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Review article

New insights on endocannabinoid transmission in psychomotor disorders

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ABSTRACT

The endocannabinoids are lipid signaling molecules that bind to cannabinoid CB_1 and CB_2 receptors and other metabotropic and ionotropic receptors. Anandamide and 2-arachidonoyl glycerol, the two best-characterized examples, are released on demand in a stimulus-dependent manner by cleavage of membrane phospholipid precursors. Together with their receptors and metabolic enzymes, the endocannabinoids play a key role in modulating neurotransmission and synaptic plasticity in the basal ganglia and other brain areas involved in the control of motor functions and motivational aspects of behavior.

This mini-review provides an update on the contribution of the endocannabinoid system to the regulation of psychomotor behaviors and its possible involvement in the pathophysiology of Parkinson's disease and schizophrenia.

Contents

1. The endocannabinoid system

The endocannabinoid (EC) system consists of a family of lipid signaling molecules (endocannabinoids) and their associated metabolic enzymes and receptors, which modulate various physiological processes, including vasodilation, immune responses, synaptic transmission, cognition, pain and motor activity to name a few.

In addition to the well-known cannabinoid CB_1/CB_2 receptors and their endogenous ligands, anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), other molecular entities, such as noladin-ether, N-arachidonoyl-dopamine and virhodamine, as well as non-CB_1/CB_2

Abbreviations: AEA, anandamide; 2-AG, 2-Arachidonoyl Glycerol; CSF, Cerebrospinal Fluid; DSE, Depolarization-induced Suppression of Excitation; DSI, Depolarization-induced Suppression of Inhibition; EC, Endocannabinoid; FAAH, Fatty Acid Amide Hydrolase; MSN, Medium Spiny Neurons; PPAR, Peroxisome Proliferator-activated Receptors; PCP, Phencyclidin; PD, Parkinson's Disease; PET, Positron Emission Tomography; SSI, Slow Self Inhibition; THC, Tetrahydrocannabinol; TRP, Transient Receptor Potential receptors; VTA, Ventral Tegmental Area.

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receptors are now considered part of the EC system (Bisogno et al., 2000; Hanus et al., 2001; Kreitzer and Stella, 2009; Porter et al., 2002). The complexity of this system has clear implications for the design and translational applications of future cannabinoid-based therapies.

This mini-review addresses recent discoveries on EC transmission within the central nervous system (CNS), focusing in particular on the contribution of traditional cannabinoid and non-CB_1/CB_2 receptors to the pathophysiology of Parkinson's disease (PD) and schizophrenia.

1.1. Endocannabinoids and their metabolizing enzymes

The endocannabinoids (ECs) are naturally occurring lipids that activate cannabinoid CB_1/CB_2 receptors and mimic the pharmacological effects of the psychoactive constituent of marijuana, Δ^9-tretrahydrocannabinol (THC). To date, arachidonoylethanolamine (AEA) and 2-AG are the two most studied ECs. Details on the EC biosynthetic enzymes and their CNS distribution have been covered by other articles and reviews (Liu et al., 2008; Nyilas et al., 2008; Simon and Cravatt, 2006; Ueda et al., 2011) and will not be discussed here.

AEA is a partial agonist at both cannabinoid receptor subtypes and can also bind to other non-CB_1/CB_2 receptors, such peroxisome proliferator-activated receptors (PPAR), TRPV1 channels and the orphan receptor GPR55 (see below).

The biological actions of AEA are terminated via a carrier-mediated uptake, whose molecular identity remains controversial (Fegley et al., 2004; Glaser et al., 2003; Hillard and Jarrahian, 2003), followed by enzymatic hydrolysis via a fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996; Wei et al., 2006). Administration of exogenous AEA to $FAAH^{-/-}$ mice may lead to the production of prostaglandin-like compounds (prostamides) through a COX-2-dependent pathway (Weber et al., 2004). Although AEA has low affinity for COX-2, this metabolic pathway may become physiologically relevant under conditions promoting COX-2 upregulation, such as neurotoxic insults and neurodegenerative disorders characterized by an inflammatory component, such as Parkinson's disease (Teismann et al., 2003; Vila et al., 2001).

Several lipoxygenases (such as, 12-LOX and 15-LOX) and P450 may also convert AEA into signaling lipids that activate classic cannabinoid receptors, as well as non-CB_1/CB_2 receptors (Kozak and Marnett, 2002; Snider et al., 2009).

2-AG, which is a full agonist at cannabinoid receptors, acts as a retrograde messenger on pre-synaptic CB_1 receptors located on excitatory and inhibitory synapses, and as an autocrine mediator of post-synaptic slow self-inhibition (SSI) in neocortical interneurons (Freund et al., 2003; Kreitzer and Regehr, 2001; Marinelli et al., 2008; Wilson and Nicoll, 2001).

Unlike AEA, 2-AG does not bind to TRPV1 or PPAR receptors, but can activate GPR55 receptors *in vitro* and a not-yet identified G-protein-coupled receptors that controls cell migration and viability (Pertwee et al., 2010; Ryberg et al., 2007).

