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Endocannabinoid Signaling and Long-term Synaptic Plasticity

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Abstract

Endocannabinoids (eCBs) are key activity-dependent signals regulating synaptic transmission throughout the CNS. Accordingly, eCBs are involved in neural functions ranging from feeding homeostasis to cognition. There is great interest in understanding how exogenous (e.g. cannabis) and endogenous cannabinoids affect behavior. As behavioral adaptations are widely considered to rely on changes in synaptic strength, the prevalence of eCB-mediated long term depression (eCB-LTD) at synapses throughout the brain merits close attention. The induction and expression of eCB-LTD, while remarkably similar at various synapses, is controlled by an array of regulatory influences which we are just beginning to uncover. This complexity endows eCB-LTD with important computational properties, such as coincidence detection and input specificity, critical for higher CNS functions like learning and memory. In this article, we review the major molecular and cellular mechanisms underlying eCB-LTD, as well as the potential physiological relevance of this widespread form of synaptic plasticity.

Keywords

Cannabinoid; CB1; LTD; LTP; synaptic transmission; STDP

Terms/Definitions

Endocannabinoid system; Endocannabinoid synthesis/release; Spike Timing-Dependent Plasticity

Introduction

Retrograde signaling by endocannabinoids (eCBs) has emerged as a major theme in the study of synaptic plasticity. Neuronal activity releases these neuromodulators, which activate the presynaptic type 1 cannabinoid receptor (CB1R, a G protein-coupled receptor), suppressing neurotransmitter release at both excitatory and inhibitory synapses in a short- and long-term manner (1-6). Examples of eCB-mediated long-term depression (eCB-LTD) have been reported throughout the brain. The discovery of eCB-LTD demonstrates that eCBs can have a long-term impact on neural function and it has certainly expanded our view on the role of eCB signaling in the CNS. As a result of the last 10 years of research on eCB-

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signaling and synaptic plasticity, eCBs have become the most prominent example of retrograde signaling molecules in the CNS. Moreover, eCB-LTD is by now one of the best examples of presynaptic forms of long-term plasticity. Since our previous review of eCB-mediated synaptic plasticity (3), a number of exciting developments have prompted a fresh appraisal of this field. Thorough review articles on eCB signaling and synaptic transmission have recently been published (5, 6), and the breadth and depth of studies focusing primarily on eCB-LTD warrants its own dedicated review. In this article, we will review the major developments regarding eCB-LTD's induction, expression, computational properties, developmental regulation, and physiological relevance.

Overview of eCB-LTD

Endocannabinoids and the CB1 receptor

Endogenous cannabinoids, or endocannabinoids (eCBs) are so called because of their close relationship to exogenous cannabinoids, the most famous being Δ^9-tetrahydrocannabinol (THC), a major psychoactive component of marijuana (7). One of the most surprising discoveries came from studies revealing a unique, previously unknown receptor for THC within the mammalian central nervous system (CNS). The Type 1 Cannabinoid receptor (CB1R) was ultimately isolated, cloned, and characterized as a G protein-coupled receptor (GPCR) that signals via the $\alpha_{i/o}$ family of G-proteins (8, 9). Soon after, CB1Rs were not only found to bind THC, but they also appeared to have an endogenous ligand; anandamide (AEA) was the first of several eCBs isolated, among which 2-arachidonyl glycerol (2-AG) is most prevalent in brain (10, 11). The physiological relevance of eCBs quickly emerged, as neuronal activity was identified as a potent stimulus for eCB release, and eCBs were found to act as retrograde messengers, regulating synaptic transmission through presynaptic CB1Rs (1). Since 2001, eCBs have been identified as triggers for short and long-term plasticity at synapses throughout the brain (3), in agreement with the ubiquitous expression of CB1Rs (12, 13).

Activation of the CB1R, and subsequent long-term reduction of transmitter release at the same synapse, defines eCB-LTD. CB1Rs also mediate short-term plasticity exemplified by Depolarization-induced Suppression of Inhibition or Excitation (DSI or DSE, respectively). DSI/DSE is well characterized in the hippocampus and cerebellum, and has been observed in other brain areas (2, 5). CB1Rs can engage a wide range of effector molecules, including (but not limited to) voltage-dependent Ca^{2+} channels (VDCCs), K^+ channels, PKA and MAPK (recently reviewed in 14).

eCB-LTD: a widespread phenomenon in the brain

The first evidence implicating eCB signaling in LTD emerged in 2002 at excitatory synapses in dorsal striatum (15). Since then, eCB-LTD has been reported in several other brain structures such as the nucleus accumbens (16), amygdala (17-19), hippocampus (20-25), visual cortex (26-29), somatosensory cortex (30, 31), prefrontal cortex (32), cerebellum (33), ventral tegmental area (VTA) (34), brain stem (35) and superior colliculus (36). As shown in Table I, it is now clear that eCB-LTD is a widely expressed phenomenon in the brain that can be observed at both excitatory and inhibitory synapses. This prevalence

strongly suggests that eCB-LTD may be a fundamental mechanism for making long-term changes to neural circuits and behavior.

Induction of eCB-LTD

Strong similarities in the pattern of eCB-LTD induction and expression are evident at both excitatory and inhibitory synapses from brainstem to cortex (3). The main objective of this section will be to define 1) synaptic events which trigger eCB production/release, 2) how eCB production, release and degradation may be regulated, and 3) which presynaptic events are required for successful induction of eCB-LTD.

Synaptic events triggering eCB-mediated synaptic plasticity

eCB-LTD induction typically begins with a transient increase in activity at glutamatergic afferents and a concomitant release of eCBs from a target (postsynaptic) neuron (Fig. 1). eCBs then travel backwards (retrogradely) across the synapse, activating CB1Rs on the presynaptic terminals of either the original afferent (homosynaptic eCB-LTD), or nearby afferents (heterosynaptic eCB-LTD) (3). In the past few years, mounting evidence indicates that eCB-LTD induction requires presynaptic activity of the target afferent, independent of its role in triggering eCB release (see below).

Induction protocols differ widely across examples of eCB-LTD (Table I). Some forms of eCB-LTD are induced by the tetanic stimulation of afferents, an approach used extensively in the study of synaptic plasticity. A number of induction protocols effectively produce eCB-LTD, from 100 pulses at 1 Hz to 100 Hz, or the more patterned theta burst stimulation (TBS). These afferent-only induction protocols for eCB-LTD have not been rigorously compared at most synapses, but at least for eCB-LTD at hippocampal inhibitory synapses, induction is effective over a broad range of frequencies (24, 37). eCB-LTD has also been found by repetitively firing presynaptic and postsynaptic neurons at fixed intervals with respect to each other. This induction protocol can yield “spike timing-dependent plasticity” (STDP), where the order and interval of the two spikes dictates the direction (i.e. t-LTD or t-LTP) and magnitude of plasticity (for a recent review, see 38). At this time, several instances of STDP are known to feature a mechanistically distinct t-LTD and t-LTP, the former being CB1R dependent (eCB-t-LTD). eCB-t-LTD's presynaptic locus of expression is indistinguishable from those forms induced with “afferent-only” stimulation protocols described above. A given synapse may well be able to support eCB-LTD induced by both afferent-only and spike timing-dependent protocols (15, 39).

