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Endogenous cannabinoid signaling at inhibitory interneurons

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Abstract

Significant progress has been made in our understanding of how endogenous cannabinoids (eCBs) signal at excitatory and inhibitory synapses in the central nervous system (CNS). This review discusses how eCBs regulate inhibitory interneurons, their synapses, and the networks in which they are embedded. eCB signaling plays a pivotal role in brain physiology by means of their synaptic signal transduction, spatiotemporal signaling profile, routing of information through inhibitory microcircuits, and experience-dependent plasticity. Understanding the normal processes underlying eCB signaling is beginning to shed light on how their dysregulation contributes to disease.

Introduction

Endocannabinoid (eCB) signaling plays a central role in reward seeking and drug addiction [1,2], anxiety and depression [3], pain [4], learning and memory [5], neurogenesis and development [6,7], and may also serve as a drug target for therapeutic intervention in obesity, autism, epilepsy, and schizophrenia [8–12]. The eCB system, comprising lipid messengers, synthetic and degradative enzymes, carrier proteins/transporters, and receptors [10,13–15], is a neuromodulatory system capable of transiently or persistently suppressing transmitter release from both excitatory and inhibitory synapses throughout the CNS [16–20]. At inhibitory synapses, short-term eCB-mediated plasticity is commonly triggered by postsynaptic depolarization, referred to as depolarization-induced suppression of inhibition (DSI), and long-term plasticity in the form of depression of inhibition, termed iLTD, is a heterosynaptic form of plasticity triggered by repetitive activity of neighboring excitatory synaptic inputs. Classically, eCBs are synthesized by activity within postsynaptic neuronal compartments, retrogradely cross the synapse, occupy presynaptically expressed type-1 cannabinoid receptors (CB₁Rs), and depress glutamate and GABA release. While eCBs are prototypical retrograde messengers [21], additional research indicates this canonical

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interpretation is complicated by their non-retrograde actions on postsynaptic CB₁Rs and transient receptor potential type-1 (TRPV₁) channels, as well as astrocytic CB₁Rs [16]. Here, we emphasize recent experimental advances examining eCB functions at interneurons including their molecular signaling cascades, spatiotemporal signaling profiles, role in microcircuits, and dysregulation in certain pathophysiological conditions. Inhibitory interneurons are a heterogeneous group that support key aspects of brain function including fine-tuning excitatory and inhibitory neuronal networks, controlling membrane excitability and sub-threshold conductances, regulating synaptic and intrinsic input/output transformations, as well as enforcing precise spike-timing and oscillations in downstream targets [22–27]. Continued exploration into the dynamic interplay between eCBs and interneurons is therefore essential for understanding brain function.

