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Invited review

Synaptic functions of endocannabinoid signaling in health and disease

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ABSTRACT

Endocannabinoids (eCBs) are a family of lipid molecules that act as key regulators of synaptic transmission and plasticity. They are synthetized "on demand" following physiological and/or pathological stimuli. Once released from postsynaptic neurons, eCBs typically act as retrograde messengers to activate presynaptic type 1 cannabinoid receptors (CB_1) and induce short- or long-term depression of neurotransmitter release. Besides this canonical mechanism of action, recent findings have revealed a number of less conventional mechanisms by which eCBs regulate neural activity and synaptic function, suggesting that eCB-mediated plasticity is mechanistically more diverse than anticipated. These mechanisms include non-retrograde signaling, signaling via astrocytes, participation in long-term potentiation, and the involvement of mitochondrial CB_1. Focusing on paradigmatic brain areas, such as hippocampus, striatum, and neocortex, we review typical and novel signaling mechanisms, and discuss the functional implications in normal brain function and brain diseases. In summary, eCB signaling may lead to different forms of synaptic plasticity through activation of a plethora of mechanisms, which provide further complexity to the functional consequences of eCB signaling.

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Contents

1. Introduction

Synaptic plasticity is critical to experience-dependent adaptations of neural circuits and normal brain function. From early

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development to adulthood, changes of synaptic function in response to environmental stimuli and individual experiences are necessary to learn new abilities, form new memories and generate new adaptive behaviors. Key mediators of synaptic plasticity, the endocannabinoids (eCBs) constitute a family of lipid molecules that are typically synthetized "on demand", following either physiological and/or pathological stimuli (Castillo et al., 2012; Kano et al., 2009; Katona and Freund, 2012) (Fig. 1). The eCB signaling system comprises (1) two G protein-coupled receptors (GPCRs), known as the cannabinoid type 1 and type 2 receptors (CB_1 and CB_2); (2) one receptor channel, the transient receptor potential vanilloid type 1 (TRPV1); (3) the endogenous ligands (eCBs), of which 2-arachidonoylglycerol (2-AG) and anandamide (AEA) are the best characterized; and (4) synthetic and degradative enzymes and transporters that regulate eCB levels (Piomelli, 2003). 2-AG originates from the metabolism of triacylglycerols by the activity of diacylglycerol (DAG) lipase in response to activation of metabotropic receptors coupled to the PLCβ (e.g. group I metabotropic glutamate receptor-mGluR1/5, muscarinic acetylcoline-mAChtypes M1/M3). The biosynthesis of AEA from the precursor *N*-arachidonoyl-phosphatidylethanolamine (NAPE) requires intracellular Ca^{2+} elevations upon depolarization and/or activation of ionotropic receptors, and the activity of the enzyme NAPE-PLD. Once released from the postsynaptic neurons, eCBs act primarily as retrograde messengers by activating presynaptic CB_1 receptors, one of the most abundant $G_{i/o}$ protein-coupled receptor in the brain. CB_1 activation decreases the probability of neurotransmitter release by diverse mechanisms, including presynaptic inhibition of Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCCs), activation of presynaptic K^+ channels and cAMP/PKA signaling (Castillo et al., 2012; Kano et al., 2009). Termination of synaptic eCB signaling is initiated by re-uptake followed by intracellular degradation. 2AG is degraded by the presynaptic enzyme monoacylglycerol lipase (MAGL) and α/β-Hydrolase domain-containing 6 (ABHD6) (Dinh et al., 2002; Marrs et al., 2010), whereas AEA from the fatty acid amide hydrolase (FAAH) (Ahn et al., 2008; Di Marzo, 2009). There is also evidence that both 2-AG and AEA can act in a non-retrograde manner (Castillo et al., 2012), 2-AG by activating postsynaptic CB_1 or CB_2, and AEA by activating TRPV1.

Furthermore, eCBs released by neurons can modulate presynaptic and postsynaptic circuit elements through the activation of CB_1 expressed on astrocytes (Metna-Laurent and Marsicano, 2015; Navarrete et al., 2014). Regulation of synaptic transmission that follows eCB mobilization occurs both on a short and long timescale. eCB-mediated short-term changes in synaptic transmission (tens of seconds) encompass depolarization-induced suppression of excitation (DSE) and inhibition (DSI) depending on whether eCBs target glutamatergic or GABAergic terminals (Castillo et al., 2012; Kano et al., 2009). Long-term synaptic changes (minute to hour) that depend upon eCB signaling can occur in response to diverse patterns of presynaptic and/or postsynaptic activity. Thus, eCBs are powerful regulators of synaptic function through the brain. By modulating both excitatory and inhibitory synaptic strength, eCBs can regulate a number of brain functions, including cognition,

