition of LTP at excitatory synapses to facilitate associative learning.[88,89,183] eCB-LTD can be spatially restricted to reduce synaptic transmission at selected presynaptic terminals, such that disinhibition can occur if effects are restricted to GABAergic synapses.[88,183] Although this has not been shown to occur in the amygdala, this metaplasticity has been shown to occur in the hippocampus, as discussed later in this review. With the advancement of genetic techniques, researcher can begin to probe synapsespecific eCB-LTD and its role in behavior. These new avenues of research will undoubtedly deepen our understanding of the physiological and functional significance of this form of synaptic plasticity and others.

SENSORY PROCESSING

Somatosensory Cortex eCB-LTD.

The roles of eCBs and CB1 receptors in somatosensory cortex have been explored mainly in relation to the development of the whisker barrel cortex (Figure 1). The whisker barrel area is a rather large part of the rodent somatosensory cortex devoted to the receipt and processing of tactile information from the facial whiskers.[184] This system is used for perception of environmental information of great value to animals that often navigate tight spaces in low-light conditions. This whisker barrel system is also well-known for its ability to adapt to changing sensory information, and several types of synaptic plasticity occur at synapses in different whisker barrel cortical layers.[185–190]

The postnatal development of whisker barrels and their physiological responses has been characterized in detail, and plasticity in these responses can be seen following trimming of whiskers during a certain developmental time period.[187,191,192] This synaptic plasticity appears to have “organizational” effects that determine subsequent synaptic interactions and physiological responses within the circuit. Among the forms of synaptic plasticity observed at glutamatergic whisker barrel synapses is a form of LTD mediated by eCBs and CB1 receptors. At synapses made by layer 4 glutamatergic neurons onto neurons in layer 2/3 of barrel cortex, evidence of LTD after whisker trimming has been observed in brain slices from rats examined at postnatal day 12.[193] This LTD has an apparent presynaptic locus of expression, and depends on retrograde eCB signaling.[194] One physiological role for this layer 2/3 eCB-LTD would be to reduce responsiveness to unimportant sensory stimuli during an important period of cortical development.[195] This idea is supported by the observation that blockade of CB1 receptor signaling leads to inappropriate whisker tuning in L2/3 neurons and blurring of the whisker map.[196] Thus, eCB-mediated plasticity is important in the early period of somatosensory cortical physiological shaping and later responsiveness to the environment.

Both GABAergic and glutamatergic synapses onto somatosensory cortex neurons are modulated by eCBs and CB1 receptors in young and young adult rodents.[197,198] This modulation occurs at synapses onto pyramidal neurons in layers 2/3 and 5, and not at synapses onto interneurons.[199] Short-term depression has been the main type of plasticity

investigated at these synapses. Interactions between eCBs and brain-derived neurotrophic factor (BDNF) have also been described in somatosensory cortex.[200,201] One such interaction involves BDNF effects on layer 2/3 pyramidal neurons leading to endocannabinoid production and release.[200,202] This stimulation involves activation of the TrkB neurotrophin receptor. This mechanism contributes to LTD induction at GABAergic synapses onto layer 2/3 pyramidal neurons, triggered by theta burst stimulation,[202] and 2-AG appears to be the eCB that mediates this LTD. At present there is very little information about how eCB-dependent plasticity in the different layers alters sensory processing mediated by this cortical area.

Endocannabinoids and CB1 receptors also participate in long-lasting "self-modulation" of layer V low-threshold spiking inhibitory interneurons and layer 2/3 pyramidal neurons in somatosensory cortex.[203–205] While this physiological change is not strictly speaking LTD, it will have a long-lasting influence on cortical function. This modulation is seen as a long-lasting hyperpolarization following induction of a brief burst of action potentials during recordings from these neurons. Pharmacological experiments indicate that the hyperpolarization involves tonic CB1 receptor activation leading to increased potassium current in the somatodendritic compartment of these neurons. The effect can be mimicked by CB1 receptor agonist application. It appears that 2-AG mediates this selfinhibition.[204] The net effect of the long-lasting self-inhibition of low-threshold spiking neurons is to provide a window during which their strong inhibition of pyramidal neurons is relieved, permitting enhanced glutamatergic cortical output,[203] while the effect in a subset of pyramidal neurons may inhibit corticocortical transmission.[205]

Visual Cortex eCB-LTD.