Endocannabinoid Signal Transduction and Interneuronal Function

The best defined eCBs are 2-arachidonoyl glycerol (2-AG) and anandamide (AEA) (for comprehensive reviews on eCB signal transduction, see [10,13–20]). 2-AG can be produced postsynaptically in an activity-dependent manner through increased Ca²⁺ influx; G_{q/11} protein coupled receptor (GPCR) activation, commonly group-I metabotropic glutamate receptors (I-mGluRs) or muscarinic acetylcholine receptors (mAChRs); or an associative/synergistic combination thereof [28] (Fig. 1a). Ca²⁺ and G_{q/11} GPCRs signal to phospholipase-C β (PLCβ) activating diacylglycerol lipase-α (DGLα) leading to 2-AG synthesis. Genetic and pharmacological studies strongly support the notion that DGLα is responsible for 2-AG synthesis at inhibitory (and excitatory) synapses [29–33] (see also [34]). The exact role Ca²⁺ plays in 2-AG synthesis remains unclear. PLCβ is a Ca²⁺-sensitive enzyme, but PLCβ appears only to regulate synaptically-driven and associative/synergistic eCB release [28]. Recent work on striatal GABAergic medium spiny neurons (MSNs) found that Ca²⁺/calmodulin-dependent protein kinase-α (CAMKIIα) negatively regulates DGLα activity [35]. In contrast with 2-AG, AEA biosynthesis appears more complex and involves several enzymes [14], most notably N-acyl-phosphatidylethanolamine phospholipase-D (NAPE-PLD). Immunohistochemical studies localized this enzyme to cerebellar Purkinje cells and certain hippocampal interneurons [36,37], and functional evidence indicates postsynaptic AEA release regulates synapse strength onto striatal MSNs [38]. Additional work is needed to ascertain the subcellular expression profile of NAPE-PLD at inhibitory synapses (reviewed in [18]). Given that NAPE-PLD and DGLα can be expressed in the same cell, what determines whether 2-AG or AEA emerges? While the answer could relate to cell-type and/or synapse-specific expression of eCB-synthesizing enzymes, recent *in vitro* studies provide alternative possibilities. For example, the pattern and/or frequency of synaptic activity [39,40], and the resting membrane potential (e.g. “up” vs. “down” state in striatal MSNs) [41] can preferentially release 2-AG or AEA. In addition, AEA might inhibit 2-AG production [42]. Alternatively, AEA could activate TRPV₁ which increases Ca²⁺ signaling to mobilize 2-AG, or compartmentalized Ca²⁺ microdomains at inhibitory synapses might selectively generate 2-AG, AEA, or both.

Presynaptic CB₁Rs are found throughout the brain, whereas CB₂Rs and TRPV₁ channel expression in the CNS remains controversial. CB₁Rs can transduce information during short-term and long-term plasticity via their G_{i/o} proteins to intracellular effectors including

voltage-gated Ca^{2+} channels, inwardly rectifying K^{+} channels, and/or PKA [13]. Presynaptic activity [43–45], calcineurin [43] (Fig 1b), the vesicle associated protein Rab3B [46], and $\text{G}_{i/o}$ coupled M_2 -type mAChRs [47] also seem to be required for iLTD. Interactions between CB_1R and other $\text{G}_{i/o}$ GPCRs such as type-2 dopamine-like receptors (D_2Rs) [48,49] have been described at inhibitory synapses (Fig 1c), suggesting additional layers of modulatory complexity in presynaptic terminals. Early studies performed in hippocampus and neocortex reported that regular-spiking, but not fast-spiking, interneurons express CB_1Rs and are therefore responsive to eCBs [25,50]. New data, however, indicates this dichotomy is not steadfast. At striatal [51], nucleus accumbens [52], visual [45] and somatosensory [53] cortical (but see [54]) fast-spiking interneuron output synapses, CB_1Rs were shown to mediate short-term plasticity. In addition, hippocampal fast-spiking interneurons can mobilize eCBs required for long-term plasticity [55]. Beyond retrograde signaling, evidence indicates 2-AG can engage postsynaptic CB_1Rs in an autocrine fashion to inhibit cortical interneuron excitability [56,57]. CB_2Rs were originally thought to be expressed only in immune cells, but accumulating evidence supports a role for these receptors in regulating inhibitory synaptic transmission [58,59]. Signaling cascades downstream of synaptic CB_2Rs remain virtually unknown. While eCBs can also target pre- and postsynaptic TRPV_1 as well as astrocytic CB_1Rs [16], our understanding of how these receptors modulate GABAergic transmission and inhibitory interneuron physiology is extremely limited. Collectively, several diverse and novel modes of eCB production and detection have been described at inhibitory interneurons, and fully characterizing eCB signaling should help elucidate higher-level circuit functions.

