Review

Biological Psychiatry

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 development, synaptic plasticity, and the response to endogenous and environmental insults. The ECS comprises cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids. The most abundant cannabinoid receptors are the CB_1 cannabinoid receptors; however, CB_2 cannabinoid receptors, transient receptor potential channels, and peroxisome proliferator activated receptors are also engaged by some cannabinoids. Exogenous cannabinoids, such as tetrahydrocannabinol, produce their biological effects through their interactions with cannabinoid receptors. The best-studied endogenous cannabinoids are 2-arachidonoyl glycerol and arachidonoyl ethanolamide (anandamide). Despite similarities in chemical structure, 2-arachidonoyl glycerol and anandamide are synthesized and degraded by distinct enzymatic pathways, which impart fundamentally different physiologic and pathophysiologic roles to these two endocannabinoids. As a result of the pervasive social use of cannabis and the involvement of endocannabinoids in a multitude of biological processes, much has been learned about the physiologic and pathophysiologic roles of the ECS. This review provides 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

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The endocannabinoid system (ECS) has emerged as an important neuromodulatory system over the last 25 years. Relevant to the topic of this special issue of *Biological Psychiatry*, perturbations of the ECS are involved in several psychiatric disorders, including schizophrenia. The ECS comprises endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and the enzymes responsible for the synthesis and degradation of endocannabinoids (Figure 1). Each of these components is introduced in this article, with an emphasis on their potential involvement in psychosis.

Endogenous cannabinoids are endogenous lipids that engage cannabinoid receptors (see later), affecting behavior in a fashion that at least partially recapitulates the effects produced by the psychoactive components of cannabis, most notably (−)-*trans*-Δ^9-tetrahydrocannabinol (THC). The first discovered and best-characterized endocannabinoids are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG). An important feature of these endocannabinoids is that their precursors are present in lipid membranes. On demand (typically by activation of certain G protein–coupled receptors [GPCRs] or by depolarization), endocannabinoids are liberated in one or two rapid enzymatic steps and released into the extracellular space. In contrast, classic neurotransmitters 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 CB_1 and CB_2 cannabinoid receptors, whereas anandamide is a low-efficacy agonist for CB_1 receptors and a very-low-efficacy agonist for CB_2 receptors (1,2). 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; the biology of these compounds is not as well developed as the biology of anandamide and 2-AG, and they will not be considered further in this review. This review introduces the components of the ECS and discusses their role in modulating synaptic transmission. Other articles 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 (e.g., peroxisome proliferator activated receptors [PPARs] and transient receptor potential [TRP] channels; discussed subsequently) also mediating some endocannabinoid actions, particularly of the acylethanolamides. As discussed in more detail in another article, polymorphisms of cannabinoid

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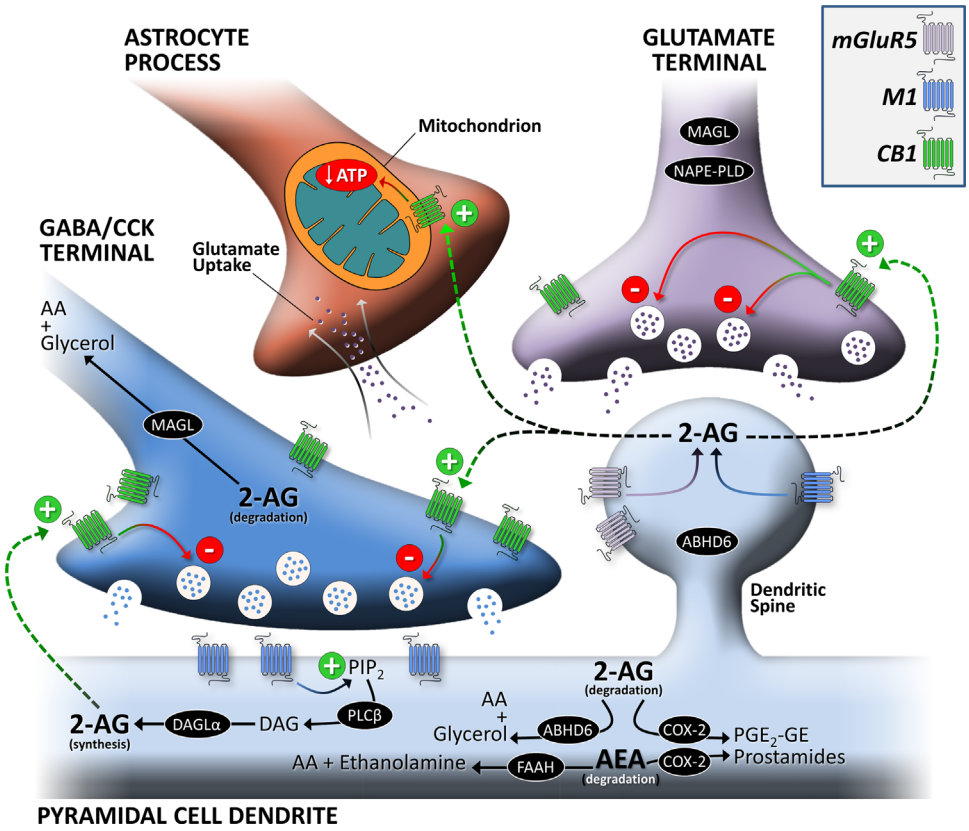