The eCBs and CB1 receptors also have important organizational roles in development of visual cortex (VC), similar to their actions in the whisker barrel system (Figure 1).[206] As in that somatosensory system, several types of synaptic plasticity in VC are involved in system development, and altering sensory input early in development alters subsequent visually driven physiology.[207] The maturation and function of VC is often assessed by examining the response of neurons in different cortical layers to light presented to one or the other eye, the well-known ocular dominance columns.[207,208] The column pattern is altered by visual deprivation to a single eye, as synapses responding to input from the two eyes appear to compete for influence on the VC neurons. This pattern of deprivation-induced plasticity in layer 2/3 VC is altered by CB1 receptor antagonist application in young animals, but this treatment does not appear to alter plasticity in layer 4.[208] Endocannabinoid-dependent LTD occurs at glutamatergic and GABAergic synapses in VC, especially in layer 2/3.[209–211] Prior monocular deprivation occludes LTD induction at glutamatergic layer 2/3 synapses.[209] The iLTD is especially prominent during the "critical period" when effects of visual deprivation are maximal. This developmental stage-dependent iLTD underlies a visual experience-dependent decrease in release probability at GABAergic synapses that helps set the final efficacy for mature synapses.[210] Keeping mice in the dark between eye opening and the onset of puberty also alters aspects of VC development, including GABA release at synapses in layer 2/3.[212] This effect is mimicked by knocking out CB1 receptors, and alterations in plasticity within layer 5 are also observed.[212] These findings indicate that eCB-LTD has

prominent roles in the physiology of developing visual cortex, but the consequences for adult visual function are not so clear. The status of eCB-LTD in adult visual cortex and roles in visual function are also still unclear.

Cerebellar eCB-LTD.

The LTD observed at granule cell/ parallel fiber (PF) synapses onto Purkinje neurons in cerebellar cortex was arguably the first form of LTD to be described in the CNS. Consequently, much is known about the mechanisms of this “cerebellar LTD” and its role in cerebellar-based forms of learning and memory including pavlovian conditioning and adaptation of reflexes.[213] Only recently was any role for eCBs in this LTD suggested. Work in the Regehr laboratory indicated that cerebellar LTD is prevented by a CB1 receptor antagonist and by inhibition of DAG lipase,[214] and cannot be induced in mice lacking CB1 receptors specifically in cerebellar granule cells.[215] This eCB/CB1 role was initially quite surprising given that the bulk of evidence indicates that cerebellar LTD involves a postsynaptic expression mechanism with no indication of a presynaptic role.[213] While this apparent conundrum has not been fully resolved, the eCB/CB1 system may help to regulate the timing of LTD induction by allowing for optimal suppression of parallel fiber inputs by subsequent activation of climbing fiber inputs.[216] Antagonism of CB1 receptors also prevents LTD at PF synapses induced by moderate frequency PF stimulation in brain slices and in vivo,[217,218] and there is evidence that presynaptic mechanisms are involved in expression of this type of LTD.[217] A presynaptically expressed form of eCB-LTD is also observed at PF synapses onto stellate interneurons.[91] Interestingly, there is evidence for an eCB role in cerebellum-dependent eyeblink conditioning,[219] but it will be interesting to examine the roles of this signaling system in other forms of cerebellum-dependent learning and memory (Figure 1).

HIPPOCAMPAL ENDOCANNABINOIDS, LEARNING AND MEMORY, SEIZURES, AND EPILEPSY

The hippocampus has well-known roles in different types of explicit learning, including spatial learning.[220,221] In addition, eCB/CB1-mediated synaptic plasticity and metaplasticity are well characterized in the hippocampus, especially at GABAergic synapses (Figure 1)[88,183] There is also extensive literature describing cannabinoid effects on learning and memory involving the hippocampus.[222–224] There is a growing body of information about how hippocampal eCBs and CB1 contribute to learning and memory. Intrahippocampal infusion of AM251 impairs consolidation of fear memory.[225] Interestingly, CB1 antagonist treatment can enhance acquisition of trace fear conditioning (a learning process known to involve the hippocampus),[226] and antagonists can enhance performance on spatial learning tasks.[227–229] Endocannabinoids also appear to contribute to spatial memory retrieval, depending on the level of emotional arousal.[230]

The explicit relationship between eCB-mediated plasticity and hippocampal-based learning and memory has been the subject of several recent studies. In mice lacking MGL, LTP induced by theta-burst stimulation at glutamatergic synapses in the CA1 subregion is enhanced.[29] These mice also show prolonged DSI that may underlie the facilitation of LTP.