Spatiotemporal Signaling Profile of Endocannabinoids at Interneurons

Two eCB signaling modes have been identified at GABAergic synapses: one phasic (i.e. activity-dependent) and one tonic (Fig. 2a) (for review, see [19]). Strong evidence supports “on-demand” phasic eCB release while more indirect findings suggest eCBs arise through preformed reserve pools [33,60] (but see [32,34]). Phasic eCB signaling underlies short- and long-term forms of inhibitory synaptic plasticity such as DSI and iLTD, respectively [17,18]. The type of synaptic plasticity (i.e. short vs. long) may rely on how long the CB_1R is occupied by eCBs [61,62]. DSI can be observed at specific inhibitory inputs or distributed more globally across the somatodendritic tree [17,18], and recent research indicates that postsynaptic activity alone (e.g. theta burst-firing that mimics CA1 pyramidal cell firing *in vivo*) triggers iLTD at both somatic and dendritic compartments [61]. Together, these findings may provide insights into how inhibition shapes somatic spike-timing, Ca^{2+} dependent plasticity processes, and dendritic integration. Phasic eCB signaling can also be observed by pairing two stimuli that are independently submaximal for eliciting changes in synapse strength. This “associativity” is thought to provide additional computational flexibility to neuronal networks, and new results from several laboratories provided evidence for long-term eCB-mediated associative iLTD [43,47,61,63]. Beyond the role that I-mGluRs and mAChRs play in eCB-mediated associative plasticity, GluK2-containing kainate [64], $\text{E}_2\alpha$ estrogen [65], neuronal protease-activated type-1 [66], and Trk [67] receptors can also mobilize eCBs at inhibitory synapses. It remains unknown if these receptors participate in long-term associative eCB signaling.

Evidence for tonic actions at inhibitory synapses is disparate, but when observed, can be mediated by 2-AG [68] or AEA [69,70]. Several groups have reported tonic eCB signaling [65,71–74], a finding not shared by others [62,75–77]. Tonic eCB signaling can be observed as an increase in GABAergic transmission in the presence of specific CB₁R antagonists, all of which exhibit inverse agonism. Inverse agonism effectively decreases the activity of a given receptor below its basal level and can only be observed when GPCRs constitutively signal in the absence of endogenous ligand [78,79]. Refuting the inverse agonist hypothesis of tonic eCB signaling, tonic effects can be blocked by chelating postsynaptic Ca²⁺ [69,72,80] or inhibiting eCB synthesizing enzymes [65,81]. These manipulations cannot distinguish between intrinsic eCB signaling arising from a specified neuron or tonic endogenous activation of I-mGluRs or mAChRs which can promote eCB mobilization [82,83]. Other potential issues to consider are the concentration of CB₁R antagonist/inverse agonist used and where a recording was made, as the health of relatively superficial cells in brain slices is likely compromised. More research is needed to ascertain the magnitude, functional relevance, and the spatial extent of tonic eCB signaling at inhibitory interneurons, as tonic GABAergic signaling can have a significant impact on neuronal input/output transformations [23,84].

Pre- and/or postsynaptic eCB degradative enzymes shape the spatiotemporal profile of eCB signaling at interneurons. Accumulating evidence indicates synaptic 2-AG signaling is primarily regulated by monoacylglycerol lipase (MGL) [68,76,85–87]. Whether changes of MGL expression/activity could be a physiological mechanism for controlling eCB signaling at the synapse is unclear. At hippocampal inhibitory synapses onto CA1 pyramidal cells, 2-AG diffusion between pyramids is more restricted than originally thought [75], even when MGL is pharmacologically inhibited [61]. In the cerebellum, 2-AG diffusion from Purkinje cells is largely unrestricted [88] but seems to be controlled by MGL expression across synapses and glia [85]. At GABAergic synapses onto hypothalamic magnocellular endocrine cells, astrocytes normally impede eCB signaling, and manipulations that lead to astrocytic retraction unmask eCB signaling [70]. These results suggest other degradative enzymes (or lack of) control eCB diffusion. Additional enzymes that terminate eCB signaling are the serine hydrolases αβ-hydrolyzing domain 6 and 12, cyclooxygenase-2, and fatty acid amide hydrolase [10,13,14], but little is known about how these enzymes regulate eCB diffusion at inhibitory synapses.

