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An introduction to the endogenous cannabinoid system

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Abstract

The endocannabinoid system (ECS) is a widespread neuromodulatory system that plays important roles in central nervous system (CNS) development, synaptic plasticity, and the response to endogenous and environmental insults. The ECS is comprised of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids. The most abundant cannabinoid receptor is the CB1 cannabinoid receptors, however CB2 cannabinoid receptors, transient receptor potential (TRP) channels, and peroxisome proliferator activated receptors (PPAR's) are also engaged by some cannabinoids. Exogenous cannabinoids, such as tetrahydrocannabinol, produce their biological effects through their interactions with cannabinoid receptors. 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide) are the best-studied endogenous cannabinoids. Despite similarities in chemical structure, 2-AG and anandamide are synthesized and degraded by distinct enzymatic pathways, which impart fundamentally different physiological and pathophysiological roles to these two endocannabinoids. Because of the pervasive social use of cannabis and the involvement of endocannabinoids in a multitude of biological processes, much has been learned about the physiological and pathophysiological roles of the ECS. This review will provide an introduction to the ECS with an emphasis on its role in synaptic plasticity and how the ECS is perturbed in schizophrenia.

Keywords

cannabinoid; cannabis; lipid signaling; retrograde messenger; schizophrenia; synaptic plasticity

Introduction

The endocannabinoid system (ECS) has emerged as an important neuromodulatory system over the last twenty-five years. Relevant to the topic of this special issue of *Biological*

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Conflict of interest

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Psychiatry, perturbations of the ECS are involved in several psychiatric disorders, including schizophrenia. The ECS is comprised of endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and the enzymes responsible for the synthesis and degradation of endocannabinoids (Fig. 1). Each of these components will be introduced in this chapter, with an emphasis on their potential involvement in psychosis.

Endogenous cannabinoids are endogenous lipids that engage cannabinoid receptors (see below), affecting behavior in a fashion that at least partially recapitulates the effects produced by the psychoactive components of cannabis, most notably Δ-9-THC ((–)-*trans*-Δ^9-tetrahydrocannabinol; THC). The first discovered and best-characterized endocannabinoids are anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol (2-AG). An important feature of these endocannabinoids is that their precursors are present in lipid membranes. Upon demand (typically by activation of certain G protein-coupled receptors or by depolarization), endocannabinoids are liberated in one or two rapid enzymatic steps and released into the extracellular space. This contrasts with classical neurotransmitters that are synthesized ahead of time and stored in synaptic vesicles. The intrinsic efficacy of the endogenous cannabinoids varies—2-AG is a high efficacy agonist for both CB_1 and CB_2 receptors, however anandamide is a low efficacy agonist at CB_1 receptors and a very low efficacy agonist at CB_2 receptors (1, 2). Thus, in systems with low receptor expression or when receptors couple weakly to signaling pathways anandamide can antagonize the effects of more efficacious agonists (3). Additional endogenous substances (e.g., virodhamine and 2-arachidonoyl glycerol ether (4)) may expand the repertoire of endocannabinoids, however the biology of these compounds are not as well developed as the biology of anandamide and 2-AG, so they will not be considered further in this review. This chapter will introduce the components of the endocannabinoid system and discuss their role in modulating synaptic transmission. Chapters 6 and 8 will consider the extensive functions of cannabinoids in neurodevelopment and how perturbation of these functions may increase an individual's risk to develop a psychiatric disorder.

Cannabinoid receptors

The effects of endocannabinoids are primarily mediated by CB_1 and CB_2 cannabinoid receptors (4), with other receptors (such as PPAR's and Transient Receptor Potential (TRP)) channels (see below)) also mediating some endocannabinoid actions, particularly of the acylethanolamides. As discussed in more detail in Chapter 12, polymorphisms of cannabinoid receptor and endocannabinoid system genes are variably associated with schizophrenia (5–8) and possibly with response to atypical antipsychotics (9). Both CB_1 and CB_2 cannabinoid receptors are G protein-coupled receptors (GPCR's), which primarily couple to G proteins of the Gi and Go classes (4). As such, their activation inhibits adenylyl cyclases and certain voltage dependent calcium channels and activates several MAP kinases and inwardly rectifying potassium channels, with some variation depending on the particular type of cell (4). Thus, activation of CB_1 or CB_2 receptors exerts diverse consequences on cellular physiology, including synaptic function, gene transcription, cell motility, etc. (4).