Stimuli for eCB production

Activity-dependent release of eCBs from the postsynaptic cell is the common trigger to all forms of eCB-LTD. Extensive studies have established that two separate processes, neurotransmitter release and neuronal depolarization, mediate eCB release (for comprehensive reviews on this topic, see (5, 40)). For example, glutamate can stimulate eCB release through activating Type I metabotropic glutamate receptors (mGluR-I), which can initiate eCB synthesis “on demand” through effectors of the $G\alpha_{q/11}$ subunit (41, 42).

Neuronal depolarization is also a potent trigger of eCB release, through a less understood Ca^{2+}-dependent process that does not depend on G proteins (1, 40).

1. Metabotropic receptor-dependent eCB release—Studies of neural tissue conducted in vivo or in acutely prepared brain slices indicate that eCB release need not be linked to special metabotropic receptors, or a particular route of Ca^{2+} entry. In addition to mGluR-I, metabotropic dopamine (Type 2; D_2), muscarinic acetylcholine (type 1/3; M_1/M_3), serotonin (type 2; 5-HT_2), orexin, and cholecystokinin receptors are all effective stimuli for eCB release (43-48). Most of these GPCRs signal through $G\alpha_{q/11}$, engaging phospholipase C (PLC) and diacylglyerol lipase (DGL), which form the eCB 2-AG (Fig. 1). However, alternative mechanisms coupling these receptors to eCB release have also been proposed. For example, in basolateral amygdala, mGluR1 appears to stimulate AEA production through a pathway involving adenylyl cyclase (AC) and cAMP-dependent protein kinase (PKA) (18). Despite the marked differences in eCB synthetic route and even eCB identity, eCB-LTD is expressed in a nearly identical fashion in amygdala and hippocampus (19), reinforcing the notion that eCB release, by any means, is a core component of eCB-LTD.

D_2Rs differ from the other metabotropic receptors named above as they typically signal through the $G\alpha_{i/o}$ pathway and stimulate formation of AEA, rather than 2-AG, although the precise synthetic pathway is not known (40, 43). D_2Rs are required for corticostriatal eCB-LTD (39, 49, 50), and several lines of evidence from slice electrophysiology suggest a role for AEA in this process (50, 51). In part due to the paucity of pharmacological tools for manipulating AEA biosynthesis, it has been difficult to determine the precise mechanism by which D_2Rs mediate eCB-LTD. D_2Rs may directly stimulate eCB release from medium spiny neurons (MSNs), or, as recently suggested, D_2Rs exert an indirect effect on eCB release via cholinergic interneurons in dorsal striatum (52). However, a recent study has shown that the presence or absence of D_2Rs on MSNs determine whether eCB-LTD can be induced at an afferent glutamatergic synapse (50), owing to a D_2R-mediated facilitation of eCB release (49). Indeed, using spike timing-dependent induction protocols, it has been recently reported that corticostriatal synapses onto D_1-expressing neurons can undergo eCB-LTD, provided induction occurs in the presence of a D_1R antagonist (39). Although these corticostriatal afferents are capable of expressing CB1R agonist-induced LTD (49, 53), it seems that specific postsynaptic factors can pose intrinsic limitations on eCB-LTD.

2. Calcium-dependent eCB release—While not universally required for eCB-LTD, Ca^{2+}-dependent mechanisms play a pivotal role in many forms of eCB-LTD (15, 16, 26, 28, 30-33, 35, 54). Like metabotropic signaling pathways, which converge through multiple pathways onto eCB release to ultimately trigger eCB-LTD, Ca^{2+}-dependent eCB release also has a similarly broad set of initiating mechanisms. Ca^{2+} influx through NMDARs, L-type and T-type VDCCs, and Ca^{2+} release from intracellular stores have all been reported to drive eCB release in brain slices (30, 31, 54-57). The source of postsynaptic Ca^{2+} differs among individual examples of eCB-LTD. Although no specific mode of Ca^{2+} rise stands as a universal requirement, it is not clear to what extent different Ca^{2+} sources can compensate for each other.

Integrating signals for eCB release

The metabotropic and Ca^{2+}-driven mechanisms can operate independently - mGluR-I can release substantial amounts of eCB even under strong Ca^{2+}-buffering conditions (18, 20, 42, 58) - but they can also act synergistically (25, 49, 59-61). Some of the enzymes mediating this cooperativity have been characterized. For example, the PLCβ isoform is critical for mGluR-I-triggered release of 2-AG (61). $G\alpha_{q/11}$, through PLCβ, provides the substrate for DGL, leading to 2-AG formation (62). In CA1 pyramidal cells of the hippocampus, activity of the isoform PLCβ1 is significantly enhanced by raising Ca^{2+} concentrations, allowing for a potential coincidence detection mechanism in the postsynaptic neuron, gating eCB release and possibly eCB-LTD (61). Another isoform of this enzyme, PLCβ4, mediates a similar process in the cerebellum, at parallel fiber to Purkinje cell synapses (59, 63). Here, activation of mGluR-I renders eCB release more sensitive to intracellular Ca^{2+} levels, raised either by direct Purkinje cell depolarization, or through stimulating powerful climbing fiber inputs to the Purkinje cell. Although eCB-LTD has not been assessed in transgenic animals lacking the various PLCβ enzymes, pharmacological blockade of PLC effectively blocks eCB-LTD in hippocampus, VTA and prefrontal cortex (20, 32, 34, 64). It remains to be seen whether similar synergy of eCB release between metabotropic and Ca^{2+} driven signals occurs with enzymes in the AEA synthetic pathway, as suggested for phospholipase D (40).

Spatial constraints on eCB production—Investigations into PLCβ have revealed a compelling picture of how the temporal pattern of synaptic input can amplify or constrain eCB production. In principle, this mechanism by PLCβ can also provide some spatial specificity to the eCB signal. Neuronal depolarization presumably triggers eCB synthesis/release wherever Ca^{2+} influx occurs; only active synaptic inputs engage the metabotropic facilitation of the eCB signal, while silent afferents would not. Even so, eCBs can trigger both homo- and heterosynaptic plasticity. How else, then, might a synapse limit the spatial impact of eCB release?

Another strategy neurons may employ to provide spatial specificity to the eCB signal is to confine the Ca^{2+} signal itself, thereby restricting the lateral extent of eCB release. This hypothesis has been explored in the context of eCB-LTD at cerebellar parallel fiber to stellate cell synapses (33). Stellate cells are especially notable for their absence of structural specializations, such as the spine head, which in other neurons effectively compartmentalize second messenger signals (65). Rather, the Ca^{2+} signal is biochemically “confined” through interactions with the Ca^{2+}-buffering protein parvalbumin as well as a generalized reduction of small molecule mobility within the dendrite (33). These mechanisms can isolate the eCB release generated by a single glutamatergic synapse from its neighboring synapse, 15 μm away.