Endocannabinoid Signaling in Inhibitory Microcircuits

Blueprints for proper mature circuit function are laid down during development, and a myriad of molecular cues, including eCBs, help organize the early CNS by influencing neural specification, migration, target selection, and synaptogenesis [6,7]. Interfering with eCB signaling can disrupt brain patterning which may underlie certain neuropsychiatric conditions like schizophrenia (see below). CB₁Rs are enriched in GABAergic axonal growth cones (as well as principal cells), and eCB signaling induces chemo-repulsion and growth cone collapse [89]. Embryonic CB₁R deletion leads to reductions in parvalbumin expression, a calcium binding protein found in fast-spiking interneurons, as assessed immunohistochemically in neocortex and striatum [90]. Disrupted eCB signaling thus appears to negatively impact network function.

Perisomatic fast-spiking interneurons help channel information through microcircuits by imparting synchrony to their targets, governing action potential generation, and enforcing precisely timed spikes and oscillations [23,25]. *In vitro* experiments showed that perisomatic fast-spiking interneurons mediate cholinergically-induced oscillations in hippocampal area CA3 [91]. Furthermore, regular-spiking, perisomatic CB₁R-expressing interneurons were found to entrain acetylcholine-induced oscillations in CA1 [92,93]. *In vivo*, CB₁R-bearing CA1 interneurons exhibit homogeneous firing characteristics with respect to extracellular oscillations [94], contrasting sharply with those in CA3 [95]. These findings highlight the need to carefully examine which interneuron cell-types contribute to and participate in neuronal oscillations.

Perisomatic inhibition may also contribute to a network property of hippocampal pyramidal cells known as phase precession. Phase precession manifests as spike-time phase advancement relative to local field potential oscillations and helps encode an animal's spatial position [96–98]. Activity-dependent eCB release may contribute to the mechanism of phase precession (examined *in vitro*), which depresses transmitter release from CB₁R-bearing GABAergic inputs thereby permitting eCB-insensitive fast-spiking interneurons to dominate and phase-advance spikes [96]. While these results are consistent with the ability of eCBs to shape spike-timing [99], somatic CB₁R-expressing inhibitory synapses may exhibit greater eCB sensitivity than dendritic inputs [100] (see also [61]), thus providing an activity-dependent eCB-mediated disinhibitory mechanism for gating somatic output [61,63]. eCB-mediated disinhibition may be a general feature of inhibitory microcircuits as it has been observed in hippocampus [61,63], striatum [41,101], and midbrain periaqueductal gray [102,103]. eCB-mediated disinhibitory states (Fig. 2b) can dynamically route excitation through neuronal networks by increasing the contrast between active and inactive cells still under inhibitory control [25,94]. Validating this hypothesis is challenging because CB₁Rs are expressed at glutamatergic, GABAergic, and neuromodulatory synapses as well as astrocytes [16], each of which probably contribute to the complex effects that cannabinoids have on network oscillations *in vivo* [104,105]. Focused attempts to selectively inactivate each of these cell-types should help disentangle the relative contribution that each makes to local circuit function.

Interneuronal synchrony is facilitated by gap junctions. Cortical fast-spiking interneurons are synchronized via gap junctions [106], and regular-spiking, CB₁R-positive forebrain interneurons [107,108] are also electrically coupled. Certain regular-spiking and fast-spiking interneurons express CB₁Rs whose activation depresses transmitter release. Thus, eCB-mediated effects at chemical inhibitory synapses, by reducing shunting inhibition, could augment electrical coupling between interneurons. Fast-spiking and regular-spiking interneurons often exhibit different modes of neurotransmitter release (i.e. synchronous vs. asynchronous, respectively) [109,110]. These release modes (and their modifiability by eCBs) may confer additional computational flexibility to oscillating electrical networks such that reduced asynchronous chemical inhibition facilitates downstream spike generation and precision.