Figure 1. Overview of the localization of endocannabinoid system components at the synapse. Schematic of an inhibitory and excitatory terminal synapsing onto the dendritic shaft of a representative cortical principal neuron. The increased number of CB_1 receptors on the CCK/GABA terminal represents the higher density of CB_1 receptors found on these axon terminals. AA, arachidonic acid; ABHD6, alpha/beta domain-containing hydrolase 6; 2-AG, 2-arachidonoyl glycerol; ATP, adenosine triphosphate; CB_1, CB_1 cannabinoid receptor; CCK, cholecystokinin; COX-2, cyclooxygenase-2; DAG, diacylglycerol; DAGLα, diacylglycerol lipase α; GABA, γ-aminobutyric acid; M_1, M_1 muscarinic receptor; MAGL, monoacylglycerol lipase; mGluR5, metabotropic glutamate receptor 5; FAAH, fatty acid aminohydrolase; NAPE-PLD, N-arachidonoyl phosphatidyl ethanolamine-preferring phospholipase D; PGE_2-GE, prostaglandin E_2 glycerol ester; PIP_2, phosphatidyl inositol bisphosphate; PLCβ, phospholipase C β.

receptor and ECS genes are variably associated with schizophrenia (5-8) and possibly with response to atypical antipsychotics (9). The CB_1 and CB_2 cannabinoid receptors are GPCRs, which primarily couple to G proteins of the G_i and G_0 classes (4). Their activation inhibits adenylyl cyclases and certain voltage-dependent calcium channels and activates several mitogen-activated protein kinases inwardly rectifying potassium channels, with some variation depending on the particular cell type (4). Activation of CB_1 or CB_2 receptors exerts diverse consequences on cellular physiology, including synaptic function, gene transcription, and cell motility (4).

CB_1 receptors are abundant in the central nervous system (CNS), particularly in cortex, basal ganglia, hippocampus, and cerebellum (10). Most CB_1 receptors are present on axon terminals and preterminal axon segments, while sparing the active zone (Figure 1) (11). Cortical and hippocampal CB_1 receptors are particularly enriched on cholecystokinin-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 the dorsal and ventral striatum (16-18). Expression is particularly high on the direct pathway axons as they enter the globus pallidus heading toward the substantia nigra (19). Cerebellar CB_1 receptors are found in parallel and climbing fibers and in basket cells (20,21). Although CB_1 receptors have been detected on many neurons, functionally relevant expression of CB_1 receptors in glial elements has also been reported by numerous independent groups (22–24).

CB_2 receptors are expressed at much lower levels in the CNS compared with CB_1 receptors. These receptors are primarily present in microglia and vascular elements (25,26). However, CB_2 receptors appear to be expressed by some neurons, particularly under certain pathologic conditions (e.g., nerve injury) (27,28); Atwood and Mackie (29) discussed the caveats on examining CB_2 receptors 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, whether this increased risk is due to neuronal CB_2 receptors, microglial CB_2 receptors, or a neurodevelopmental role of CB_2 receptors remains an unanswered but important question. CB_2 receptors appear to be highly inducible, with expression in CB_2 receptors increasing up to 100-fold after tissue injury or during inflammation (33). It remains to be determined whether observed increases in CNS CB_2 receptors 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 actions of anandamide appear to be variable. Anandamide also activates PPAR-α and PPAR-γ, with significant effects on gene transcription (35,36). Increasing anandamide by decreasing its degradation through inhibition of fatty acid aminohydrolase (FAAH) also increases levels of other N-acylamides, which can modulate PPAR-α (37,38).