The spatial distribution of eCB-synthetic machinery may also impact synaptic transmission. As discussed above, DGL plays a key role in mGluR-dependent eCB production and several forms of eCB-LTD. Anatomical studies have revealed differential sub-cellular localization with respect to the synapse in various brain structures (66-69). The relevance of these findings to eCB-LTD induction remains unexplored.

eCB degradation—Enzymes regulating the eCB lifetime in the synaptic cleft are also potentially significant targets for regulating eCB-LTD induction. The degradation of 2-AG and AEA largely depends on the enzymes monoacylglycerol lipase (MGL) and FAAH, respectively (40). Other enzymes may also participate in eCB catabolism, although with less specificity (e.g. COX-2) (70, 71). In hippocampus, where 2-AG is very likely to be the dominant functional eCB, electron microscopic studies reveal a predominantly presynaptic pattern of MGL expression, supporting a role in regulating the effective concentration of eCBs near their site of action (72). Consistent with this idea, MGL inhibition can transform a subthreshold tetanus into an effective stimulus for eCB-LTD in the prefrontal cortex (32), mirroring similar results with FAAH inhibitors in eCB-LTD in neocortex, amygdala and dorsal striatum (18, 26, 50). At present, it is not known if MGL or FAAH activity is dynamically regulated in neurons, although some data have also shown that elevated intracellular Ca^{2+} levels can inhibit MGL activity in microglia (73). Regulating MGL in this way offers a potential mechanism whereby presynaptic activity, and Ca^{2+} within the terminal, might hold sway over the duration of CB1R activation, and possibly eCB-LTD.

A regulated eCB efflux step?—Several aspects of eCB release are still poorly understood, but may prove to be important points of control over eCB-LTD. A recent study has suggested that efflux of newly synthesized eCBs can be regulated by postsynaptic activity. Adermark and Lovinger (2007) loaded postsynaptic striatal MSNs with AEA or 2-AG and found that pairs of test stimuli (0.1 Hz) could induce a CB1R-dependent suppression of excitatory transmission, independent of mGluR-I activation, postsynaptic Ca^{2+} or postsynaptic membrane potential. Since afferent stimulation did not modulate direct presynaptic inhibition by a CB1R agonist, the authors hypothesized that afferent activity regulates a late step in eCB release/mobilization, prior to CB1R activation. Accordingly, postsynaptic loading with blockers of the putative eCB membrane transporter (EMT), prevented the synaptic depression induced by combined postsynaptic AEA application and afferent activation (74). Indeed, Lovinger and co-workers have previously shown that postsynaptic loading of EMT blockers prevents eCB-LTD in dorsal striatum (75), an observation also confirmed by others in somatosensory cortex (31). Whether postsynaptic activity governs other forms of eCB-LTD through the putative EMT is unknown, as this type of regulation may be a synapse specific phenomenon. In contrast to the situation at excitatory synapses, postsynaptically loaded eCBs suppresses inhibitory synapses onto MSNs regardless of afferent activity (74).

Presynaptic activity and eCB-LTD

The foregoing discussion has primarily focused on presynaptic (afferent) activity as a regulator of eCB release. However, several lines of evidence suggest that eCB-LTD requires presynaptic activity as a cofactor for induction that is independent of eCB release and CB1R activation. Coincident activation of CB1Rs and presynaptic activity provides an additional mechanism to ensure synapse specificity, such that only active fibers undergo eCB-LTD.

Spike timing-dependent eCB-LTD and presynaptic NMDARs—In a series of elegant experiments using cell-pair recordings in L5 of visual cortex, Sjöstrom and co-workers (2003) provided the first evidence that presynaptic activation of NMDARs is

required for the induction of eCB-LTD, here induced by spike timing-dependent protocols (or eCB-t-LTD). They showed that exogenous activation of CB1Rs, a manipulation that short-cuts eCB release from the postsynaptic pyramidal neuron, induces LTD only if the presynaptic neuron is activated at a relatively high frequency, and importantly, this LTD is blocked by the NMDAR antagonist D-APV (26). Sjöstrom et al (2003) postulated that coincident activation of presynaptic NMDA and CB1 receptors is required for the induction of eCB-t-LTD. Further support for the presynaptic NMDAR requirement has been independently provided by other groups studying somatosensory cortex (30, 31) and visual cortex (28, 76), showing that bath application of NMDAR antagonists blocks eCB-LTD, but blockade disrupting postsynaptic NMDAR function with either hyperpolarization or the inclusion of MK-801 in the postsynaptic recording pipette, does not affect the induction of eCB-LTD. A recent study in somatosensory cortex has provided direct evidence that presynaptic NMDARs are required for t-LTD induction. Indeed, loading presynaptic neurons with MK-801 in synaptically coupled cell-pairs selectively abolished t-LTD, without affecting t-LTP (77). A still open question is how presynaptic NMDARs and CB1Rs interact to induce a long-lasting reduction in transmitter release. It is tempting to postulate that Ca^{2+} influx through presynaptic NMDARs might be required to activate some metabolic process at the presynaptic terminal. Alternatively, presynaptic NMDAR could signal in a Ca^{2+}-independent manner. These possibilities remain to be tested.

CB1Rs are insufficient for eCB-LTD and presynaptic activity is required—The involvement of presynaptic NMDARs may represent a unique aspect linking the various forms of eCB-t-LTD (26, 28, 31). However, the fact that several examples of eCB-LTD are NMDAR-independent immediately raises the question: is presynaptic Ca^{2+} entry, or even presynaptic activity, a general requirement of eCB-LTD induction? Experiments performed with eCB-t-LTD showed that CB1R agonists alone do not trigger long-term plasticity without coincident activity (26, 31). CB1R activation, alone, is similarly unable to trigger eCB-LTD in hippocampus, dorsal striatum and VTA (22, 34, 53, 64, 75, 78-80). Data from hippocampus and striatum show that eCB-LTD requires minutes of CB1R activation after a brief induction stimulus (20, 75), suggesting that another induction signal, such as presynaptic activity, may be integrated during that period to induce eCB-LTD. This issue has been investigated in some detail for eCB-LTD in dorsal striatum and at CA1 inhibitory synapses.

Recent evidence shows that eCB-LTD in the dorsal striatum requires low-frequency presynaptic activity during the period of CB1R activation (53). The authors propose that this dual requirement confers synapse specificity onto eCB-LTD under conditions of (e.g.) eCB spillover. This finding is consistent with a previous report showing that CB1R activation alone cannot induce striatal eCB-LTD (75). The requirement for presynaptic activity fits well with the fact that CB1R activation for more than 5 minutes after the induction tetanus is also necessary for eCB-LTD in the hippocampus (20) and striatum (75). In these studies, the role of afferent stimulation may either have been 1) to supply activity at the test synapse, or 2) to release a cofactor crucial for induction. This latter concern is not trivial, given that this eCB-LTD may involve a complex interplay between dopamine receptors and cholinergic interneurons, in addition to events at the glutamatergic corticostriatal synapse (52, 81). Our

own experiments in the hippocampus using interneuron-pyramidal cell pairs provide direct experimental evidence that eCBs and presynaptic activity at the test synapse interact to induce eCB-LTD. Under conditions of maximal eCB release (i.e. minutes of mGluR-I activation), we found that firing these interneurons produces eCB-LTD, whereas holding neurons silent during eCB release effectively prevents induction of eCB-LTD (78).

Timing of afferent activity – milliseconds vs minutes—Most evidence indicates that eCB-LTD induction requires presynaptic activity, in addition to CB1R activation. The timing requirements for presynaptic activity, however, seem to differ significantly among synapses. There is some evidence to suggest that these timing requirements reflect signal integration at the presynaptic terminal, rather than special conditions needed for eCB release. In L5 pyramidal cells of visual cortex, even manipulations which extended the lifetime of eCBs in the synaptic cleft did not remove spike timing dependence; rather they only broadened the time window where post-before-pre firing could trigger eCB-LTD (26). Similarly, in the dorsal cochlear nucleus, blocking the t-LTP component broadened the effective time window for eCB-LTD induction without changing the required order of spikes (35). It is tempting to speculate that the requirement of a presynaptic NMDAR, which as yet occurs exclusively in eCB-t-LTD, confers a timing property (82). eCB-t-LTD mediates coincidence detection on the order of milliseconds. For eCB-t-LTD in somatosensory cortex, this strict timing requirement may reflect its proposed physiological role in rodent whisker desensitization (83). In hippocampus and dorsal striatum, eCB-LTD seems to integrate aggregate events occurring over minutes to yield eCB-LTD. At present, the significance of this timing requirement is not known, but in principle it allows for an associativity between synaptic events on two very different time scales.