CB_1 receptors are abundant in the central nervous system (CNS), particularly in cortex, basal ganglia, hippocampus, and cerebellum (10). The majority of CB_1 receptors are present

on axon terminals and pre-terminal axon segments, while sparing the active zone (11) (Fig. 1). Cortical and hippocampal CB_1 receptors are particularly enriched on cholecystokinin (CCK) positive interneurons (low threshold spiking interneurons) (12–14), and are widely expressed at lower (but still functionally important) levels in glutamatergic neurons (15). CB_1 receptors are highly abundant in medium spiny neurons in both the dorsal and ventral striatum (16–18). Expression is particularly high on the direct pathway axons as they enter the globus pallidus heading towards the substantia nigra (19). Cerebellar CB_1 receptors are found in parallel and climbing fibers, as well as in basket cells (20, 21). While CB_1 has been detected on many neurons, functionally relevant expression of CB_1 in glial elements has also been reported by a number of independent groups (22–24).

CB_2 receptors are expressed at much lower levels in the CNS compared to CB_1. This receptor is primarily present in microglia and vascular elements (25, 26). However, CB_2 does appear to be expressed by some neurons, particularly under certain pathological conditions (e.g., nerve injury) (27, 28), and see (29) for a discussion of the caveats on examining CB_2 in the brain. Accumulating genetic and animal model evidence suggests a link between CB_2 receptors and an increased risk for schizophrenia (5, 30–32), however if this due to neuronal CB_2, microglial CB_2, or a neurodevelopmental role of CB_2 remains an unknown, but important question. A particularly interesting feature of CB_2 receptors is that they appear to be highly inducible, with expression in CB_2 increasing up to 100 fold following tissue injury or during inflammation (33). It remains to be determined whether observed increases in CNS CB_2 is due to increased expression of CB_2 on cells intrinsic to the CNS, or is a result of the migration (e.g. CB_2-expressing monocytes) of peripheral immune cells into the CNS.

TRP channels, especially TRPV1, are activated by anandamide under certain conditions (34). The relative roles of cannabinoid receptors and TRP channels in anandamide's actions appear variable. Anandamide also activates PPARalpha and gamma, with significant effects on gene transcription (35, 36). It is important to keep in mind that increasing anandamide by decreasing its degradation by inhibition of fatty acid aminohydrolase (FAAH) also increases levels of other N-acylamides, which can modulate PPARα (37, 38).

Endocannabinoid synthesis

Despite anandamide and 2-AG both containing arachidonic acid, their routes of synthesis and degradation in vivo are almost completely distinct and are mediated by different enzymes (39). Most anandamide appears to be produced from N-arachidonoyl phosphatidyl ethanol (NAPE), while 2-AG is produced from 2-arachidonoyl-containing phospholipids, primarily arachidonoyl-containing phosphatidyl inositol bis-phosphate (PIP2) (Fig. 2). An important consideration in 2-AG biology is that, in addition to serving as an endogenous ligand for cannabinoid receptors, 2-AG is an important metabolic intermediate in lipid synthesis and also serves as a major source of arachidonic acid in prostaglandin synthesis (40). Thus, manipulation of 2-AG production and degradation can have wide-ranging effects that are quite independent of ECS. For example, 2-AG in the brain, liver, and lung, but not in the gut, heart, kidney, or spleen, is the major source of arachidonic acid used for prostaglandin synthesis (40). A second implication is that the measurement of bulk tissue

levels of 2-AG is an indirect measure of “synaptically-active” or “interstitial” 2-AG, which is most relevant for cannabinoid receptor signaling and might be more accurately measured by microdialysis (41).