In spatial and object recognition tasks, these MGL knockout mice show improved performance, consistent with the idea that disinhibitory eCB-dependent synaptic plasticity can facilitate both LTP and learning. Using a trace-conditioning task, Zhu and co-workers showed that mice with deficiency in an eCB-mediated form of metaplasticity involving iLTD and enhanced LTP perform poorly.[231] Enhancing eCB signaling with an MGL inhibitor enhanced acquisition and performance on this temporally based associative learning task. This enhancement was associated with changes in iLTD indicative of in vivo metaplastitity. In contrast, strong inhibition of MGL impairs LTP in the hippocampal CA1 region, and forms of learning involving the hippocampus.[232] The different effects of the MGL inhibitors in these two studies may reflect the task used or the efficacy of the inhibitor in enhancing hippocampal 2-AG levels. Impairment of LTP and hippocampal-based learning and memory was also observed with a FAAH inhibitor.[233] The effects of experimental manipulations that alter eCBs and CB1 may also depend on the extent to which a given manipulation alters eCB suppression of GABAergic transmission,[88] which would favor LTP and learning, versus inhibiting glutamatergic transmission, which might impair LTP.[41]

Endocannabinoid and CB receptors roles in brain hyperexcitability, seizures, and epilepsy have been investigated since the discovery of these biomolecules. Effects of eCBs on GABAergic and glutamatergic synapses in brain regions with key roles in limbic and tonic-clonic seizures can alter the balance of synaptic excitation and inhibition in ways that may promote or reduce seizure susceptibility. This topic was recently reviewed in some depth, [55,234,235] and thus, only a brief summary is presented here. Alterations in eCB signaling in relation to epilepsy are best characterized in the hippocampal formation, as this brain region has important roles in limbic seizures (Figure 1). A temporal pattern of changes in tissue eCB levels and CB1 expression has been observed in epilepsy models. Downregulation of CB1 expression is generally observed throughout the hippocampal formation in the acute seizure phase, followed by upregulation in the chronic epileptic phase,[55,234,236] but changes in receptor levels and function also vary across hippocampal subregions in some seizure models.[237] Both 2-AG and AEA levels are increased in the acute phases of pilocarpine and kainic acid-induced seizures, but there is not as much information on eCB levels in the chronic phase.[55,238] Retrograde signaling by eCBs at GABAergic hippocampal synapses is also increased in animal models of seizure disorders.[239] This enhanced modulation likely results in enhanced excitability in this brain region.

Increased CB1 expression on GABAergic terminals is also observed in post-mortem tissue from human epilepsy patients, although downregulation was also observed on glutamatergic terminals.[240,241] Examination of the living human brain using positron emission tomography imaging with a CB1 ligand has revealed increased CB1 binding in the temporal lobe ipsilateral to a seizure focus in patients with temporal lobe epilepsy and hippocampal sclerosis, while binding was decreased bilaterally in the insular cortex.[242] However, it is not clear if these changes are due to alterations in receptor expression or differences in eCB occupancy of the receptors during the imaging period. It is interesting in this context that AEA levels are reduced in cerebrospinal fluid of temporal lobe epilepsy patients.[243] Overall, these findings indicate that the eCB/CB1 signaling system is altered by seizures and in epileptic disorders, but more information is needed to determine the role of eCBmediated synaptic plasticity in the development of these disorders.

There is also ample evidence that altering eCB/CB1 signaling affects seizures and epilepsy in animal models, but the effects of experimental manipulations of this system have been mixed. Peripheral administration of efficacious CB1 agonists generally has an anticonvulsant effect in a variety of animal seizure models, although seizure-enhancing effects have also been observed.[244–246] When CB1 antagonists are administered peripherally, they produce mainly pro-convulsant effects in these models.[238,247–250] However, antagonists can prevent development of experimental febrile or head-injuryinduced seizures especially when given early in the development of epilepsy.[251,252] Deleting CB1 receptors from glutamatergic forebrain synapses enhances kainic acid induced convulsions, consistent with a role for excess synaptic excitation due to loss of eCB modulation.[253] While compounds targeted at the eCB/CB1 signaling system clearly affect seizures and epileptic disorders, therapeutic use of any such compounds will require a more precise understanding of the interactions with different circuits involved in different seizure types and forms of epilepsy.

The finding that cannabidiol, a phytocannabinoid that does not interact with CB1 receptors, has some efficacy for reduction of seizures in animal models and in certain childhood epilepsies needs to be mentioned in the context of this discussion.[235,254,255] However, it must also be noted that there is no strong evidence that this action involves eCBs or CB receptors.