Presynaptic calcium and eCB-LTD—As suggested previously, the known involvement of presynaptic NMDARs in some forms of eCB-t-LTD may indicate a requirement for presynaptic Ca^{2+} in the induction of eCB-LTD. Our data (78) and that of Singla et al (2007), although indirect, support a role for presynaptic Ca^{2+} in the induction of eCB-LTD. Support for this hypothesis comes from experiments in both dorsal striatum (53) and in hippocampal inhibitory synapses, several methods of disrupting presynaptic Ca^{2+} dynamics all blocked eCB-LTD, strongly suggesting that interneuron spikes regulate this form of plasticity by raising Ca^{2+} at the nerve terminal. In addition, induction of eCB-LTD at hippocampal synapses also requires activation of the Ca^{2+}-sensitive phosphatase calcineurin (78). Together, these observations lead us to propose a mechanism where firing, by raising Ca^{2+} levels at the presynaptic terminal, activates calcineurin, thereby shifting the balance of kinase and phosphatase activity in the presynaptic terminal, finally inducing eCB-LTD (see below).

In conclusion, most evidence indicates that both pre- and postsynaptic activity can control eCB-LTD induction. These regulatory mechanisms endow eCB-LTD with at least two forms of associativity as summarized in Figure 2. In the postsynaptic compartment, glutamate release and activity-dependent Ca^{2+} rise facilitates eCB mobilization, a process mediated by PLC. Presynaptic associativity involves CB1R activation by eCBs and presynaptic firing,

which increases Ca^{2+} concentration, both required to engage long-term suppression of transmitter release.

Expression Mechanisms

The molecular mechanisms of eCB-LTD's expression and maintenance are just beginning to emerge. It was recognized early on that CB1R activation is necessary for induction but not during expression of eCB-LTD. Accordingly, washing in a CB1R antagonist after eCB-LTD is established fails to reverse plasticity in all synapses where this manipulation has been tested (20, 26, 75). Here we will discuss what processes downstream CB1R activation can explain the long-term reduction of transmitter release reported during eCB-LTD. Changes in the amount of transmitter release can result from modifications of the presynaptic action potential-induced Ca^{2+} influx and/or the downstream release machinery, as well as changes in excitability of the afferent axon.

Role of cAMP/PKA cascade in eCB-LTD

One of the most striking requirements distinguishing eCB-LTD induction from eCB-dependent short-term depression such as DSI/DSE is the extended duration of CB1R activity (several minutes) (3). This relatively long induction period suggests that CB1Rs may engage a different signaling process than the one mediating transient suppression of transmitter release. We have recently investigated this possibility in the hippocampus, where inhibitory synapses can undergo both short- and long-term eCB-mediated plasticity (DSI and I-LTD, respectively) (20). Here, a direct comparison of the expression mechanisms underlying these two forms of depression can be made at synapses impinging on the same target cell (19).

Compelling evidence indicates that the transient suppression of transmitter release occurring during DSI/DSE is mainly due to CB1R-dependent inhibition of presynaptic VDCCs (84-87), a process likely mediated by the $G_{\beta\gamma}$ subunits (84). The relatively fast decay of DSI (<1 min) likely reflects the transient profile of eCB production and CB1R engagement. We hypothesized that the increased time requirement for eCB-dependent I-LTD induction could reflect the recruitment of the $\alpha_{i/o}$ effector limb of the CB1R G protein signaling cascade, which inhibits the cAMP/Protein Kinase A (PKA) pathway (88, 89). Indeed, we found that inhibiting PKA activity with selective blockers, or raising cAMP levels by continuous activation of adenylyl cyclase, prevents I-LTD without affecting DSI (19). More recently, we reported that presynaptic phosphatase activity may complement the CB1R-dependent inhibition of PKA during eCB-LTD induction. Specifically, inhibiting the Ca^{2+}-activated phosphatase, calcineurin, fully blocked I-LTD, once again leaving DSI intact (78). In addition, postsynaptic blockade of PKA and calcineurin had no effect on either I-LTD or DSI, supporting the idea that these kinase and phosphatase activities occur presynaptically. Altogether these findings indicate that 1) the signaling pathways downstream CB1Rs that mediate transient vs. long- lasting depression of transmitter release differ, and 2) a CB1R-mediated reduction of cAMP/PKA activity underlies I-LTD.

The involvement of the cAMP/PKA pathway in eCB-LTD has also been reported in other brain structures. As in the hippocampus, inhibiting PKA or raising cAMP levels interfere with eCB-LTD at glutamatergic synapses in the nucleus accumbens (90). In addition,

protein kinase inhibitors reportedly prevent striatal eCB-LTD (91), although in this case, PKA may also be required postsynaptically for AEA production, as suggested for eCB-LTD in the amygdala (18). The cAMP/PKA cascade could also mediate the eCB-LTD recently reported at excitatory hippocampal synapses in neonatal rats (23). Thus, most evidence suggests that CB1R-dependent inhibition of the cAMP/PKA signaling pathway is a critical step in eCB-LTD at both excitatory and inhibitory synapses. Whether this pathway also mediates eCB-LTD in other brain areas remains to be tested; it is formally possible that other signaling pathways downstream CB1Rs could also participate.

eCB-LTD expressed by changes in the release machinery

Modulation of the cAMP/PKA pathway has been previously implicated in presynaptic forms of LTP and LTD (for a review, see 92). A common theme in these forms of plasticity is that their expression mechanism relies on changes in the transmitter release machinery (93-95). In particular, the active zone protein RIM1α, which is phosphorylated by PKA in vitro (94), is a demonstrated requirement for PKA-dependent LTP at several excitatory synapses, including the mossy fiber to CA3 pyramidal cell synapse (93), the parallel fiber to Purkinje cell synapse (93, 94), and the Schaffer collateral to CA1 pyramidal synapse (96). Using RIM1α knockout mice, we have recently found that I-LTD in the hippocampus and amygdala also requires RIM1α (19). In addition, the reduction of mIPSC frequency (but not amplitude) mediated by a CB1R agonist or a PKA blocker was markedly reduced in these mice, strongly suggesting that CB1Rs and PKA can target the release machinery in a RIM1α-dependent manner. Thus, changes in the release machinery via cAMP/PKA signaling and RIM1α may represent a general mechanism underlying presynaptic forms of long-term plasticity (LTP and LTD) at both excitatory and inhibitory synapses.