Synthesis of anandamide has been proposed to occur by multiple pathways (Fig. 2A), presumably this varies among brain regions and different pathways may be favored for distinct physiological and pathophysiological processes. Several groups have found alterations in levels of anandamide and related acylamides in schizophrenic individuals (42–44) and this is discussed in more detail in Chapter 14. Interestingly, D2-like dopamine receptor stimulation increases anandamide levels in the striatum and CB_1 receptor antagonists suppress the increased locomotion seen with a D2-like receptor agonist (45). Thus, elucidating anandamide synthetic pathways may be important for understanding the etiology of schizophrenia. Four routes for anandamide synthesis have been proposed: NAPE-PLD (46), NAPE-phospholipase C (PLC) followed by phosphatase (47), dual hydrolysis of the acyl groups by the phospholipase B, ABHD4, followed by hydrolysis by GDE1 (48), and hydrolysis of one acyl group, followed by the liberation of anandamide by the action of a lyso-NAPE-PLD (49) (Fig. 2A). Hydrolysis of NAPE by a NAPE-specific phospholipase D was the first route identified for synthesis of anandamide from cells (50). A mammalian calcium-stimulated NAPE-PLD has been cloned and characterized (51). Genetic deletion of NAPE-PLD has variable effects on anandamide levels (47, 52, 53) and NAPE-PLD distribution only partially overlaps with CB_1 receptor distribution. The next best understood route of anandamide synthesis is cleavage of the NAPE phosphodiester bond by a NAPE-selective phospholipase C (PLC) followed by dephosphorylation of the resulting phospho-anandamide (47) to liberate anandamide. This pathway has been most thoroughly studied in immune cells; however it may also be present in brain (47). The remaining two synthetic pathways have been delineated in expression systems, but their roles in producing CNS anandamide remain to be elucidated (49).

The synthetic pathways for 2-AG are simpler than those for anandamide (Fig. 2C). Most 2-AG appears to be made by the sequential hydrolysis of an arachidonoyl-containing PIP2 (often 1-stearoyl-2-arachidonoyl-sn-glycerol (54, 55)) by a PLCβ followed by hydrolysis of the resulting diacylglycerol by diacylglycerol lipase (DAGL) (56). The first pathway will be engaged following the stimulation of receptors that activate PLC (e.g., receptors such group I metabotropic glutamate, M1 or M3 muscarinic, orexin A, etc.) will often lead to production of 2-AG. Two isoforms of DAGL have been found, DAGLα and DAGLβ (57). Based on knockout mice data, DAGLα appears to be the isoform responsible for most 2-AG production that is contributes to synaptic plasticity in the adult CNS (58, 59). Anatomical studies place receptors such as mGluR5 and DAGLα in close proximity to one another in dendritic spines, apposed to presynaptic CB1 receptors (60–62). While DAGLα seems the dominant 2-AG producing lipase in adult CNS, DAGLβ may contribute to synaptic 2-AG under certain conditions (63) and plays an important role in the generation of 2-AG during immune responses (64). A secondary pathway for 2-AG synthesis could be cleavage of the phosphatidyl inositol precursor by a phospholipase A, followed by hydrolysis of the phosphate ester bond by a lyso-phospholipase C, however the importance of this pathway in brain remains to be established.