FUNCTIONAL RELEVANCE OF ENDOCANNABINOID LTP

In addition to well characterized eCB and CB1 receptor roles in LTD, participation of these molecules in LTP has also been postulated.[95,256,257] Using a spike-timing-dependent plasticity (STDP) procedure with a low number of pre- and postsynaptic spike pairings, Cui and co-workers observed a form of LTP at glutamatergic synapses onto dorsal striatal MSNs that is blocked by inhibition of eCB production and a CB1 receptor inverse agonist, and is lost in CB1 receptor KO mice.[256] A role for TRPV1 in this STDP-LTP has also been proposed based on antagonist actions, but it would be helpful to determine if this form of plasticity is lost in animals lacking TRPV1. A role for dopamine in this STDP-LTP has also been postulated based on blockage by a D2 receptor antagonist or a combination of D1 and D2 receptor antagonists. The locus of the mechanisms responsible for this increased synaptic transmission appears to be presynaptic. Interestingly, both eCB-LTD and LTP can be induced in the same neuron by altering the number of pre- and postsynaptic spike pairs. A form of LTP involving eCBs and CB1 receptors has also been reported in the hippocampal CA1 region.[258] This eCB-LTP requires group I mGluR activation, and appears to involve retrograde 2-AG signaling resulting in presynaptic facilitation of glutamate release specific to Schaffer collateral synapses.

A form of LTP that requires CB1 receptors has also been observed in whisker barrel cortex layer V pyramidal neurons of young rats.[259] Activation of blood flow in the whisker barrel cortex of adult rat by whisker stimulation is potentiated by CB1 receptor agonist administration, but there are mixed effects of a CB1 receptor inverse agonist depending on the route of peripheral administration that remain unexplained.[260,261] This type of plasticity may provide a mechanism for strengthening synapses during relatively short windows of

intense combined afferent and postsynaptic coactivation, such as might take place in associative learning tasks. However, it remains to be determined if eCB-LTP occurs in vivo.

CONCLUSIONS

In the last two decades, the eCB system has emerged as a key regulator of synaptic function. Short-term and long-term forms of eCB mediated synaptic plasticity have been reported in many different brain regions at both inhibitory and excitatory synapses. While there is ample evidence that altering eCB-CB1 signaling affects many behaviors, to date, there is no direct evidence that eCB mediated LTD or LTP in vivo contributes to these behaviors per se. Three general circuit mechanisms emerge again and again for eCB mediated LTD and LTP that may influence behaviors. Endocannabinoid LTD can participate in two of these circuit effects. One mechanism is the net disinhibition of local circuits, in which inhibition of GABAergic synapses allows for enhanced synaptic output at a subset of synapses. On the other hand, eCB-LTD can exert its inhibitory actions on neural circuits on a micro and macro level to suppress unwanted neuronal activity. Lastly, eCB-LTP can strengthen synapses to reinforce or maintain a certain behavior. These complex changes in potentiation, inhibition, and disinhibition in synaptic output are delicately modulated by eCBs to help shape synaptic and behavioral function. Understanding how these mechanisms contribute to behavior will require determining if and when these types of plasticity take place in vivo during behavioral performance or learning and memory. Preventing this plasticity in a temporally and spatially specific manner can then be used to determine if eCB-mediated long-lasting synaptic plasticity has a crucial role in these in vivo processes. With the powerful new approaches available to the modern neurobiologist it should now be possible to perform such experiments. Ultimately, this line of research will produce a better understanding of mechanisms involved in learning, memory, effects of drugs of abuse, and addiction.

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ABBREVIATIONS

2-AG	2-arachidonoylglycerol
AEA	arachidonoylethanolamine
DSE	depolarization-induced suppression of excitation
LTD	long-term depression
LTP	long-term potentiation