According to the PKA/RIM1α model of presynaptic plasticity a reduction of PKA activity (e.g. via CB1R activation) enables RIM1α dephosphorylation, which translates into depression of transmitter release. Conversely, increases in PKA activity and RIM1α phosphorylation lead to LTP (19, 93, 94, 97). A previous report suggested that phosphorylation of RIM1α at Serine 413 is necessary for presynaptic LTP in parallel fiber synapses formed in vitro by cultured cerebellar neurons (94). To test whether RIM1α phophorylation/dephosphorylation is indeed required for PKA-dependent forms of plasticity reported in acute brain slices, Thomas Südhof and co-workers have recently generated knock-in mice in which serine 413 is mutated to alanine. Surprisingly, mossy fiber LTP, cerebellar LTP, and hippocampal I-LTD, are all normal in these transgenic mice (98). These findings strongly suggest that although the RIM1α complex is essential for presynaptic long-term plasticity, PKA regulates this type of plasticity by a mechanism distinct from RIM1α phosphorylation at S413. Indeed, PKA-dependent modulation of transmitter release can occur as a result of the phosphorylation/desphosphorylation of several other presynaptic proteins involved in exocytosis (for a review, see 99). Future studies to identify the nature of such presynaptic protein(s) in PKA/RIM1α-dependent forms of plasticity, including eCB-LTD, are warranted.

eCB-LTD expressed by changes in voltage-dependent calcium channels

Manzoni and co-workers have recently reported that blockade of P/Q-type, but not L- or N-type VDCCs, occludes eCB-LTD at excitatory synapses in the nucleus accumbens (90). Previous work by this group showed that these synapses can undergo an mGluR2/3-dependent form of LTD that also depends on the cAMP/PKA pathway, and whose expression mechanism likely involves a selective reduction in the contribution of P/Q-type VDCCs to glutamate release (100). Importantly, mGluR2/3-dependent LTD and eCB-LTD mutually occlude, supporting the idea that both forms of plasticity could share a common mechanism (101). Together, these observations suggest that a PKA-dependent reduction of presynaptic Ca^{2+} influx via P/Q-type VDCCs could underlie both forms of LTD. The involvement of P/Q-type VDCCs in the expression of a presynaptic form of LTD has been previously demonstrated at mossy fiber synapses onto stratum lucidum interneurons in the hippocampus (102). Indeed, using two-photon Ca^{2+} imaging from anatomically defined mossy fiber terminals, Pelkey and co-workers (2006) have directly shown that expression of mGluR7-dependent LTD is due to a long-lasting reduction of presynaptic Ca^{2+} influx via P/Q-type VDCCs. Whether eCB-LTD in nucleus accumbens or other brain structures is also associated with a long-term reduction of presynaptic Ca^{2+} signals has not been examined. Selective depression of P/Q-type VDCC function has also been reported in amphetamine-induced, CB1R-dependent LTD of excitatory synaptic transmission in the amygdala (103). Interestingly, this form of plasticity is accompanied by a change in the frequency, but not amplitude, of miniature EPSCs, suggesting a second (parallel) mechanism of expression downstream Ca^{2+} influx. Whether eCB-LTD at a given presynaptic terminal can express both RIM1α-dependent and P/Q-type VDCC-dependent mechanisms remains unknown.

eCB-LTD expressed by changes in presynaptic excitability

A third expression mechanism has been suggested by a recent study describing a heterosynaptic eCB-LTD of glutamatergic synaptic transmission in the developing CA1 area of the hippocampus (23). This form of eCB-LTD is associated with a decrease of fiber volley amplitude, suggesting a reduction of presynaptic excitability. Importantly, LTD of both synaptic transmission and fiber volley amplitude are mimicked by a CB1R agonist, and blocked by a CB1R antagonist. Moreover, depression of fiber volleys is impaired by K^+ channel blockers (23). These observations strongly suggest that heterosynaptic eCB-LTD at excitatory synapses in the immature hippocampus is likely due to a CB1R-dependent reduction of presynaptic excitability through activating K^+ channels at presynaptic fibers. It will be interesting to see whether a similar expression mechanism also underlies the heterosynaptic eCB-LTD recently reported at glutamatergic synapses in the immature visual cortex (29).

Developmental Regulation of eCB-LTD

The refinement of neural circuits during postnatal development is believed to involve activity-dependent changes in synaptic strength. Presumably paralleling the ongoing changes in pre- and postsynaptic properties, induction mechanisms of synaptic plasticity adjust over development. Consistent with this notion, several recent studies have shown that eCB-LTD can be developmentally regulated. From a mechanistic perspective, regulation of

eCB-LTD likely reflects developmental changes in eCB signaling (e.g. eCB production/degradation, CB1R number/function). For example, the probability that high frequency stimulation induces striatal LTD increases in brain slices from rats during the third and fourth postnatal week (104), a change that has been associated with a developmental increase in AEA levels in striatal tissue (51). In the hippocampus, the magnitude of eCB-mediated I-LTD is reportedly greater in adolescent rats (postnatal day 28-35) than in adults (postnatal day 75-110), in tandem with the reduced ability of a CB1R agonist to suppress inhibitory neurotransmission (22). It is unclear whether this developmental regulation reflects differences in CB1R number and/or function at GABAergic terminals, although binding studies have reported maximal CB1R expression levels on postnatal day 30-40 (105).

As described above, glutamatergic synapses in the immature hippocampus (postnatal day 2-10) can express a form of heterosynaptic eCB-LTD, reportedly due to a reduction of presynaptic excitability (23). This form of plasticity becomes less prominent during development and it cannot be induced in the mature hippocampus. At present, the mechanism of this developmental change is unknown. Similar heterosynaptic eCB-LTD has been recently shown in the immature visual cortex (29). High frequency stimulation of excitatory inputs to L2/3 neurons induces heterosynaptic eCB-LTD in most mice at postnatal day 7–20 but not at postnatal day 35–41. Interestingly, brain-derived neurotrophic factor (BDNF), which may be released from strongly activated presynaptic sites, appears to prevent the induction of homosynaptic eCB-LTD. Presumably, an interaction between the CB1R and TrkB (the high-affinity receptors for BDNF) at active presynaptic terminals leads to the blockade of CB1R signaling. A developmental upregulation of BDNF expression, diffusion of BDNF in cortical tissues, and a concomitant reduction in CB1R expression, have been proposed as potential mechanisms underlying the developmental regulation of heterosynaptic eCB-LTD in visual cortex (29).

Developmental changes in any of the major pre- and postsynaptic determinants of eCB-LTD could regulate this form of plasticity. A developmental loss of presynaptic NMDARs has been reported in visual cortex, occurring abruptly at the onset of the critical period for receptive field plasticity (>P23 in rats) (76). During the peak of the critical period for ocular dominance (P23-30), t-LTD in L2/3 of visual cortex requires activation of postsynaptic NMDARs (76). Given that most studies on eCB-dependent t-LTD in neocortex have been performed in young rodents, and show a requirement fo presynaptic NMDARs, future studies will be necessary to determine whether older animals retain this form of plasticity.

eCB-LTD Metaplasticity

Metaplasticity, the plasticity of synaptic plasticity, refers to an enduring change in the ability of neurons or synapses to generate synaptic plasticity (for a recent review, see 106). eCBs are known to mediate metaplasticity by triggering long-term suppression of inhibitory transmission (i.e. I-LTD) and facilitating subsequent induction of LTP at excitatory inputs (18, 37). Recent work suggests that eCB signaling itself can be subject to metaplasticity. Indeed, repetitive stimulation in CA1 produces a long-term up-regulation of eCB signaling as indicated by an enduring enhancement of the magnitude of DSI (24, 107). In one study,

DSI potentiation could be triggered by low-frequency stimulation (LFS) (24), whereas in another study induction required strong HFS, as well as the co-activation of mGluRs, AMPA/kainate receptors, and CB1Rs (107). While the mechanism underlying DSI potentiation induced by LFS has not been explored, an up-regulation of CB1R number likely mediates eCB plasticity induced by strong HFS (107). This mechanism has previously been implicated in the DSI potentiation that occurs following febrile seizures in rats (108). A subsequent study by Alger and co-workers has shown that the long-lasting potentiation of DSI can be triggered by brief activation of mGluR-I (25). This study showed that the transient postsynaptic Ca^{2+} rise that occurs by a single episode of DSI can facilitate subsequent mGluR-I-dependent mobilization of eCBs and the induction of I-LTD (25). The Ca^{2+}-dependent process that causes this remarkable form of metaplasticity is unknown. In summary, these examples underscore that eCB signaling, and as a result eCB-mediated plasticity, can be dynamically regulated. Because some induction protocols can trigger simultaneous LTP and LTD, regulation of eCB signaling can be important in modulating the balance between the two.