Contribution of Endocannabinoid Signaling at Interneurons to Behavior and Disease

Evidence suggests that eCB-mediated inhibitory synaptic plasticity occurs *in vivo*, and interfering with eCB signaling has aversive effects on learning and memory [5,111]. Mice constitutively lacking CB₁R or Rab3B protein exhibit disrupted eCB-mediated iLTD at synapses onto principal amygdala [112] or hippocampal [46] neurons, respectively. These *in vitro* findings correlated with alterations in the extinction of learned memories, albeit in opposite directions. To circumvent issues inherent in knock-out strategies, an innovative micro-RNA knock-down strategy was recently employed to specifically address the contribution of CB₁R-expressing GABAergic neurons to behavior [113]. Baseline learning and memory was unaffected, but mice showed elevated and persistent auditory fear conditioning. To extend these findings, this mouse could be used in conjunction with optogenetic tools to selectively stimulate or inactivate CB₁R-expressing interneurons.

Normal experience-dependent maturation of neocortical GABAergic transmission requires eCB-dependent plasticity at inhibitory synapses [45]. In murine visual cortex, inhibition matures relatively slowly until puberty and is thought to sculpt circuits required for sensory processing during the critical period of ocular dominance plasticity. There is evidence that eCB-mediated iLTD likely drives GABAergic transmission into a more mature state [45]. While sequential maturation of GABAergic synaptic transmission has been observed across visual cortical layers, eCB signaling is relevant in L2/3 but not L4 [114]. eCB-mediated iLTD can be reactivated in mature animals re-exposed to dark conditions, indicating critical windows can be reopened by sensory experience [115]. Exactly how this form of plasticity is reinitiated remains to be determined.

Diet and stress can also powerfully influence eCB signaling *in vivo* [116]. Diet-induced obese mice exhibit enhanced eCB-mediated short-term and long-term hippocampal inhibitory synaptic plasticity [117]. In hypothalamic satiety circuits, food deprivation and acute restraint stress suppresses eCB-mediated iLTD, which favors long-term potentiation by nitric oxide at GABAergic synapses [118]. Several studies found that stress alters eCB signaling [119–123], which is presumably controlled by an elusive membrane-bound G_{q/11}-coupled glucocorticoid receptor. Altered eCB signaling might be a general feature of stressful events.

Beyond their involvement in inhibitory microcircuits and certain behavioral states, dysregulated eCB signaling is observed in animal models of human neuropsychiatric disorders such as autism, epilepsy, and schizophrenia [3,8–11]. Recent data indicates tonic, not phasic, eCB signaling is dysregulated at CA1 hippocampal inhibitory synapses in which the autism-associated, cell-adhesion molecule neuroligin-3 was disrupted [73]. This finding also suggests neuroligin-3 orchestrates the putative tonic eCB release machinery, but the mechanism for this action is totally unknown. In Fragile X syndrome, the most common single-gene cause of autism, disruption of the mRNA binding Fragile X mental retardation protein (FMRP) causes local dysregulation of I-mGluR signal transduction. In FMRP null mice, where coupling between I-mGluR activation and eCB mobilization is likely altered, eCB signaling was enhanced at inhibitory synapses in the hippocampus [124] and dorsal

striatum [125] but impaired at excitatory synapses in the ventral striatum and prefrontal cortex [126]. Dysregulated eCB signaling also contributes to epilepsy [127,128]. GABAergic CB₁Rs are generally pro-convulsive whereas glutamatergic CB₁Rs exhibit neuroprotection against seizures. CB₁R agonists can be pro- or anti-convulsive, the discrepancies possibly resulting from differences in experimental epilepsy models and/or eCB-mediated effects on inhibitory vs. excitatory transmission. In addition, evidence indicates perturbations to GABAergic synaptic transmission, such as reduced CB₁R expression, are correlated with schizophrenia [129,130]. Neuregulin-1 is elevated in schizophrenics and prolonged treatment of hippocampal slice cultures with neuregulin-1 enhances MGL expression and curtails 2-AG-mediated forms of inhibitory synaptic plasticity [86]. Together, these findings suggest the role of eCB signaling should be further considered in neuropsychiatric conditions and as therapeutic targets.