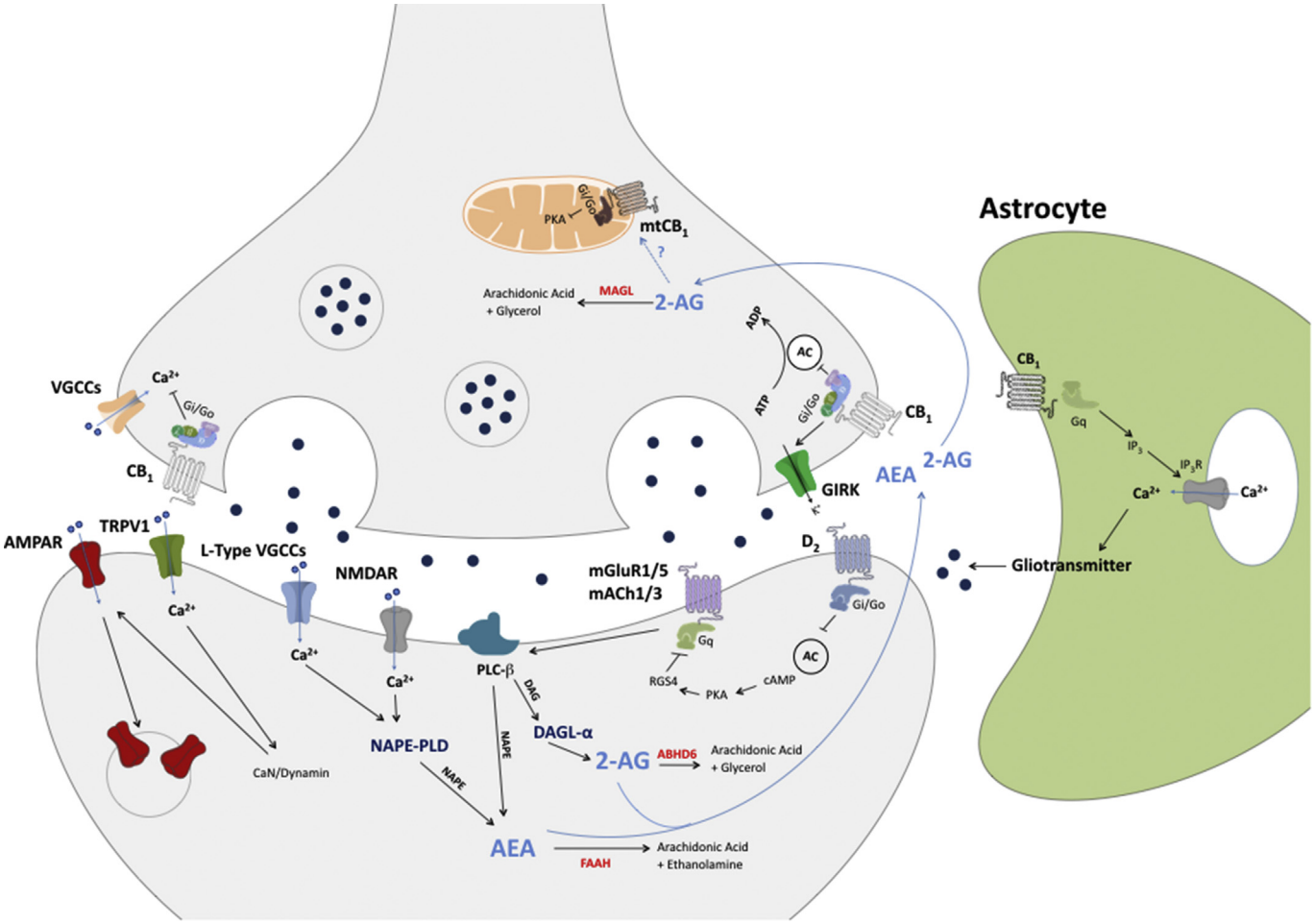

Fig. 1. Schematic of eCB signaling at the synapse.

motor control, emotion, reward and feeding behaviors. Dysregulation of the eCB system has been implicated in neuropsychiatric conditions, such as depression, autism, schizophrenia, addiction, stress and anxiety (Hillard et al., 2012; Mechoulam and Parker, 2013; Parsons and Hurd, 2015; Volkow et al., 2017). Here, we will discuss recent advances on eCB signaling and synaptic function, emphasizing brain areas where eCBs are thought to regulate learning-, motor- and reward-guided behaviors both in health and disease.

2. eCB signaling at hippocampal and neocortical synapses

eCBs modulate synaptic function primarily through their effects on presynaptically expressed CB_1 receptors in both GABAergic and glutamatergic terminals (Castillo et al., 2012; Kano et al., 2009). In the hippocampus, where CB_1 receptors are predominantly expressed at inhibitory terminals (Freund et al., 2003), eCBs exert a profound effect on inhibition by reducing GABA release in a transient (Wilson and Nicoll, 2001) or long-lasting manner by triggering long-term depression (LTD) of inhibition (iLTD) (Chevaleyre and Castillo, 2003) (for a review, see Younts and Castillo, 2014). Disinhibition can robustly shift the excitatory-inhibitory balance in a network and by this means contribute to associative learning (Letzkus et al., 2015). By reducing inhibition, eCBs facilitate the induction of excitatory long-term potentiation (LTP) at Schaffer collateral (SC) to CA1 pyramidal cell synapse (SC-CA1) (Carlson et al., 2002; Chevaleyre and Castillo, 2004). Changes in the inducibility of LTP, a phenomenon known as metaplasticity, could play an important role in learning and memory. Remarkably, eCB-dependent metaplasticity initially described in vitro (Chevaleyre and Castillo, 2004) has recently been reported *in vivo* and could contribute to the formation of temporal associative memories (Xu et al., 2014). In addition, eCB-iLTD is involved the potentiation of excitatory postsynaptic potential (EPSP)-spike coupling (E-S coupling) (Chevaleyre and Castillo, 2003). Intriguingly, exogenous application of β−amyloid peptide ($A\beta_{1\text{-}42}$), whose accumulation occurs in Alzheimer's disease, prevents eCB-mediated disinhibition and subsequent E-S coupling potentiation presumably by interfering with CB_1 signaling (Orr et al., 2014). Although the downstream targets remain to be elucidated, this action of Aβ on eCB signaling represents a mechanism that could underlie the cognitive decline in Alzheimer's disease.

While eCB-mediated short-term plasticity (i.e. DSI/DSE) relies on the CB_1-mediated inhibition of presynaptic calcium influx through voltage-gated calcium channels (Kano et al., 2009) (Fig. 1), how CB_1 activation leads to long-lasting suppression of transmitter release (i.e. eCB-LTD) is poorly understood (Castillo et al., 2012). Several effectors downstream CB_1 have been identified, including PKA signaling, the active zone protein RIM1α, and voltage-gated calcium channels, although alternative downstream CB_1 signaling cascades (Njoo et al., 2015; Roland et al., 2014) leading to structural changes could also be involved. A recent study demonstrated that activation of CB_1 receptors stimulates protein synthesis in axon terminals to induce eCB-iLTD in the hippocampus (Younts et al., 2016). In addition, CB_1 activation enhances protein translation via mTOR signaling. Moreover, using super-resolution stochastic optical reconstruction microscopy (STORM), this study provided evidence that eukaryotic ribosomal proteins are present in CB_1-expressing presynaptic terminals. Newly synthesized proteins may act as a molecular switch to persistently reduce GABA release. Previous work demonstrated a requirement for protein synthesis in striatal eCB-LTD (Adermark et al., 2009; Yin et al., 2006), but not in the nucleus accumbens (Jung et al., 2012). Future work will have to determine the identity of the newly synthesized proteins and how exactly these proteins reduce transmitter release in a long-lasting manner.