Functional Relevance of eCB-LTD

Reflecting the widespread distribution of the CB1R in the CNS (12, 13), exogenous ligands for CB1R impact a broad range of CNS functions, ranging from homeostatic control of feeding to associative memory formation; some of these CB1R ligands have also been associated with neuropsychiatric disorders. However, ascribing specific roles for eCB-LTD in these behaviors has been challenging. Here we will discuss the most promising avenues of investigation linking eCBs and eCB-LTD to normal and pathological physiology.

Sensory deprivation

LTD is a leading model to explain the synaptic weakening that occurs at cortical synapses after a period of sensory deprivation (109-111), but see (112, 113). Studies in both somatosensory and visual cortices have revealed that this LTD-like phenomenon mechanistically resembles eCB-LTD reported in vitro. Feldman and co-workers have recently shown that whisker removal weakens L4-L2/3 synapses in rat barrel cortex by decreasing presynaptic function (114), mirroring the expression mechanism of eCB-t-LTD described at these synapses (31) (see above). Similarly, monocular deprivation (MD) depresses visually evoked responses within multiple layers of visual cortex (115, 116). Bear and co-workers found that a previously described LTD at L4-L2/3 synapses in vitro (117), thought to contribute to this MD-induced synaptic depression, is CB1R dependent (28). Most notably, in brain slices prepared after whisker deprivation or MD, eCB-t-LTD is abolished, suggesting that sensory deprivation may have occluded eCB-t-LTD and therefore may share a common mechanism (28, 114).

Data from genetic and pharmacological interference with CB1Rs support a role for eCB-LTD in sensory-driven cortical plasticity. Anatomical analysis of the barrel cortex in CB1-/- mice revealed abnormal barrel maps (118). During a brief period of MD, systemic application of the CB1R antagonist AM251 fully prevented the depression of inputs to L2/3 of visual cortex in vivo, the same area which expresses eCB-LTD (28, 119). Whether eCB-t-LTD causally drives the loss of cortical responses to deprived sensory inputs remains to be

determined. In addition, short-term plasticity mediated by eCBs, such as DSI/DSE (120, 121), could also contribute to these forms of cortical plasticity.

Associative learning

Long-term changes in synaptic strength are also believed to underlie associative memory formation in hippocampus and amygdala (122). The first studies to show a role for the eCB/CB1R system in hippocampus and amygdala-specific learning tasks (the Morris Water Maze and cued fear conditioning, respectively) used CB1-/- mice or systemically applied CB1R antagonists (17, 123). These and subsequent studies found that eCBs and CB1Rs were specifically required for extinguishing an established fear or spatial memory, but were not needed to acquire these types of memories (17, 123-126). In addition, FAAH inhibitors, which enhance eCB signaling, facilitated extinction of cue-shock associations as well as memories of a hidden platform's former position in the Morris Water Maze (126, 127). While these findings may point to an underlying involvement of eCB-LTD, a number of eCB-mediated effects on synaptic transmission have been noted in these two main structures. eCB-LTD has been described at inhibitory synapses in CA1 and basolateral amygdala (17, 20), and, in developing hippocampus, at excitatory synapses (23). Hippocampal synapses also express DSI and DSE (1, 3). In addition, in both hippocampus and amygdala, eCB-LTD also modulates excitability and the induction of LTP at excitatory synapses, a process widely thought to underlie memory acquisition (18, 20, 37). Marsicano and colleagues have developed a promising strategy to address the contribution of CB1Rs at excitatory and inhibitory terminals in the context of epilepsy, generating a line of transgenic mice with selective deletions of the CB1R in either forebrain GABAergic interneurons or in principal neurons (128). Identifying unique molecular determinants of eCB-LTD versus DSI/DSE will further aid in resolving these issues.

Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disorder characterized by hallmark motor symptoms such as rigidity, bradykinesia and akinesia, as well as the progressive loss of the dopaminergic neurons in the substantia nigra pars compacta. In addition to dopamine depletion, PD is also thought to involve a reactive increase in corticostriatal excitatory drive in the basal ganglia via the indirect (striatopallidal) pathway, a circuit identified by MSNs exclusively expressing the D_2R rather than D_1R (129). Accordingly, strategies to treat these symptoms are aimed not only at replacing the missing dopamine, but also at reducing transmission through the indirect pathway. As a D_2R-dependent mechanism which suppresses corticostriatial transmission (4, 39, 50, 130), striatal eCB-LTD is a potential therapeutic target in PD. In fact, a recent study has shown that in vivo administration of the FAAH inhibitor URB597, reduces parkinsonian motor deficits in dopamine depleted animal models of PD, but only when administered together with a D_2R agonist, which presumably triggers eCB release (43, 50). A direct demonstration that this effect is mediated by eCBs awaits confirmation. Interestingly, striatal eCB-LTD was also abolished in these animal models, but rescued in the presence of URB597 or the D2R agonist quinpirole (50). Motor abnormalities observed in animal models of PD can also be corrected by treatment with an mGluR5 antagonist (131). Interestingly, MSNs express high levels of mGluR5 (but not mGluR1) (68), whose activation can mobilize eCB release (42) and trigger “chemical” eCB-

LTD at striatopallidal MSNs (50). Together, these studies suggest that a reduction of eCB production, particularly in the indirect pathway, could be an important mechanism contributing to the pathophysiology of PD, presumably by eliminating eCB-LTD. Therefore, manipulations of this pathway by modulating eCB production may provide an alternative approach for the treatment of striatal-based brain disorders, such as PD.

Drug Addiction

Like PD, drug addiction is a robust behavioral phenomenon particularly amenable to analysis in animals, as its major pathological features are reproducible across species. The rewarding properties of exogenous cannabinoids are well known (132, 133). However, the process of addiction not only involves the acute, rewarding effects of a drug, but may also involve long term neural adaptations induced by the drug of abuse (134, 135). These adaptations are thought to include changes of synaptic strength, especially in the VTA, a midbrain area densely populated by dopaminergic neurons, and the NAc, which receives prominent projections from the VTA (136-138). At least one such behavioral adaptation, sensitization to the rewarding properties of cocaine, is known to require eCBs and CB1Rs, based on experiments with CB1R antagonists and CB1R-/- mice (recently reviewed in 139). In addition, eCB-LTD in both VTA and NAc can be modulated by in vivo exposure to drugs of abuse, including cocaine (34, 140-142). Repetitive cocaine exposure in vivo fully occludes eCB-LTD at GABAergic synapses in VTA (34). This reduced GABAergic inhibition has been linked to a facilitation of LTP at nearby excitatory synapses in VTA (143), believed to be critical for inducing behavioral sensitization (136). A similar process has been described in NAc, where a single dose of cocaine abolishes eCB-LTD at excitatory synapses (140), however, diminished mGluR5-driven eCB release appears to account for that effect, rather than true occlusion of eCB-LTD at the presynaptic terminal. The role of the eCB/CB1R signaling system in addiction appears to vary depending on the specific drug of abuse (139), indicating a need to examine the interaction of other drugs of abuse with eCB-LTD in these critical brain areas.