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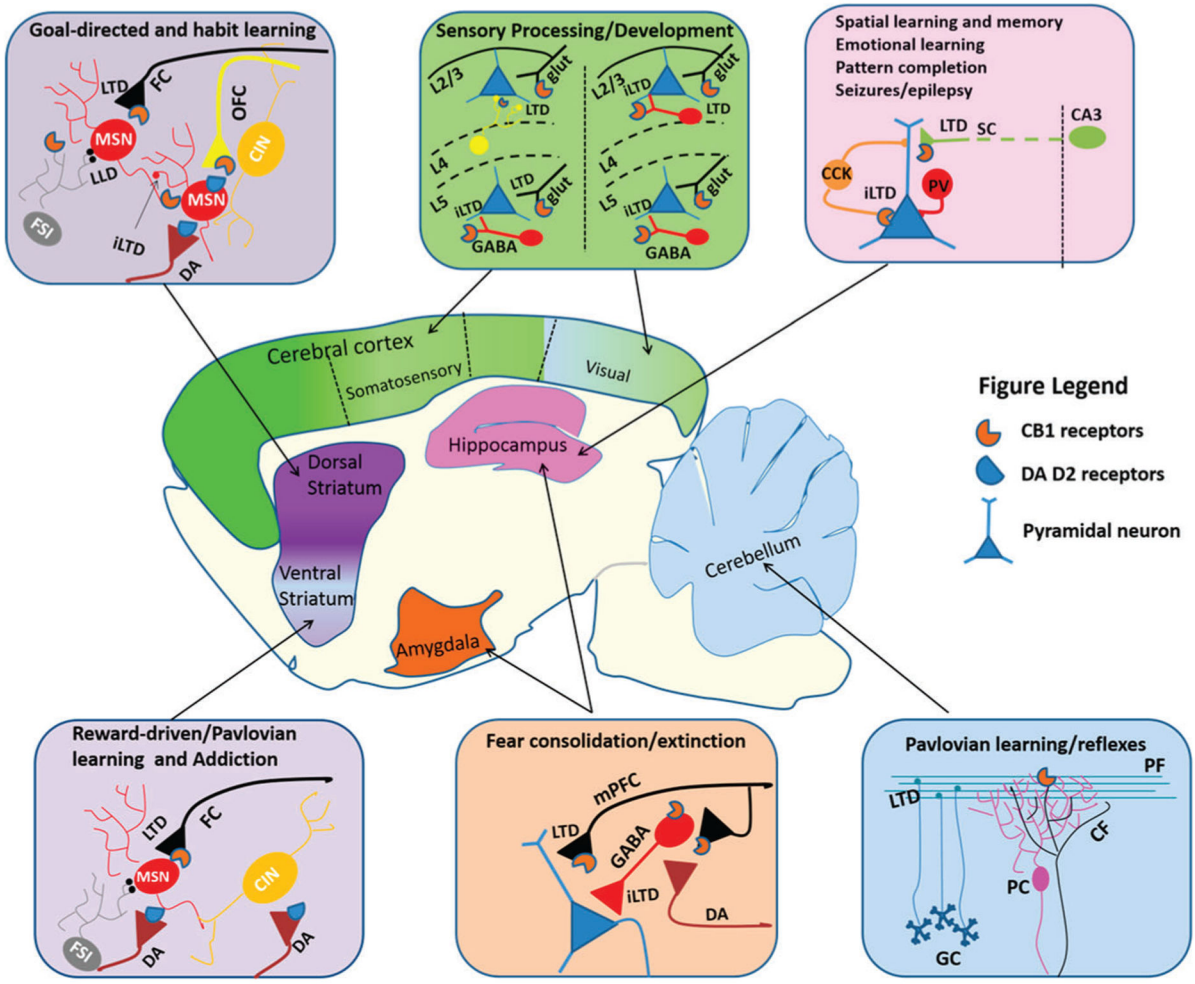

Figure 1.

Proposed eCB mediated synaptic plasticity functional map in rodent brain. Schematic illustration of brain structures, specialized functions, and microcircuitry involved in eCB-LTD. eCBs have the potential to modulate goal-directed, habitual, and reward-driven behaviors in the striatum by DA regulation of eCB mediated LTD at excitatory synapses and eCB mediated LLD and LTD at inhibitory synapses. eCBs work in a layer specific manner at excitatory and inhibitory synapses in the somatosensory and visual cortices to process incoming sensory information. Hippocampal eCB synaptic depression has been reported at CCK-basket cell interneuron-pyramidal cell synapses and at excitatory terminals of Schaffer collaterals arising from CA3. There, eCB-mediated plasticity is postulated to play an important role in learning and memory formation, and can contribute to seizures and epileptic disorders. In the cerebellar cortex, eCBs mediate synaptic depression of Purkinje cell inputs to control motor learning and conditioning of reflexes. eCB mediated changes in synaptic transmission in the hippocampus and amygdala modulate fear-associated memory formation. DA, dopamine; FC, frontal cotex; OFC, obritofrontal cortex, MSN, medium spiny neuron; CIN, cholinergic interneuron; FSI, fast-spiking interneurons; glut,

glutamatergic; PC, purkinje cell; PF, parallel fibers; CF, climbing fibers; GC, granule cell; CCK, cholecytokinin; SC, Schaffer collaterals; PV, parvalbumin positive neurons.