In the entorhinal cortex-hippocampus circuit, eCB signaling has been implicated in input-timing-dependent plasticity (Basu et al., 2013; Xu et al., 2012), a form of heterosynaptic plasticity at SC-CA1 synapses that is induced by pairing SC and perforant path (PP) inputs from the entorhinal cortex (EC) (Dudman et al., 2007). This plasticity involves both eCB-iLTD from cholecystokinin (CCK)-positive (CB_1-containing) interneuron and SC-CA1 LTP (Basu et al., 2013). Input-timing-dependent plasticity requires precise timing of both SC inputs onto CCK interneurons and PP inputs to postsynaptic CA1 pyramidal cells. Presynaptic eCB-iLTD of feedforward inhibition in CCK interneurons may enable activation of CA1 pyramidal cells to facilitate information salience.

It is well established that in the rodent neocortex eCBs mediate spike timing-dependent LTD (t-LTD) at excitatory synapses, which is typically induced by pairing induction protocols (i.e. postsynaptic firing precedes presynaptic firing) (Caporale and Dan, 2008; Heifets and Castillo, 2009). In the mouse hippocampus, eCB-mediated t-LTD has also been reported at glutamatergic inputs onto principal cells (e.g. SC-CA1 synapses) and interneurons (Andrade-Talavera et al., 2016; Peterfi et al., 2012). Intriguingly, using similar induction protocols, as well as other protocols that typically induce robust eCB-LTD at inhibitory synapses (including chemical induction with CB_1 or mGluR agonists), other studies were unable to induce eCB-LTD at SC-CA1 synapses (Rouach and Nicoll, 2003; Younts et al., 2013), or even at the glutamatergic mossy cell to dentate granule cell synapse (Chiu and Castillo, 2008), which expresses uniquely high levels of presynaptic CB_1 (Katona et al., 2006; Uchigashima et al., 2011). This discrepancy could be due to slightly different experimental conditions used by these studies.

Besides the classical retrograde eCB signaling, there is growing evidence that eCBs can signal in a non-retrograde manner. An early study in neocortex demonstrated that repetitive activation of a subtype of GABAergic interneuron triggers a CB_1-dependent postsynaptic hyperpolarization, which reduced its excitability (Bacci et al., 2004). This slow self-inhibition resulted from activity-dependent rises in intracellular Ca^{2+}, mobilization of 2-AG, and activation of CB_1 that couple to a G protein-coupled inwardly rectifying K^+ channel. Recent evidence indicates that CB_2 can mediate a similar form of self-inhibition both in the hippocampus and neocortex (see below). A provocative recent report has suggested that 2-AG activation of CB_1 receptors in dendrites modulates the h-current (I_h), a key regulator of dendritic excitability, in a subset of CA1 pyramidal neurons, i.e. superficial but not deep neurons (Maroso et al., 2016). Activation of this CB_1-I_h pathway, which involves a non-canonical signaling cascade, impairs integration of excitatory synaptic inputs, LTP and spatial memory formation. AEA can also act in a non-retrograde manner by activating TRPV1 channels (Castillo et al., 2012). In the dentate gyrus, TRPV1 activation by AEA induces a postsynaptically expressed LTD of medial perforant path inputs onto dentate granule cells (Chavez et al., 2010). Here, activation of type 5 metabotropic glutamate receptors (mGluR5) by glutamate released during repetitive activity, presumably via PLC and Ca^{2+} release from intracellular stores, promotes the synthesis of AEA that activates TRPV1 channels. A mechanistically similar form of LTD was also reported in the nucleus accumbens (Grueter et al., 2010) and in the bed nucleus of the stria terminalis (Puente et al., 2011).

Recent studies indicate that eCBs can mediate LTP by unconventional mechanisms both in the hippocampus and neocortex. At SC-CA1 synapses, eCBs can trigger LTP of glutamate release through stimulation of astrocyte−neuron signaling (Gomez-Gonzalo et al., 2015) (see below). In the dentate gyrus in vitro, high frequency stimulation of lateral perforant path inputs (LPP) triggers a presynaptically expressed form of LTP whose induction requires

postsynaptic NMDAR and mGluR5-dependent calcium rise, 2-AG mobilization from the postsynaptic compartment and activation of presynaptic CB_1 receptors (Wang et al., 2016). How exactly CB_1 activation leads to a long-lasting increase of glutamate release is unclear but it could involve reorganization of the presynaptic actin cytoskeleton in LPP terminals. In the rodent barrel cortex in vitro, eCBs facilitate the induction of an NMDAR and Brain-Derived Neurotrophic Factor (BDNF)-dependent form LTP at excitatory inputs onto basal dendrites of layer 5 pyramidal neurons (Maglio et al., 2017). In this case, action potential bursts release eCBs, which by reducing inhibitory synaptic transmission, facilitate the generation of calcium spikes and calcium dependent release of BDNF, two critical requirements for the induction of this form of LTP. The notion that eCBs can trigger LTP is not novel, or exclusive to the hippocampus and neocortex. An early study in goldfish reported that eCBs release upon repetitive stimulation from the Mauthner cell lateral dendrite, activates CB_1 receptors located on nearby varicosities, which in turn evokes the release of dopamine that activates dopamine D1/D5 receptors to induce LTP of electrical and chemical transmission via a cAMP/PKA-mediated postsynaptic mechanism (Cachope et al., 2007). The mechanism by which CB_1 activation evokes the release of dopamine remains unknown. Lastly, eCB-dependent LTP has also been described in the dorsal striatum (see below).

Hippocampal astrocytes have been shown to express functional CB_1, which upon stimulation by eCBs elevate the intracellular calcium levels through calcium mobilization from the internal stores (Navarrete and Araque, 2008) (Fig. 1). The intracellular signaling cascade involved in this phenomenon has been shown to display certain peculiarities in astrocytes. While CB_1 are considered to be preferentially coupled to pertussis toxin (PTX)-sensitive $G_{i/o}$ proteins that reduce cAMP levels (Piomelli, 2003), CB_1-evoked calcium elevations in astrocytes are mediated by activation of $G_{q/11}$ proteins that stimulate phospholipase C-mediated IP_3 production and activation of IP_3Rs in the internal calcium stores (Navarrete and Araque, 2008). The eCB-evoked astrocyte calcium signal has been demonstrated in hippocampus (Gomez-Gonzalo et al., 2015; Navarrete and Araque, 2008, 2010), neocortex (Min and Nevian, 2012), dorsal striatum (Martin et al., 2015), as well as in cortical and hippocampal human brain tissue (Navarrete et al., 2013), suggesting that eCB signaling between neurons and astrocytes is a general mechanism.