Future Directions and Concluding Remarks

eCBs are now well established as mediators of synaptic plasticity. Extensive work demonstrates that eCB-LTD is a widespread phenomenon in the brain expressed by both excitatory and inhibitory synapses. As the list of synapses expressing eCB-LTD increases, so does our understanding of the induction/expression mechanisms and computational power of this form of plasticity. eCBs also mediate short-term plasticity and, by regulating inhibitory transmission, they can also modulate the induction of eCB-independent forms of plasticity such as LTP (3). All these actions combined clearly highlight the unique position of eCBs as regulators of synaptic function.

In addition to eCB-LTD, eCBs have been implicated in other forms of long-term plasticity. For example, in the cerebellum, Safo & Regehr found that a well studied form of postsynaptically expressed LTD between parallel fibers and Purkinje cells depends on retrograde release of 2-AG and activation of presynaptic CB1Rs (144). The authors suggest that a second (anterograde) signal is interposed between terminals bearing the CB1R and the Purkinje cell, where LTD is ultimately expressed. Interestingly, a similar situation has been

observed in the VIIIth nerve to Mauthner cell mixed (electrical and chemical) synapse in goldfish (145), where presynaptic CB1Rs stimulate dopamine release from immunocytochemically identified dopaminergic terminals, triggering a postsynaptic LTP of both electrical and chemical neurotransmission. This CB1R-dependent regulation of a second neuromodulator might also account for an eCB-dependent LTP of excitatory transmission described in lamprey spinal cord (146). These cases possibly represent a novel class of eCB-mediated plasticity; however, they also join an existing literature where eCB-dependent processes modulate an otherwise eCB-independent form of plasticity (3). Here, the familiar retrograde eCB-CB1R signaling system forms a component of a more complex induction process. The most striking departure from eCB-LTD is the novel functional role for CB1Rs, which, rather than suppressing neurotransmitter release, stimulate release of a key factor for inducing synaptic plasticity. Other novel roles for CB1R in long-term plasticity may come to light, given evidence of functional CB1Rs at postsynaptic sites in neocortex (147).

Although protein synthesis is a known requirement in some forms of LTD (148, 149), thus far, only one study has directly examined the contribution of protein synthesis in eCB-LTD. Yin et al. (2006) found that inhibition of protein translation, but not transcription, prevents striatal eCB-LTD, implicating new protein synthesis in this form of plasticity (150). The authors provide evidence that rapid protein translation, likely occurring at the presynaptic axon/terminal, is critical for the expression of striatal LTD. Future studies will have to determine whether presynaptic protein translation is a general requirement for the maintenance of eCB-LTD in other brain structures. It will also be important to identify the presynaptic signaling pathways (e.g. Ca^{2+}, PKA) that promote local protein synthesis, as well as the nature of the newly-synthesized protein(s) required for the long-lasting reduction in transmitter release.

Recent progress in eCB signaling and eCB-mediated synaptic plasticity provides new targets for developing experimental tools and potential therapies for neuropsychiatric disorders. The existing literature on eCB and synaptic plasticity raises several important questions, as well. For example, it is unclear how long eCB-LTD can persist. No study has yet addressed whether structural alterations of the synapse and active zone accompany eCB-LTD in the maintenance phase. The reversal of eCB-LTD is another critically underexamined issue, which has been extensively explored in other forms of plasticity. In the laboratory, induction paradigms are commonly selected based on their effectiveness rather than their physiological significance. Further research will have to determine whether the two induction paradigms commonly used to trigger eCB-LTD can occur in vivo. Of equal importance will be elucidating the functional and computational roles of eCB-LTD. Given the widespread importance of the eCB-CB1R signaling pathway in both synaptic physiology and behavior we predict tremendous interest in this field in the coming years.

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Acronyms

2-AG	2-arachidonylglycerol
AEA	Anandamide
eCB	Endocannabinoid
LTD/LTP	Long-term depression/potentiation
EPSC/IPSC	Excitatory/Inhibitory Postsynaptic Current
HFS	High-frequency stimulation (∼100Hz)
LFS	Low-frequency stimulation (∼1Hz)
t-LTD	LTD induced by spike-timing dependent protocols
I-LTD	Long-term depression at inhibitory synapses
STDP	Spike timing-dependent plasticity

Summary Points

1. Endogenous cannabinoids (eCBs) can have a long-term impact in neural function by mediating eCB-LTD. This form of plasticity has now been observed in several brain structures at both excitatory and inhibitory synapses.
2. Despite the variety of stimulation protocols and experimental conditions used for its induction, nearly every synapse studied still expresses eCB-LTD as a long lasting reduction of neurotransmitter release. eCB-LTD is by now one of the best examples of presynaptic forms of long-term plasticity
3. The emerging molecular details of induction and expression of eCB-LTD at various synapses reveal many points of regulation. Important determinants of eCB-LTD induction are the enzymes involved in eCB synthesis, degradation, and (perhaps) release, as well as the cAMP/PKA signaling pathway downstream CB1Rs.
4. CB1R activation per se is not sufficient for eCB-LTD induction at a number of synapses. Rather, the presynaptic terminal seems to integrate multiple signals to generate eCB-LTD. At several synapses, presynaptic regulatory mechanisms of eCB-LTD induction translate into key computational properties, such as synapse specificity and associativity.