2-AG is uptaken intracellularly through the AEA transporter, and can be metabolized by either FAAH, or the serine hydrolase MAGL, which represents the main 2-AG hydrolyzing enzyme in neurons (Beltramo and Piomelli, 2000; Dinh et al., 2002; Long et al., 2009; Muccioli et al., 2007; Schlosburg et al., 2010). Pharmacological inhibition of MAGL increases 2-AG levels in the brain (Hohmann et al., 2005), potentiates its effects *in vitro* and *in vivo* (Long et al., 2009; Makara et al., 2005), and significantly reduces brain arachidonic acid and associated eicosanoids under basal and neuroinflammatory conditions, suggesting that MAGL is a CNS metabolic node coupling EC to prostaglandin signaling (Nomura et al., 2011).

MAGL genetic ablation has been shown to alter EC-mediated synaptic plasticity in mouse hippocampus and cerebellum via 2-AG-induced persistent activation and consequential desensitization of CB_1 receptors (Pan et al., 2011; Zhong et al., 2011). Interestingly, although $MAGL^{-/-}$ mice have normal locomotor activity, they show enhanced learning behavior, suggesting the involvement of MAGL in the regulation of cognitive function (Chanda et al., 2010; Pan et al., 2011).

Recently, Marrs et al. (2010) showed that the knockdown of the serine hydrolase alpha-beta-hydrolase domain 6 (ABHD6) reduced 2-AG hydrolysis *in vitro* and increased the efficacy of 2-AG-induced stimulation of cell migration. Also, inhibition of either ABHD6 or MAGL had similar effects on the CB_1-dependent stimulation of long-term depression in mouse cortical excitatory synapses, suggesting that ABHD6 may control the amount of 2-AG reaching pre-synaptic CB_1 receptors (Marrs et al., 2010).

1.2. Cannabinoid and GPR55 receptors

The two main metabotropic cannabinoid receptors, CB_1 and CB_2, are $G_{i/o}$-coupled receptors (GPCR) that initiate, upon activation, signaling events typically associated with this class of G proteins, i.e. inhibition of cAMP accumulation and protein kinase (PKA) activity (Pertwee et al., 2010). Stimulation of CB_1 receptors has been shown to inhibit N and P/Q-type voltage-gated Ca^{2+} channels and M-type K^+ channels (Schweitzer, 2000; Twitchell et al., 1997), and to activate A-type and inwardly rectifying K^+ currents, which have been implicated in the CB_1-mediated depression of GABA and glutamate release (Gerdeman and Lovinger, 2001; Kreitzer and Regehr, 2001; Mu et al., 1999; Wilson et al., 2001). CB_1 receptors can also indirectly modulate the activity of dopaminergic pathways via pre- and post-synaptic mechanisms (for review, see Laviolette and Grace, 2006).

Distinct cannabinoid ligands, and/or concomitant activation of other GPCR, may promote the coupling of CB_1 receptors to different G_i isoforms (Glass and Felder, 1997; Mukhopadhyay and Howlett, 2005; Shoemaker et al., 2005), as well as the formation of heterodimers with dopamine D_2 and mu-opioid receptors (Hojo et al., 2008; Kearn et al., 2005). Different cannabinoid agonists may also stabilize unique cannabinoid receptor conformations, thus leading to functional selectivity in downstream signaling and diverging effects on receptor internalization and desensitization (Atwood et al., 2012; Straiker et al., 2011).

CB_1 receptors are mainly localized pre-synaptically, which is consistent with their proposed modulatory role of inhibitory and excitatory neurotransmission (Piomelli, 2003). Within the striatum, a brain area relevant to the pathophysiology of PD and schizophrenia, most studies agree that CB_1 receptors are expressed on parvalbumin-positive GABAergic interneurons, on cholinergic subpopulations (Fusco et al., 2004; Uchigashima et al., 2007), on collaterals from GABAergic medium spiny neurons (MSN), and on glutamatergic, but not dopaminergic, afferents (Gerdeman and Lovinger, 2001; Köfalvi et al., 2005; Matyas et al., 2006; Pickel et al., 2006; Uchigashima et al., 2007). CB_1 are also expressed in MSN terminals projecting to the globus pallidus (medial and lateral segments) and to the substantia nigra, as well as on the projections of the subthalamic nucleus to the substantia nigra (Julian et al., 2003; Mailleux and Vanderhaeghen, 1992; Martin et al., 2008). By contrast, the presence of CB_1 receptors in the somatodendritic area of MSN remains controversial (Köfalvi et al., 2005; Matyas et al., 2006; Rodriguez et al., 2001; Uchigashima et al., 2007).

In cortical areas, CB_1 receptors are localized in layers I and IV and, at lower density, in the intermediate layers (Egerton et al., 2006; Herkenham et al., 1991). In primates and humans, CB_1 receptors are highly expressed in the axon terminals of a subpopulation of GABAergic CCK-positive interneurons targeting the perisomatic-region of pyramidal neurons of the dorsolateral prefrontal cortex (Eggan et al., 2008, 2010). Optical density measurements of CB_1 mRNA have shown the highest density in layer II, whereas weak or no expression have been observed in layers I, IV and V (Eggan et al., 2008). In contrast, immunohistochemistry studies indicate that CB_1 expression increases progressively across layers II and III, forms a distinct band in layer IV, falls sharply in layer V and increases again in layer VI (Eggan et al., 2008). From a functional standpoint, this scenario is further complicated by