Endocannabinoid degradation

Anandamide degradation in the CNS is primarily by the enzyme fatty acid amino hydrolase (FAAH) (Fig. 2B) (65). As its name suggests, FAAH degrades multiple fatty acid amides, including palmitoyl and oleoyl ethanolamide. This has important experimental and therapeutic implications as inhibition of FAAH increases levels of these ethanolamides, which have widespread actions independent of cannabinoid receptors for example, (34, 38). A second pathway for anandamide degradation is via oxidation by cyclooxygenase-2 (COX-2), to create prostamides (Fig. 2B) (66). These compounds have distinct biological actions that are independent of cannabinoid receptors, have their own unique pharmacology and have a significant role as a therapy for intraocular hypertension (66, 67). The differences in structure between arachidonic acid and anandamide are sufficient to allow the development of COX-2 inhibitors that inhibit anandamide oxidation without affecting prostaglandin formation (68). Furthermore, COX-2 is reasonably selective for anandamide over other acyl ethanolamides, so its inhibition offers a more selective way to increase anandamide when compared to inhibition of FAAH (69). A third potential route of anandamide degradation is via N-acylethanolamine-hydrolyzing acid amidase (NAAA) (Fig. 2B) (70). Inhibition of FAAH may shunt anandamide metabolism to one of these alternative pathways, altering cell functions that may be independent of cannabinoid receptor engagement.

2-AG degradation is primarily due to three hydrolytic enzymes, monoacylglycerol lipase (MGL) and alpha/beta domain hydrolases 6 and 12 (ABHD6 and 12) (Fig. 2D)(71). Additionally, 2-AG can be oxidized by COX-2 (69), and hydrolyzed under some conditions by FAAH. The first three enzymes have different subcellular localizations, which likely define degradation of 2-AG in different cellular compartments. MGL is widespread and in the adult nervous system is primarily localized in synaptic terminals (72). It appears to account for the majority of 2-AG hydrolysis in a broad survey of brain 2-AG hydrolytic activity (71). One consequence of MGL inhibition is increased 2-AG signaling at CNS CB1 receptors e.g. (73–76), however, it also reduces available levels of arachidonic acid, which is required for prostaglandin synthesis. Subsequently, prostaglandin-mediated inflammatory processes are lessened by MGL inhibition (40). In contrast to the presynaptic localization of MGL (17, 18), ABHD6 is primarily localized to dendrites and dendritic spines of excitatory neurons in cortex (77). Inhibition of ABHD6 also increases 2-AG signaling through CB1 receptors in the CNS (77, 78). ABHD6 also has significant functions outside of the CNS e.g., (79, 80), which will complicate the application of ABHD6-based therapies to CNS disorders. ABHD12 is the other major hydrolytic enzyme suggested to be involved in the hydrolysis of 2-AG in brain. While its role in 2-AG metabolism *in vivo* is not firmly established, it plays a significant role in the degradation of long chain lyso-phosphatidylserines (81). Intriguingly, in humans ABHD12 loss of function mutations are associated with the neurodegenerative PHARC syndrome (82) and increased levels of long chain lysophosphatidyl serine (83). COX-2 metabolism of 2-AG (Fig. 2D) in the CNS is considerable, as evidenced by increased 2-AG signaling through CB1 receptors followed by inhibition of COX-2 (84, 85). Interestingly, a major oxidative metabolite of 2-AG, PGE_2-glycerol ester (PGE_2-GE), potentiates synaptic transmission, enhances synaptic plasticity,

and produces hyperalgesia (86–88). As 2-AG acting via CB_1 receptors generally suppresses synaptic transmission and neuronal excitability (see below) and PGE_2-GE is excitatory, changes in COX-2 levels or activity may have profound effects on CNS network activity.

Endocannabinoids as retrograde synaptic messengers

The presynaptic localization of CB_1 receptors and their ability to inhibit synaptic transmission, coupled with the postsynaptic localization of some endocannabinoid synthesizing enzymes, and the observation that postsynaptic activity (specifically, increases in intracellular calcium and activation of Gq/11-linked G protein-coupled receptors) increase endocannabinoid production, suggest that endocannabinoids, particularly 2-AG, may be a retrograde messenger. This hypothesis is supported by considerable experimental evidence (reviewed by, (89)). Three basic forms on endocannabinoid-mediated synaptic plasticity involving endocannabinoids as retrograde messengers have been described (Fig. 3). These are: (1) depolarization-induced suppression of inhibition (DSI)/depolarization-induced suppression of excitation (DSE), (2) metabotropic-induced suppression of inhibition (MSI)/ metabotropic-induced suppression of excitation (MSE) (also known as synaptically-evoked suppression of inhibition/excitation (SSE/SSI) (21) or endocannabinoid-mediated short term depression (eCB-STD) (89)), and (3) endocannabinoid-mediated long term depression (eCB-LTD).