Calcium elevations in astrocytes have been shown to stimulate the release of gliotransmitters which by acting on neuronal transmitter receptors, regulate synaptic transmission and plasticity (Araque et al., 2014). This functional interaction between astrocytes and neurons have led to the establishment of the tripartite synapse, a functional concept that encapsulates the existence of signaling between astrocytes and neurons and its crucial role in synaptic function (Araque et al., 1999; Perea et al., 2009). In the hippocampus, eCB release from pyramidal neurons activates astrocytes that release the gliotransmitter glutamate (Navarrete and Araque, 2008), which increases neuronal excitability by activating NMDARs and evoking slow inward currents in CA1 pyramidal neurons (Fellin et al., 2004; Navarrete and Araque, 2008; Parri et al., 2001; Perea and Araque, 2005), These results indicate that eCB signaling is involved in reciprocal astrocyte-communication. Remarkably, the glutamate released by astrocytes as a result of eCB release from one neuron may impact adjacent neurons, suggesting that astrocytes responding to eCBs act as a bridge for non-synaptic communication between neurons.

Astrocytic activation by eCBs and the consequent gliotransmitter release may have relevant regulatory consequences on synaptic transmission and plasticity. In contrast to the canonical eCB retrograde signaling between neuronal synaptic elements that leads to synaptic depression though activation of presynaptic CB1, eCB signaling in astrocytes have been shown to transiently potentiate synaptic transmission. This synaptic potentiation was originally reported at CA3-CA1 synapses in the hippocampus, where eCB-induced astrocytic release of glutamate activates presynaptic metabotropic glutamate receptors that enhance neurotransmitter release (Navarrete and Araque, 2010). Here, the eCB-induced astrocyte-mediated synaptic potentiation occurs in synapses contacting adjacent non-stimulated neurons relatively far away from the eCB source. Therefore, eCBs may have opposite and complementary regulatory effects, namely, canonical synaptic depression at local synapses, and synaptic potentiation at distant synapses through activation of astrocytes. The physiological meaning of the latter phenomenon, termed lateral synaptic regulation (Covelo and Araque, 2016), remains unknown, but it could serve a homeostatic mechanism of synaptic transmission to scale synaptic inputs. Indeed, active synapses would induce eCB release from the postsynaptic cell that would depress incoming inputs, while simultaneously enhance adjacent less active synapses through astrocytic activation, thus contributing to maintain a homogeneous level of activity in different synaptic inputs. Recently, lateral synaptic regulation has also been shown in DS (Martin et al., 2015) (see below), suggesting a general mechanism by which eCB signaling in astrocytes can regulate synaptic function.

In addition to the transient synaptic regulation described above, eCBs can mediate long-term synaptic plasticity through different mechanisms that involve CB_1 activation in astrocytes. Spike timing-dependent long-term depression (t-LTD) in hippocampal CA3-CA1 synapses has been demonstrated to be mediated by eCBs and to require astrocyte activation and the release of the gliotransmitter D-serine. The proposed mechanism involves D-serine release from astrocytes activated by eCBs, which allows the activation of presynaptic NMDARs by synaptically released glutamate, leading to the hippocampal t-LTD (Andrade-Talavera et al., 2016). A similar mechanism of t-LTD was identified in the neocortex, but rather than D-serine, glutamate was identified as the gliotransmitter involved in this brain area. eCBs released during t-LTD induction protocol elevates astrocytic calcium and stimulates the release of the astrocytic glutamate, which by activating presynaptic NMDA receptors induces the t-LTD (Min and Nevian, 2012). Additionally, using a different stimulation paradigm, it was shown that eCB-mediated release of glutamate from hippocampal astrocytes also leads to long-term plasticity (Gomez-Gonzalo et al., 2015). The coincidence of eCB signaling in astrocytes and postsynaptic activity triggers LTP of transmitter release at single CA3-CA1 synapses. Induction of this astrocyte-mediated LTP requires the concurrent activation of astrocytic and neuronal signaling cascades, including eCB-evoked astrocyte calcium signal that stimulates glutamate release, postsynaptic nitric oxide production, activation of presynaptic protein kinase C and group I metabotropic glutamate receptors. Taken together, these evidences indicate that astrocyte activation by eCBs lead to long-term changes in hippocampal synaptic strength.

Activation of CB_1 receptors in astrocytes, by regulating synaptic function, may have important consequences on animal behavior. Taking advantage of transgenic mice lacking CB1 selectively in astrocytes, it has been reported that CB_1 activation in hippocampal astrocytes likely mediates the impairment of spatial working memory and LTD at CA3-CA1 synapses induced by THC (Han et al., 2012).

In addition to the classical localization in the presynaptic plasma membrane (Freund et al., 2003), CB_1 receptors have also been reported in brain mitochondria, and activation of these receptors alters mitochondrial energetic activity (Benard et al., 2012) (Fig. 1). A follow-up study showed that disrupting the trafficking of CB_1 to

mitochondria in mouse hippocampal neurons prevents cannabinoid-induced suppression of excitatory synaptic transmission (e.g. SC-CA1), as well as memory impairment in a novel object recognition task (Hebert-Chatelain et al., 2016). Although eCB-mediated plasticity was not formally investigated in this study, the above observations suggest that mitochondrial CB_1 is primarily responsible for CB_1-mediated suppression of synaptic transmission, an intriguing scenario given that the majority of presynaptic CB_1 receptors —which are located in the plasma membrane— remained largely unchanged by removing mitochondrial CB_1 (Hebert-Chatelain et al., 2016). Future studies are necessary to determine the specific contribution of CB_1 receptors at the plasma membrane and at mitochondrial membranes.

An unexpected functional connection between eCBs and the synaptic cell-adhesion molecules neuroligin-3 and β-neurexins has recently been identified. Neuroligins are postsynaptic cell-adhesion molecules that interact with presynaptic neurexins. Rare mutations in neuroligins and neurexins predispose to autism, including a neuroligin-3 amino acid substitution (R451C) and a neuroligin-3 deletion. A study on the respective mouse models, a neuroligin-3 (R451C) knockin (KI) and a neuroligin-3 knockout (KO), showed an increase in GABA release probability at CB_1-expressing inhibitory synapses onto CA1 pyramidal cells, and this enhancement was due to impaired tonic but not phasic eCB signaling (Foldy et al., 2013). A similar enhancement mediated by impaired eCB-signaling was observed at cortical inhibitory synapses in the neuroligin-3 (R451C) KI mouse (Speed et al., 2015). Together, these studies suggest that disrupted eCB signaling may contribute to autism pathophysiology. Neuroligin-3 could be required to specifically localize the release machinery for tonic eCB release to CB_1-containing synapses. In another study that used β-neurexin-specific conditional KO mice, it has been reported that β-neurexins also decrease tonic eCB signaling presumably by suppressing 2-AG synthesis. Intriguingly, this action was observed at hippocampal excitatory but not inhibitory synapses. How exactly β-neurexin transsynaptically modifies 2-AG synthesis remains unsolved.