Summary and Open Questions

Significant progress has been made in our understanding of how eCBs signal at inhibitory interneurons and their functional consequences in normal and pathophysiological circuits, but several questions remain unanswered. What mechanisms underlie specific pre- and/or postsynaptic activity patterns of 2-AG and/or AEA mobilization, and what function do they serve? Which factor(s) determine whether eCBs affect synapses, intrinsic excitability, or both? How are eCBs transported across the synaptic cleft? What are the relative contributions that various degradative enzymes have on the eCB spatiotemporal signaling profile? What is the precise role of tonic eCB release? How does eCB-mediated disinhibition influence local circuit function *in vivo* and is runaway disinhibition related to neuropsychiatric conditions such as autism, epilepsy and schizophrenia? While eCB signaling can impact many interneuronal functions, they are only one piece of a larger puzzle. The field should soon have answers to these and other outstanding questions as genetic manipulation of CB₁R expressing interneurons *in vivo* is now possible [113,131].

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Highlights

- Endocannabinoids (eCBs) are powerful modulators of inhibitory synaptic transmission
- eCBs control inhibitory synapses in an activity-dependent (i.e. phasic) or tonic manner
- By regulating inhibitory microcircuits, eCB signaling contributes to behavior
- Dysregulated eCB signaling contributes to common neuropsychiatric conditions

Figure 1. Pre- and postsynaptic mechanisms for associative iLTD

a) Postsynaptic activity (e.g. Ca²⁺ influx through voltage-gated Ca²⁺ channels, VGCCs) along with metabotropic receptor activation (e.g. mGluR and mAChR) engages phospholipase-C β (PLCβ) and then diacylglycerol lipase α (DGLα) followed by mobilization of 2-AG. DGLα can also be stimulated via an uncharacterized, Ca²⁺-dependent mechanism.

b) Presynaptic activity, leading to Ca²⁺ influx (here, VGCCs), along with CB₁R stimulation shifts protein kinase A (PKA)/calcineurin (CaN) activity to favor dephosphorylation of an unknown target (T) essential for eCB-mediated iLTD.

c) Concomitant presynaptic CB₁R activation plus dopamine (DA)-like type 2 (D₂R), μ opioid (μOR), and/or orexin-1 (OX₁) receptors might cooperatively reduce adenylyl cyclase (AC)/PKA signaling [20]. Alternatively, heterodimeric signaling interactions may switch G_{i/o} signaling to G_s, actually promoting AC/PKA activity (not shown).

Figure 2. Endocannabinoid-mediated disinhibition and possible functional outcomes

a) Phasic eCB signaling schematics are based on experimental data obtained in the CA1 area of the hippocampus. Dendritic disinhibition requires afferent activity, glutamate release, I-mGluR activation, and mobilization of eCBs that heterosynaptically depress nearby inhibitory synapses [62]. Somatic disinhibition can be elicited by pairing perforant path and Schaffer Collateral (Sch) inputs [63]. Somatodendritic disinhibition can be triggered with postsynaptic activity alone, which presumably leads to cell-wide increases in Ca^{2+} signaling (and eCB mobilization) in response to invading back-propagating action potentials [61]. The spatial profile for tonic eCB signaling remains unknown.

b) Hypothetical input (e.g. rate or timing)/output (e.g. firing frequency or probability) transformations inspired by experimentation and modeling [84,132] highlight the potential functional significance of eCB-mediated disinhibition on excitation. These possibilities are not exhaustive nor do we consider here plasticity occurring at excitatory synapses.