DSI/DSE

Depolarization-induced suppression of inhibition (or excitation) (Fig. 3A) is found in many neurons. DSI is the transient suppression of inhibitory input onto a neuron following the strong activation (repeated action potential or a step depolarization) that last for a few tens of seconds (90, 91). DSE is precisely the same phenomenon, except excitatory inputs are affected (92). In 2001 three groups published the finding that endocannabinoids are likely the retrograde messenger for DSI and DSE in hippocampus and cerebellum (92–94). A general finding is that inhibitory synapses are more sensitive to depolarization-induced suppression of synaptic transmission than excitatory synapses (95). A great deal of work in subsequent years has investigated mechanisms and extended these results to many other neurons and brain regions, suggesting endocannabinoids (likely, 2-AG) are a major contributor to short term synaptic plasticity reviewed by (89, 96, 97).

Interestingly, tonic activation of CB_1 receptors by endocannabinoids is evident at several inhibitory synapses (98, 99), which may have important functional consequences when these synapses are exposed to THC. While DSE/DSI are primarily discussed in terms of inhibition of glutamate or GABA release, it is important to keep in mind that activation of CB_1 receptors can also inhibit release of peptides, such as CCK often found in CB_1 receptor positive terminals (100).

MSI/MSE

Metabotropic induced suppression of inhibition (or excitation) (Fig. 3B) is a similarly ubiquitous form of endocannabinoid-mediated short-term synaptic plasticity. It occurs following the engagement of a post-synaptic Gq/11-linked GPCR and the activation of a

phospholipase Cβ. The diacylglycerol produced by the phospholipase C is then deacylated by diacyl glycerol lipase to yield 2-AG, which diffuses presynaptically to activate CB_1 receptors and suppress synaptic transmission. MSI and MSE are elicited by a wide number of Gq/11 coupled GPCR's, including mGluR1, mGluR5, M1, M3, orexinA, CCK_A, and α1 adrenergic receptors, among others (89). The calcium sensitivity of PLCβ1 (101) results in a synergistic interaction between depolarization- and metabotropic-induced suppressions of inhibition/excitation. Thus, these two forms of retrograde synaptic plasticity can serve as a coincidence detector of Gq/11-linked signaling and post-synaptic depolarization or calcium influx (102, 103).

LTD

Long-term depression (LTD) is a ubiquitous form of a long-lasting inhibition of synaptic strength and is elicited by multiple mechanisms. Endocannabinoids can induce both homosynaptic and heterosynaptic LTD (eLTD) (Fig. 3C). Homosynaptic eLTD is LTD at the synapse being stimulated. It is typically evoked by persistent low frequency stimulation and is prominent at glutamatergic synapse in both dorsal and ventral striatum (104, 105). Heterosynaptic eLTD occurs at synapses adjacent to the stimulated synapses. For example, stimulation of Schaffer collaterals in hippocampal CA1 leads to a persistent decrease in GABAergic inhibition of CA1 pyramidal neurons (106). The mechanism of eLTD at hippocampal inhibitory synapses appears to require inhibition of adenylyl cyclase and the involvement of the presynaptic proteins, RIM1α and RAB3B (107, 108). This is a very interesting form of *metaplasticity* as by removing inhibition, eLTD of inhibitory synapses increases dendritic excitability, which will potentiate excitatory transmission over a narrow spatial domain (109). eLTD appears to be involved in the maturation of cortical circuits (110), so it is tempting to speculate that its disruption by THC and related cannabinoids in cannabis might lead to subtle developmental abnormalities, which when accompanied by other environmental or genetic insults may predispose an individual to psychiatric disease. Mechanistically diverse forms of endocannabinoid-induced LTD have also been described, which either involve (111), or don't involve (112) CB_1 receptors.