The eCB system comprises two G protein-coupled receptors, CB_1 and CB_2, which mediate almost all effects of exogenous and endogenous cannabinoids. The neuronal expression of CB_2 receptors has been a matter of debate. Although CB_2 receptors are typically found in the immune system and are poorly expressed in the CNS, there is growing evidence for a role of these receptors in the brain (den Boon et al., 2012; Xi et al., 2011). Using CB_2 KO mice and selective pharmacology, a recent study demonstrated that CB_2 receptors are expressed in hippocampal principal neurons and mediate a cell type-specific self-inhibitory plasticity in CA3 and CA2 pyramidal neurons by modulating the activity of the sodium-bicarbonate co-transporter (Stempel et al., 2016). This CB_2-mediated plasticity is induced by repetitive action potential firing that mobilizes 2-AG and is expressed as a long-lasting hyperpolarization that reduces spike probability and alter gamma oscillations *in vivo*. These findings are reminiscent of a previous study showing that CB_2 receptors mediate an activity-induced self-inhibition in medial prefrontal cortical pyramidal neurons, but in this case the receptors were localized to intracellular compartments and coupled to calcium-activated chloride channels (den Boon et al., 2012). Collectively, these findings suggest that CB_2 receptors play a complementary role to presynaptic CB_1 and may represent a novel therapeutic target for neurological diseases.

3. Endocannabinoids at striatal circuits

3.1. Dorsal striatum

The dorsal striatum (DS) of the basal ganglia plays a critical role in voluntary movement, learning and motivation, and represents the primary site of dysfunction in psychomotor diseases. The DS integrates glutamatergic excitatory inputs from the cortex and the thalamus. These inputs converge on striatal projection neurons (SPNs) of the direct (dSPN) and indirect (iSPN) pathways, which play distinct roles in controlling motor output and hedonic states (Bateup et al., 2010; Cui et al., 2013; Koralek et al., 2012; Kravitz et al., 2010, 2012; Tecuapetla et al., 2016; Vicente et al., 2016; Yin et al., 2009).

CB_1 are highly expressed at corticostriatal terminals (Hohmann and Herkenham, 2000) (Martin et al., 2008). This is consistent with a wealth of studies demonstrating that the eCB retrograde signaling is a fundamental means by which the activity of SPNs fine tunes the synaptic gain at excitatory cortical afferents to the DS (Castillo et al., 2012; Cerovic et al., 2013; Mathur and Lovinger, 2012). SPNs synthesize and release eCBs upon the synergistic activation of group I mGluRs and dopamine D_2 receptors (by inhibition of regulator of G-protein signaling 4, RGS4), and by Ca^{2+} entry via voltage-gated calcium channels (VGCCs) and NMDA receptors (Lovinger and Mathur, 2012; Uchigashima et al., 2007; Wang et al., 2006; Yin and Lovinger, 2006) (Fig. 1). The classical knowledge points at striatal eCB signaling as a powerful neuromodulatory system that acts by depressing corticostriatal inputs on a short- (via inhibition of glutamate release and DSE) and long timescale (via eCB-LTD) (Gerdeman and Lovinger, 2001, 2003; Gerdeman et al., 2002; Ronesi and Lovinger, 2005; Shen et al., 2008; Trusel et al., 2015; Wang et al., 2006). DSE requires stimulation patterns that depolarize the postsynaptic SPNs and enhance intracellular Ca^{2+} levels (Uchigashima et al., 2007). eCB-LTD of excitatory synaptic responses occurs either in response to afferent stimulation (10–100 Hz) (Gerdeman et al., 2002; Kreitzer and Malenka, 2007; Ronesi and Lovinger, 2005; Trusel et al., 2015; Wang et al., 2006) or in response to a post-pre paring protocol, in which the postsynaptic spike precedes the presynaptic stimulation (Fino et al., 2010; Nazzaro et al., 2012; Paille et al., 2013; Shen et al., 2008, 2015; Wu et al., 2015). The expression and maintenance of eCB-LTD involves coincident presynaptic mechanisms, which may include protein synthesis (Yin et al., 2006). The consensual view is that eCB-LTD can be reliably induced at glutamatergic synapses on identified iSPNs (Adermark and Lovinger, 2007; Trusel et al., 2015; Wang et al., 2006). In identified dSPNs, eCB-LTD is critically dependent on the relative strength or timing of convergent synaptic inputs (e.g., cortical and thalamic inputs) and on neuromodulation (Bagetta et al., 2011; Nazzaro et al., 2012; Shen et al., 2008, 2015; Wu et al., 2015). Thus, while eCB-LTD may not be cell-type-specific *per se*, the threshold for the induction of this form of plasticity can be modulated in the two SPN subpopulations in a cell-type-specific manner. In the lateral part of the dorsal striatum, eCB signaling is also required for synaptic depotentiation, the reversal of LTP. eCB-mediated synaptic depotentiation, which occurs at previously potentiated synapses following low-frequency afferent stimulation (2 Hz), does not involve VGCCs and requires activation of mGluR5 (Nazzaro et al., 2012). Contrary to cortical inputs, thalamostriatal synapses are devoid of presynaptic CB_1 (Wu et al., 2015), suggesting that eCB signaling by this receptor subtype may not be critical for the thalamic control of striatal function. Consistent with this, LTD at thalamostriatal synapses is reported to be NMDA-mediated and not CB_1-mediated. The role of TRPV1 in regulating thalamostriatal synapses remains, however, unexplored.

eCBs also promote LTP via both CB_1 and TRPV1 and on 2-AG elevations (Cui et al., 2015, 2016). The emerging picture is that eCBs are bidirectional rather than unidirectional neuromodulators of striatal functions. The proposed model suggests that both the levels and timing of eCB release control the direction (depression vs potentiation) of changes in synaptic strength (Cui et al., 2016). As

discussed below, eCBs released from SPNs can also activate astrocytic CB_1 and by this means potentiate corticostriatal synaptic transmission.

eCBs modulate GABAergic synapses impinging on SPNs by mediating both depolarization-induced suppression of inhibition (DSI) (Tanimura et al., 2010) and inhibitory LTD (iLTD) (Adermark et al., 2009). CB_1 receptors located on GABAergic afferents from local interneurons appear to be more sensitive to eCBs released from SPNs after VGCCs activation in the absence of afferent stimulation (Adermark et al., 2009). CB_1 receptors are also localized on local axon collaterals originating from SPNs. These axon collaterals connect to interneurons and other SPNs, and form numerous inhibitory (GABA) synapses onto spines and dendritic shafts of these neurons (Kubota and Kawaguchi, 2000; Van Waes et al., 2012; Wilson, 2007). Electrophysiological findings suggest that CB_1 activation inhibits GABAergic synaptic transmission between paired SPNs, and this effect is mediated by presynaptic CB_1 receptors (Freiman et al., 2006). As to whether and how this affects synaptic plasticity phenomena in the two connected SPNs remains to be established.