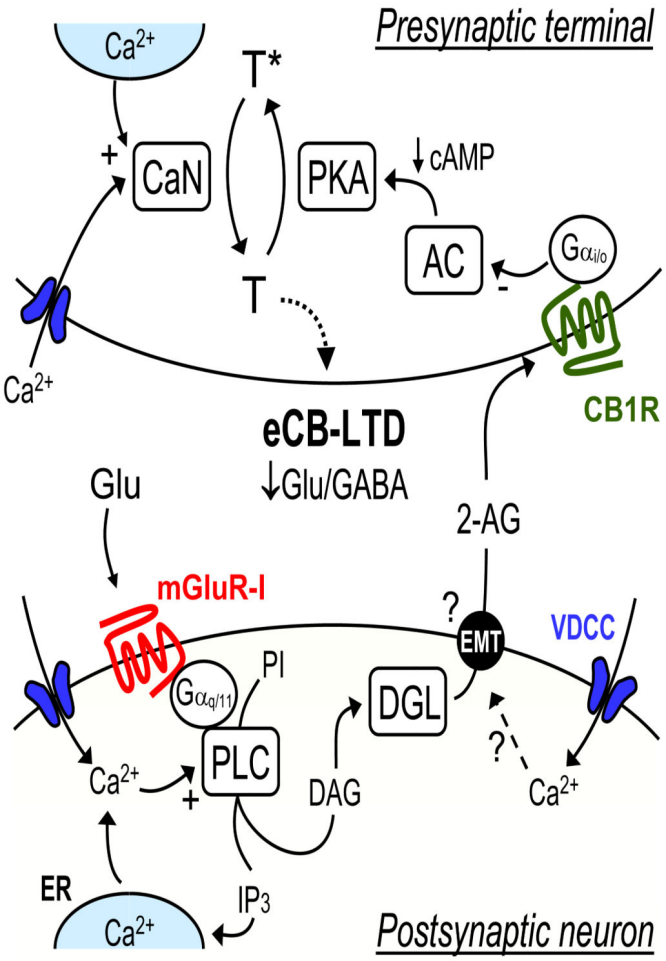

Figure 1. Schematic summary of the eCB-LTD induction mechanism

One of the most common initial steps of induction is the activation of postsynaptic group I metabotropic glutamate receptors (mGluR-I), following repetitive activation of excitatory inputs. These receptors couple to Phopholipase C (PLC) via $G\alpha_{q/11}$ subunits and promote diacylglycerol (DAG) formation (from Phosphatdylinositol, PI), which is then converted into the eCB 2-arachidonoylglycerol (2-AG) by Diacylglycerol Lipase (DGL). 2-AG is then released from the postsynaptic neuron by a mechanism that presumably requires an eCB membrane transporter (EMT), and binds presynaptic CB1Rs. Postsynaptic Ca^{2+} can contribute to eCB mobilization either by stimulating PLC, or in a PLC-independent, uncharacterized manner. This Ca^{2+} rise can be through voltage-dependent Ca2+channels (VDCC) actived by action potentials (e.g. during spike timing-dependent protocols), NMDARs, or released from the Endoplasmic Reticulum (ER), e.g. by the PLC product, inositol 1,4,5-trisposphate (IP3). In some synapses, induction of eCB-LTD by “afferent-only” stimulation protocols can occur independently of postsynaptic Ca2+. At the presynaptic terminal, the CB1R inhibits adenylyl cyclase (AC) via $G\alpha_{i/o}$, reducing PKA activity. Induction of eCB-LTD may also require a presynaptic Ca^{2+} rise through presynaptic VDCCs, NMDARs (not shown) or release from Ca^{2+} internal stores. Activation of the Ca^{2+}-sensitive phosphatase calcineurin (CaN), in conjunction with the reduction in PKA activity, shifts the kinase/phosphatase activity balance, thereby promoting

dephosphorylation of a presynaptic target (T) that mediates a long-lasting reduction of transmitter release. For clarity, eCB-LTD mediated by AEA is not shown.

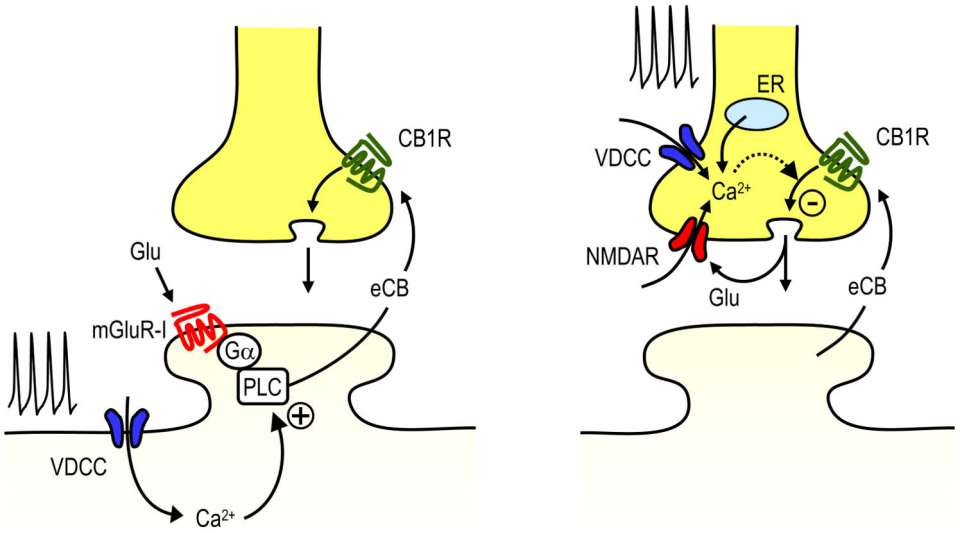

Figure 2. Potential mechanisms of associativity involved in eCB-LTD induction

Postsynaptic compartment (left): the postsynaptic neuron can integrate action potential firing (which promotes Ca^{2+} rise via VDCCs) and synaptic release of glutamate (which activates mGluR-I) to facilitate eCB mobilization and eCB-LTD induction. Other Ca^{2+} sources (e.g. NMDARs and Ca^{2+} internal stores) could also contribute. In this model, PLC operates as a coincidence detector (61). Presynaptic compartment (right): the presynaptic terminal can also integrate two signals, eCBs (which activate presynaptic CB1Rs) and presynaptic firing (which promotes a Ca^{2+} rise via VDCCs and NMDARs). Ca^{2+} stores (endoplasmic reticulum, ER) may also contribute to this process. The presynaptic NMDAR may operate as a coincidence detector during a brief time window (26). In addition, the activity-dependent Ca^{2+} rise that occurs during minutes of CB1R activation likely promotes dephosphorylation of a presynaptic target downstream of the CB1R, the latter of which is an essential step for eCB-LTD induction (78).

Table I

eCB-LTD is a widespread phenomenon the brain

Examples of eCB-LTD confirmed using CB1R antagonists, CB1R knockout mice or both. STDP, spike timing-dependent plasticity; HFS, high-frequency stimulation (100 Hz); LFS, low-frequency stimulation (1 Hz).

Brain Structure	Synapse	Induction protocol	References
Neocortex			
Visual	*Excitatory* inputs, L5 pyramidal cell-pairs	STDP (postsynaptic bursts) STDP and LFS	(26, 27) (28)
	Excitatory inputs, L4 → L2/3 pyramidal neurons (immature visual cortex)	TBS	(29)
Somatosensory (barrel cortex)	*Excitatory* inputs to L2/3 pyramidal neurons	STDP (postsynaptic bursts)	(30, 31)
Prefrontal	L2/3 → L5/6	Moderate 10 Hz stimulation for 10 min	(32)
Hippocampus	*Inhibitory* inputs to CA1 pyramidal cells	HFS, TBS	(20-22, 24, 25)
	Excitatory inputs to CA1 pyramidal cells (immature hippocampus)	HFS	(23)
Amygdala	*Inhibitory* inputs to basolateral amygdala	LFS	(17-19)
Dorsal Striatum	*Excitatory* inputs to medium spiny neurons	LFS, STDP	(15, 39, 49, 50)
Nucleus Accumbens	*Excitatory* inputs to medium spiny neurons	Moderate 13 Hz stimulation for 10 min	(16, 142)
Cerebellum	*Excitatory* inputs to Stellate Interneurons	4 bouts of 25 stimuli at 30 Hz, delivered at 0.33 Hz	(33)
Ventral Tegmental Area (VTA)	*Inhibitory* inputs to dopamine neurons	Moderate 10 Hz stimulation for 5 min	(34)
Dorsal Cochlear Nucleus	*Excitatory* inputs to Cartwheel cells	STDP	(35)
Superior Colliculus	*Inhibitory* inputs to tectal neurons in vitro	HFS	(36)