SSI

In addition to inducing several forms of synaptic plasticity, endocannabinoids, particularly 2-AG, also can directly suppress neuronal excitability through a process termed slow-self inhibition (SSI) (113) (Fig. 3D). SSI is most prominent in low threshold-spiking cortical interneurons (113) and cerebellar basket cells (114), but also appears to be present in some cortical principal cells (115). The mechanism of SSI appears to involve synthesis of 2-AG during intense stimulation of the neuron, activation of somatic CB_1 receptors, and activation of a somatic potassium conductance, likely an inwardly rectifying potassium channel (116).

Interactions between THC and endocannabinoids

The predicted and observed interactions between THC and the endocannabinoids with CB_1 receptors are potentially complex and deserve additional consideration. Both THC and anandamide are low efficacy agonists e.g., (2). Under conditions of either low receptor density or limiting post-receptor effectors (117), they may *antagonize* CB_1 receptor

signaling elicited by 2-AG. Indeed, this has been observed in several systems (111, 118, 119). However, in other systems THC (and anandamide) acts as an efficacious CB_1 receptor agonist (120, 121). So, what is going on in the brain of a person imbibing in cannabis? Evidence that acute responses to cannabis involves both agonism and antagonism of CB_1 receptor signaling is the observation that even repeated, very high doses of the CB_1 receptor antagonist, rimonabant, modestly attenuated the subjective measures of "high," while substantially suppressing the tachycardia induced by cannabis (122). This contrasts to the rapid reversal of the subjective effects of morphine following the administration of naloxone (123). Similarly, oral rimonabant did not elicit a precipitated withdrawal syndrome in humans taking moderate doses of THC in a supervised environment (124). However, following chronic high dose THC in rodents, rimonabant elicits a robust withdrawal syndrome (125). These two observations may be reconciled by noting that the THC's low efficacy, coupled with the sparse receptor occupancy likely attained in casual human cannabis use, compared to what can be achieved in experimental models, in the clinical setting (126, 127), or with cannabis strains of high THC content (128, 129), may result in milder acute effects in population studies. Finally, the use of highly potent, highly efficacious cannabinoid receptors agonists typically present in synthetic marijuana preparations ("spice") results in a greater incidence of adverse psychiatric effects, that may be attributable to their higher intrinsic efficacy (130). In summary, the interactions of THC, CB_1, and the endocannabinoids are more complex than THC simply "hijacking" CB_1 receptors as another agonist and need to be carefully considered.

Summary

An involvement of the endocannabinoid system with schizophrenia is supported both by the epidemiological observation that increased cannabis use is associated with a heightened risk for schizophrenia and that acute consumption of cannabis or synthetic cannabinoids can elicit psychotic symptoms in susceptible individuals. It is likely that the former observation has its basis in cannabis interfering with the neurodevelopmental roles of endocannabinoids, while the latter observation is due to interactions between THC in cannabis with ongoing endocannabinoid-mediated synaptic plasticity. Focusing on the latter, several challenges remain: 1. What is the role and mechanism by which cannabidiol attenuates the acute effects of THC? 2. Will the synthetic cannabinoids found in "spice" preparations produce more severe psychotic symptoms? 3. What are the roles of CB_1 receptors on non-neuronal CNS cells (oligodendrocytes, astrocytes, and microglia) in mediating the acute effects of cannabis? 4. What is the role and mechanism underlying the relationship between CB_2 and schizophrenia? 5. Is there a physiological basis for the observation that many schizophrenic patients regularly use cannabis? 6. Will manipulations of the endocannabinoid system by therapeutically beneficial in schizophrenia? The answers to these questions will greatly enhance our understanding of the relationship between cannabis, the endocannabinoid system and schizophrenia.