Consistent with a crucial role of eCBs as striatal synaptic neuromodulators, pharmacological or genetic manipulations of the endogenous cannabinoid system profoundly influences DS-dependent behaviors. Acute exposure to the exogenous ligand Δ9-tetrahydrocannabinol (THC), or CB_1 deletion, impairs stimulus-response habit formation (Gremel et al., 2016; Hilario et al., 2007; Hilario and Costa, 2008), whilst persistent activation of eCB signaling by chronic THC administration promotes a bias towards habitual behavior (Nazzaro et al., 2012). This latter manipulation results in a reduction of eCB-mediated plasticity (LTD and synaptic depotentiation) secondary to CB_1 downregulation and desensitization. Regardless whether habitual behavior is impaired or facilitated by manipulations of the eCB signaling, the emerging view is that affecting CB_1 -mediated regulation of glutamatergic and GABAergic function may interfere with the normal acquisition and consolidation of memory processing dependent upon the DS.

In animal exposed to chronic alcohol administration, increased 2-AG levels are associated with deficits in eCB-LTD in the dorsolateral striatum and with facilitation of reversal learning (Depoy et al., 2013; DePoy et al., 2015). In animal model of Parkinson's disease, impaired eCB-LTD, secondary to striatal dopamine depletion, is directly related to motor dysfunctions that characterize this pathology. Specifically, it has been shown that the loss of dopaminergic innervation results in deficits of D_2-dependent eCB production (Fig. 1) and consequent loss of eCB-LTD at corticostriatal synapses of iSPNs (Kreitzer and Malenka, 2007; Trusel et al., 2015). Administrating in-vivo D_2 receptor agonists (Kreitzer and Malenka, 2007) or activating signaling downstream of D_2 receptors (Trusel et al., 2015) restores proper eCB synaptic functions and ameliorated motor dysfunctions, including motor learning.

The eCB-evoked astrocyte calcium signal and consequent synaptic regulation has been recently demonstrated in DS, where eCB-induced lateral synaptic regulation has been shown to be mediated by astrocytic glutamate release and to selectively occur between homotypic, but not heterotypic, dSPN and iSPNs (Martin et al., 2015).

3.2. Nucleus accumbens

The nucleus accumbens (NAc), or ventral striatum, is a component of the mesolimbic reward pathway that enables adaptive behavioral responding to rewards and reward-predictive cues, and plays a key role in the reinforcing properties of addictive drugs for a recent review, see (Francis and Lobo, 2017; Scofield et al., 2016). The NAc receives glutamatergic excitatory inputs from the prefrontal cortex (PFC), the amygdala, the thalamus and ventral hippocampus, together with dopaminergic neuromodulatory afferents from the ventral tegmental area (VTA). Similar to the DS, GABAergic SPNs in the NAc belong to two neuronal subpopulations, mainly enriched either in dopamine D1 or D2 receptors. The segregation into direct and indirect output pathways is, however, less straight forward compared to the DS. Indeed, D_1-and D_2- NAc expressing neurons have overlapping projections to ventral pallidum (Smith et al., 2013). The NAc can be divided into two distinct areas: a central core surrounded by an outer shell. Whilst the NAc shell could be conceived as a transitional zone between the striatum and the extended amygdala, the NAc core is more functionally linked to the dorsal striatum, and is involved in the cognitive processing of motor programs related to reward and reinforcement (Sesack and Grace, 2010; Smith et al., 2013).

The key molecular constituents of eCB signaling complex are expressed in the core of the NAc. In this sub region, the enzyme DGLα (Matyas et al., 2007) can be detected in SPN dendrites that face pre-synaptic CB_1 receptor located on glutamatergic projections from the medial PFC (mPFC) (Robbe et al., 2001), as well as at the level of local GABAergic interneurons (Manzoni and Bockaert, 2001). Consistent with these anatomical observations, pharmacological activation of NAc CB_1 receptors inhibits both inhibitory and excitatory synaptic transmission (Hoffman et al., 2003; Manzoni and Bockaert, 2001; Robbe et al., 2001). Furthermore, moderate frequency stimulation (13 Hz) of cortical afferents to the NAc core induces a form of eCB-LTD, which is dependent upon mGluR5 activation and Ca^{2+} release from internal stores (Robbe et al., 2002). In NAc D_2-SPNs, but not in NAc D_1-SPNs, low frequency stimulation (3 Hz) results in LTD of excitatory synaptic responses; this form of synaptic plasticity requires postsynaptic TRPV1 activation, relies on Ca^{2+}-mediated AMPAR endocytosis, and is only partially dependent on CB_1 (Grueter et al., 2010). On the one hand, TRPV1-mediated LTD in iSPNs is prevented by in-vivo cocaine administration. On the other hand, genetic deletion of TRPV1 enhanced behavioral sensitization in response to repeated administration of this drug of abuse (Grueter et al., 2010). Thus, these observations support the behavioral relevance of this cell-type specific form of synaptic plasticity due to activation of postsynaptic TRPV1 channels by the eCB AEA. eCBs released by NAc SPNs are also involved in Hebbian spike-timing- dependent LTD (t-LTD) (Bosch-Bouju et al., 2016).

Anatomical and functional observations suggest a cross talk between the NAc eCB system and the serotonergic (5-HT) signaling in regulating NAc synaptic plasticity. In the core NAc core, CB_1 and the 5-HT_2 receptor subtype appear to co-localize at excitatory terminals (Best and Regehr, 2008). On a functional level, prolonged (20 min) low frequency (4 Hz) stimulation of glutamatergic afferents to this NAc sub region triggers a form of LTD that requires activation of 5-HT_2R, CB_1 and L-type VGCCs. Recent work revealed that social play, one of the earliest forms of non-mother directed social behavior observed in mammals, implicates a functional interaction between CB_1 and Mu Opioid Receptors in the NAc of rats and mice (Manduca et al., 2016). Thus, the regulation of positively valenced social behavior by morphine, synthetic cannabinoids and 2-AG implicates reciprocal interaction between the two cognate presynaptic receptors, perhaps within a heterodimer complex.