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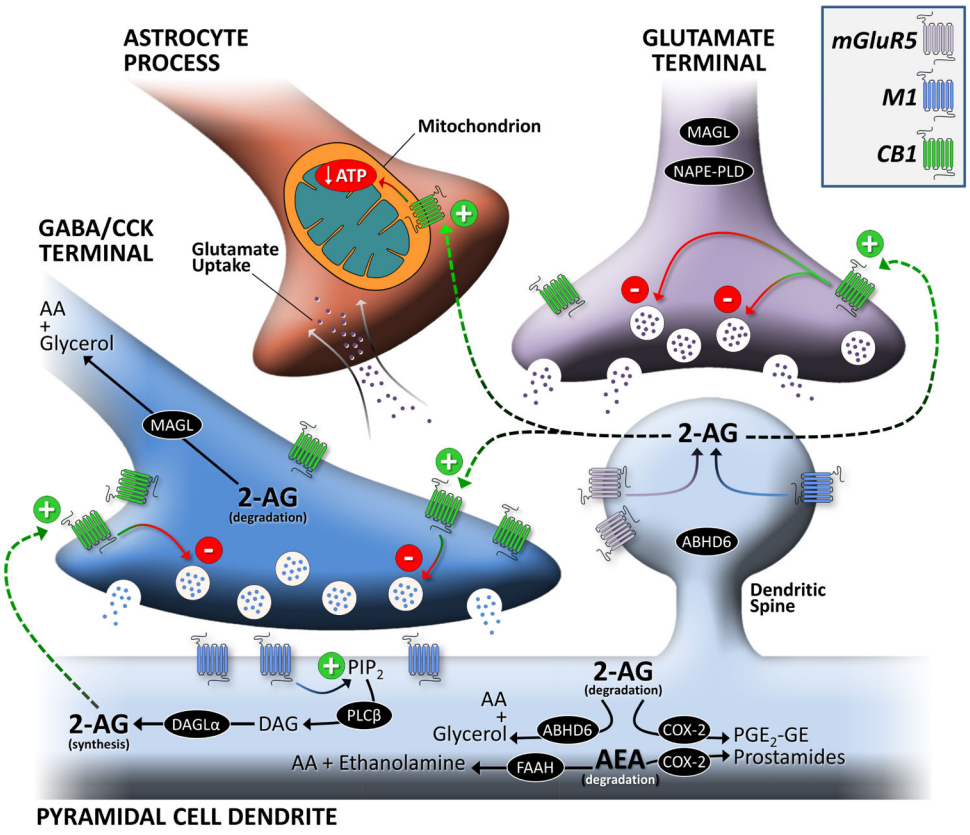

Fig. 1. Overview of the localization of endocannabinoid system components at the synapse

Schematic of an inhibitory and excitatory terminal synapsing onto the dendritic shaft of a representative cortical principal neuron. Abbreviations: ABHD6, alpha/beta domain-containing hydrolase 6; CB_1, CB_1 cannabinoid receptor; CCK, cholecystokinin; COX-2, cyclooxygenase-2; DAGLα, diacylglycerol lipase α; M1, M1 muscarinic receptor; MAGL, monoacylglycerol lipase; mGluR5, metabotropic glutamate receptor 5; NAPE-PLD, N-arachidonoyl phosphatidyl ethanolamine-preferring phospholipase D; PLCβ, phospholipase C β. The increased number of CB_1 receptors on the CCK/GABA terminal represents the higher density of CB_1 receptors found on these axon terminals.

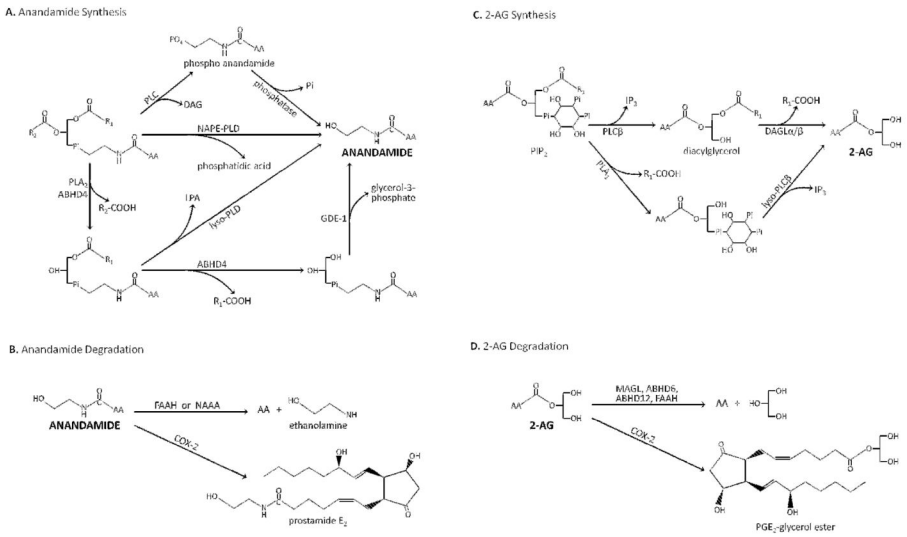

Fig. 2. Potential synthetic and degradative pathways for anandamide and 2-AG

A. Primary synthetic pathways for anandamide. **B.** Primary degradative pathways for anandamide. **C.** Primary synthetic pathways for 2-AG. **D.** Primary degradative pathways for 2-AG. Only major pathways are shown. More comprehensive details can be found in recent reviews (131–133). Abbreviations: AA, arachidonic acid; ABHD4, alpha/beta domain-containing hydrolase 4; ABHD6, alpha/beta domain-containing hydrolase 6; ABHD12, alpha/beta domain-containing hydrolase 12; COX-2, cyclooxygenase-2; DAG, diacylglycerol; DAGL, diacylglycerol lipase; FAAH, fatty acid aminohydrolase; GDE-1, glycerophosphodiesterase GDE-1; IP_3, inositol tris-phosphate; LPA, lyso-phosphatidic acid; lyso-PLC, lyso-phospholipid-preferring phospholipase C; MAGL, monoacyl glycerol lipase; NAAA, N-acyl ethanolamine amino hydrolase; NAPE-PLD, N-arachidonoyl phosphatidyl ethanol-preferring phospholipase D; PIP_2, phosphatidyl inositol bis-phosphate; Pi, PO_4; PLA_2, phospholipase A_2; PLC, phospholipase C;

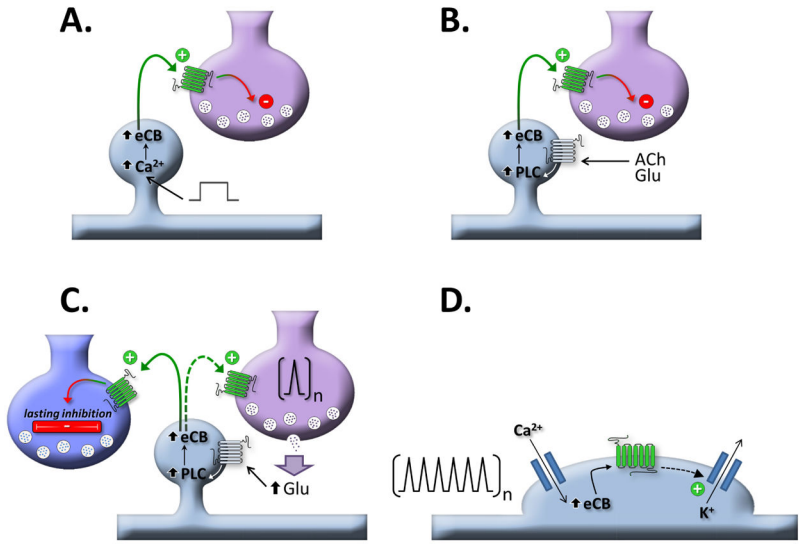

Fig. 3. Forms of endocannabinoid-mediated synaptic plasticity and endocannabinoid mediated cell-autonomous regulation of excitability

A. Depolarization-induced suppression of excitation/inhibition. **B.** Metabotropic-induced suppression of excitation/inhibition. **C.** Homosynaptic and heterosynaptic long-term depression. **D.** Slow self inhibition. See text for details.