Within both the DS and NAc, fast-spiking (FS) interneurons provide tonic inhibition and timing-dependent feedforward inhibition to SPNs upon excitation. Studies performed in the NAc showed that SPNs feed-forward inhibition from CB_1-expressing FS interneurons is stronger than lateral inhibition from SPNs collaterals (Winters et al., 2012). Given the lack of evidence for CB_1 expression on NAc SPN collaterals, it is possible that eCB released upon SPNs activity selectively modulates inhibitory transmission from CB_1 positive FS interneurons.

Studies investigating maladaptive alterations of eCB-mediated synaptic plasticity in the NAc have primarily focused on the effects of drugs of abuse, and THC in particular. Both single (Mato et al., 2004) and repeated (Hoffman et al., 2003; Mato et al., 2005) exposure to THC impairs eCB-LTD in the NAc. Additionally, accumbal eCB-LTD is abolished by a single exposure to cocaine (Fourgeaud et al., 2004) or upon cocaine self-administration (McCutcheon et al., 2011a, 2011b). Upon extended withdrawal from cocaine self-administration, there is enhanced sensitivity to CB_1 agonists that suggest a persistent attenuation of eCB tone (McCutcheon et al., 2011b). Only very recent work has provided evidence that NAc eCB signaling can be affected by other forms of experience-dependent plasticity, in addition to exposure to addictive drugs (Bosch-Bouju et al., 2016). In mice exposed to chronic social defeat stress, a manipulation that generates robust anxiety-like behavior, NAc eCB-mediated t-LTD is attenuated in non-anxious mice and abolished in anxious mice. Furthermore, anxiety-like behavior in stressed animals is directly associated with their ability to produce t-LTD, supporting the role of NAc synaptic eCB signaling in the adaptive response and resiliency to psychosocial stress (Bosch-Bouju et al., 2016).

4. eCB signaling in prefrontal cortex

The complex internal circuit organization and extensive connectivity of the mammalian PFC endows this functional network hub in the brain with essential roles in the regulation of our thoughts, actions, and emotions (Goldman-Rakic, 1990; Seamans et al., 1995). Compromised hubs are deleterious to the entire network's integrity and PFC malfunctions are a common denominator in neuropsychiatric diseases (Goto et al., 2010). Here recent evidences illustrating the participation of dysregulation of the eCB system in PFC-related neuropsychiatric synaptopathies will be reviewed.

Similar to other brain regions (Kano et al., 2009; Katona and Freund, 2012), the highest concentrations of CB_1 mRNA in the PFC are found in interneurons. CB_1 immunoreactivity is also detected in glutamatergic fibers across the PFC surrounding pyramidal neurons in deep (layers 5/6) and superficial cortical layers (layer 2) (Egertová and Elphick, 2000; Lafourcade et al., 2007). A similar pattern of CB_1 immunohistochemistry is found in primate and human PFC tissue (Eggan et al., 2010; Long et al., 2012). Both the AEA and 2-AG synthesis/degradation molecular machinery are found in close quarter with elements of the postsynaptic 2-AG/mGluR5 signaling complex system. Thus, eCBs in the PFC can regulate excitatory and inhibitory synaptic transmission, but also neuromodulatory tone (Katona and Freund, 2012; Lafourcade et al., 2007). Despite the high expression of CB_1 in PFC interneurons, eCB-mediated plasticity is more prevalent at excitatory synapses and shows layer specificity. Layer 5 pyramidal rat neurons express both short-term plasticity of glutamatergic synapses (e.g. DSE) (Fortin and Levine, 2007; Heng et al., 2011) and LTD (Lafourcade et al., 2007; Lovelace et al., 2014; Marrs et al., 2010). DSI protocols fail in deep layers PFC neurons (Fortin and Levine, 2007; Marrs et al., 2010). However, a significant portion of inhibitory synapses (>30%) co-express CB_1 and D_2 receptors and appear sensitive to eCB modulation upon D_2 co-activation (Chiu et al., 2010). While eCB-mediated long-term plasticity has not been reported in superficial layers of the PFC, DSI was found in layer 2/3 PFC neurons (Yoshino et al., 2011).

4.1. Experience-dependent adaptations of eCB signaling at PFC circuits

Dysfunctional or abnormal activity in the PFC has been linked to control over drug-seeking behavior (George and Koob, 2010; Goldstein and Volkow, 2011). Genetic evidence indicates that eCB signaling in the PFC contributes to ethanol consumption/preference in rats (Hansson et al., 2007) and humans (Hirvonen et al., 2013). Chronic ethanol reduces CB_1 density in animals (Vinod et al., 2006) and humans (Ceccarini et al., 2014). Ethanol disrupts PFC mediated cognitive processes and CB_1 and eCB-LTD down-regulation is proposed to participate to the shift in the regulation of behavior from PFC to DS (Depoy et al., 2013). Similarly, rodent and human data converge to show that cocaine perturbs several components of the eCB system in the PFC (Bystrowska et al., 2014; Ho et al., 2008). Consistent with this observation, PFC eCB-LTD is abolished in rats self-administering cocaine (Kasanetz et al., 2013). Alterations of eCB signaling in the PFC have been reported with the withdrawal of other drugs of abuse, including morphine (Viganò et al., 2004), the psychostimulant methylphenidate (Burgos et al., 2015), and nicotine (Cippitelli et al., 2011).

Cannabis has profound consequences on eCB signaling in the PFC. While adults seem resistant to most protracted effects of cannabis exposure (Realini et al., 2011; Schneider and Koch, 2003), adolescent exposure precipitates the development of such aberrant behaviors as addiction and psychosis (for reviews see: Hurd et al., 2014). In animal models, PFC-dependent cognitive functions are impaired in adulthood following cannabis exposure during development (Lovelace et al., 2015; Raver et al., 2013). Enhanced deficits resulting from cannabis use in schizophrenic subjects provide further evidence supporting a role for dysfunction in the eCB system. Schizophrenic individuals show increased responses to THC with regards to multiple symptoms of the disease (D'Souza et al., 2005) including increased frequency and intensity of psychotic episodes (Foti et al., 2010) and adolescent cannabis use positively correlates with increased likelihood severity of schizophrenia (for reviews, see: Casadio et al., 2011).

The PFC is linked genetically, anatomically and functionally to autism spectrum disorders (ASD) (Willsey et al., 2013). Fragile X syndrome (FXS) is an X-chromosome-linked hereditary disorder often linked to autism (Garber et al., 2008) with behavioral signatures linked to PFC directed actions: loss of executive control, deficits in working memory, abnormal social interaction (Cornish et al., 2008). In the *Fmr1* KO mouse model, hippocampal synaptic eCB signaling is enhanced at both excitatory and inhibitory synapse (Tang and Alger, 2015; Zhang and Alger, 2010) and CB_1 antagonism normalizes altered hippocampal based behavior (Busquets-Garcia et al., 2013). In contrast, current evidence points to age-dependent deficits in eCB plasticity in the PFC of *Fmr1* KO mice. The severe deficit in eCB-LTD observed during early adulthood in *Fmr1* KO mouse (Jung et al., 2012), self rectifies later in life due to the engagement of TRPV1 (Martin et al., 2016). Pharmacological treatment of *Fmr1* KO animals with a drug that enhances eCB signaling, JZL184, has been shown to restore selective behavioral deficits (Jung et al., 2012). The use of cannabis results in acute and chronic deficits in cognition. Consistent with this notion, PFC deficits in eCB signaling have been linked to genetic intellectual disability. In the PFC of the Dyrk1A mice model of Down syndrome, eCB-LTD is impaired as a result reduced 2-AG production but not CB_1 function and enhancement of 2-AG levels with the MAGL inhibitor JZL184 effectively restores eCB-LTD (Thomazeau et al., 2014), and promisingly, treatment of mice with JZL184 also restores some of the cognitive deficits found in the Ts65Dn mouse model of DS (Lysenko et al., 2014), suggesting the eCB system may \be a therapeutic target in DS.

Dysfunctional eCB signaling has been linked to emotional disorders in humans (Lutz et al., 2015; McEwen et al., 2015). Genetic deletion of MAGL increased 2-AG levels in the PFC, enhanced the excitatory drive to the PFC and was associated to an anxiogenic

phenotype through desensitized CB_1 signaling (Imperatore et al., 2015). Increased anxiety-like behaviors were also observed in mice fed with a diet deficient in n-3 polyunsaturated fats, which elevates 2-AG levels (Watanabe et al., 2003) and induces a desensitized or uncoupled state in presynaptic CB_1 in the PFC (Lafourcade et al., 2011). While CB_1 antagonism enhances stress-induced neuronal responses in the PFC (Patel et al., 2005), direct or indirect CB_1 activation in the PFC protects against stress conditions (Rubino et al., 2008) and enhances the extinction of both learned and innate fear responses (Lin et al., 2009). Conversely, stressful experience alters eCB signaling in the PFC. Chronic or repeated stress in rodents decreases and increases AEA and 2-AG signaling, respectively (Bortolato et al., 2007; Rademacher et al., 2008) (Patel et al., 2005) (Hill et al., 2011) and down regulates CB_1 mRNA (Campos et al., 2013). Furthermore, chronic stress differentially alters eCB signaling in the PFC in adolescent rats as compared to adult rats. Repeated stress in adult or adolescent rats causes increased CB_1 binding in the PFC, however while eCB signaling in adult rats normalizes over a subsequent 40-day recovery period, adolescents exhibit sustained CB_1 down regulation following stress-exposure. Indeed, adolescent rats exposed to chronic stress conditions exhibit lasting deficits in PFC function and increased CB_1 binding in the PFC (Abush and Akirav, 2013; Lee and Hill, 2013). The emerging picture is that the PFC eCB system integrates multiple stress and anxiety responses.

5. Conclusions

Research in the last decade continue to show that eCBs are powerful regulators of synaptic function throughout the brain. Significant progress has been made in our understanding of how eCBs signal at neurons and their functional consequences in normal and pathophysiological circuits. While retrograde signaling involving inhibition of transmitter release via presynaptic CB_1 remains as the most common mechanism by which eCBs regulate synaptic function, growing evidence indicates that less conventional mechanisms, including non-retrograde signaling and the involvement of astrocytes, may also play a significant role in regulating brain function. Determining the relative contribution of these remarkably diverse mechanisms both in normal and disease states is an important challenge ahead.

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List of abbreviations

2-AG	2-arachidonoyl glycerol
AEA	anandamide
Δ9-THC	delta-9-tetrahydrocannabinol
ABHD6	alpha/beta hydrolase domain 6
AEA	anandamide
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	brain-derived neurotrphic factor
CA1	cornu ammonis 1
cAMP	cyclic adenosine monophosphate
CB	cannabinoid receptor
CB1	type 1- cannabinoid receptor
CB2	type 2- cannabinoid receptor
CCK	cholecystokinin
DAG	diacylglycerol
DAGL:	diaciglycerol lipase
DSI	depolarization-induced suppression of inhibition
DSE	depolarization-induced suppression excitation
DS	dorsal striatum
eCB	endocannabinoid
eCB-LTD	endocannabinoid-mediated LTD
EPSP	excitatory postsynaptic potential
FAAH	fatty acid amide hydrolase
GABA	gamma-aminobutyric acid
iLTD	inhibitory LTD
IP3	inositol-trisphosphate
KO	knock out
LFS	low-frequency stimulation
LPP	lateral performant path inputs
LTD	long-term depression
LTP	long-term potentiation
MAGL	monoacylglycerol lipase
mGluR 1/5	group I metabotropic glutamate receptor 1 and 5
mACh M1/M3	muscarinic acetylcoline receptor M1 and M3
NAc	nucleus accumbens
NAPE	*N*-arachidonoylphosphatidylethanolamine
NAPE-PLD	phospholipase D
NMDA	N-Methyl-D-aspartate r
NM II	non-muscle myosin II
PFC	prefrontal cortex
PLC	phospholipase C beta
PKA	Protein kinase A
PP	perforant path
RGS4	regulator of G-protein signaling 4
RIM1	type alpha-Rab3 interacting molecule 1
SPN	striatal projection neuron
STDP	spike timing-dependent plasticity
tLTD	spike-time dependent LTD
TRPV1	transient receptor potential vanilloid-1
VGCCs	voltage-gated Ca^{2+} channels
VTA	ventral tegmental area

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