Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2012 July 2; 38(1): 51–58. doi:10.1016/j.pnpbp.2012.04.002.

New insights on endocannabinoid transmission in psychomotor disorders

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Abstract

The endocannabinoids are lipid signaling molecules that bind to cannabinoid CB₁ and CB₂ 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.

Keywords

cannabinoid; endocannabinoid; basal ganglia; Parkinson; schizophrenia; dyskinesia

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 CB₁/CB₂ 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-CB₁/CB₂ receptors are now considered part of the EC system (Hanus *et al.*, 2001; Bisogno *et al.*, 2000; Porter *et al.*, 2002; Kreitzer and Stella, 2009). The complexity of this system has clear implications for the design and translational applications of future cannabinoid-based therapies.

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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-CB₁/CB₂ 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 CB₁/CB₂ receptors and mimic the pharmacological effects of the psychoactive constituent of marijuana, Δ^9 -tetrahydrocannabinol (THC). To date, arachidonylethanolamine (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 (Simon and Cravatt, 2006; Liu *et al.*, 2008; Nyilas *et al.*, 2008; 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-CB₁/CB₂ 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 Jarrahan, 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 (Vila *et al.*, 2001; Teismann *et al.*, 2003).

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-CB₁/CB₂ 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 CB₁ receptors located on excitatory and inhibitory synapses, and as an autocrine mediator of post-synaptic slow self-inhibition (SSI) in neocortical interneurons (Kreitzer and Regehr, 2001; Wilson and Nicoll, 2001; Freund *et al.*, 2003; Marinelli *et al.*, 2008).

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 (Ryberg *et al.*, 2007; Pertwee *et al.*, 2010).

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; Muccioli *et al.*, 2007; Long *et al.*, 2009; 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 CB₁ receptors (Zhong *et al.*, 2011; Pan *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 and co-workers (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 CB₁-dependent stimulation of long-term depression in mouse cortical excitatory synapses, suggesting that ABHD6 may control the amount of 2-AG reaching pre-synaptic CB₁ receptors (Marrs *et al.*, 2010).

1.2 Cannabinoid and GPR55 receptors

The two main metabotropic cannabinoid receptors, CB₁ and CB₂, 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 CB₁ receptors has been shown to inhibit N and P/Q-type voltage-gated Ca²⁺ channels and M-type K⁺ channels (Twitchell *et al.*, 1997; Schweitzer, 2000), and to activate A-type and inwardly rectifying K⁺ currents, which have been implicated in the CB₁-mediated depression of GABA and glutamate release (Mu *et al.*, 1999; Kreitzer and Regehr, 2001; Wilson *et al.*, 2001; Gerdeman and Lovinger, 2001). CB₁ 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 CB₁ 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 D₂ 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 (Straiker *et al.*, 2011; Atwood *et al.*, 2012).

CB₁ 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 CB₁ 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). CB₁ 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 (Mailleux and Vanderhaeghen, 1992; Julian *et al.*, 2003; Martin *et al.*, 2008). By contrast, the presence of CB₁ 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, CB₁ receptors are localized in layers I and IV and, at lower density, in the intermediate layers (Herkenham *et al.*, 1991; Egerton *et al.*, 2006). In primates and humans, CB₁ 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 (Eggen *et al.*, 2008; Eggen *et al.*, 2010). Optical density

measurements of CB₁ 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 CB₁ 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 the fact that the human CB₁ receptor presents two splicing variants diverging in their amino-terminus sequences (Ryberg *et al.*, 2005). When expressed in hippocampal neurons cultured from CB^{-/-} mice, each variant exhibits distinct signaling properties and produces a less pronounced inhibition of synaptic transmission relative to rodent CB₁ (Straiker *et al.*, 2011).

Unlike CB₁, CB₂ receptors are primarily localized in immuno-competent cells, of which they modulate the mobility and function (Ramirez *et al.*, 2005; Walter and Stella, 2004). Although small levels of CB₂ have been detected in the basal ganglia and glial cells, their presence and distribution in neuronal populations of the brain is still debated (Sagredo *et al.*, 2009; Onaivi, 2011). Several studies have shown that CB₂ receptors are generally upregulated in astrocytes and microglia in response to disease-related neuroinflammatory events, and after neurotoxic insults (Fernandez-Ruiz, 2009; Palazuelos *et al.*, 2009; Price *et al.*, 2009).

The persistence of cannabinoid-like effects after administration of cannabinoid agonists in CB₁^{-/-} and CB₂^{-/-} mice, as well as in mutant mice lacking CB₁ receptors in neuronal subpopulations, clearly indicates that these drugs recognize other non-CB₁/CB₂ targets in the CNS (Marsicano *et al.*, 2002; Begg *et al.*, 2005; Brown, 2007). Among these targets, the orphan receptor GPR55 has received a lot of attention in the last decade (Godlewski *et al.*, 2009; Sawzdargo *et al.*, 1999). GPR55 mRNA is predominantly expressed in the striatum and, to a lesser extent, in the hippocampus, thalamus and cerebellum (Sawzdargo *et al.*, 1999). These data, however, have not been validated by measuring the corresponding protein levels, and neither AEA nor 2-AG have shown consistent pharmacological effects upon stimulation of GPR55 receptors (Yin *et al.*, 2009). Furthermore, GPR55 is activated, rather than inhibited, by the CB₁ antagonists rimonabant and AM251, and blocked by the cannabinoid agonist CP55,940 (Johns *et al.*, 2007; Kapur *et al.*, 2009; Ryberg *et al.*, 2007). Therefore, as GPR55 is phylogenetically distinct from CB₁/CB₂ receptors and is activated by the non-cannabinoid endogenous ligand, lysophosphatidylinositol, this receptor is currently viewed as a non-CB receptor with a binding site for cannabinoid ligands (McPartland *et al.*, 2006; Henstridge *et al.*, 2011).

1.2 TRP channels and other non-CB₁/CB₂ receptors

Exogenous and endogenous cannabinoids interact with at least five distinct transient receptor potential (TRP) receptors, which are ligand-gated ion channels generating a cation inward flow upon activation (Starowicz *et al.*, 2007; Patapoutian *et al.*, 2009). AEA binds to the VR1 subtype (TRPV1) with low-affinity, and inhibition of the AEA degrading enzyme FAAH has been shown to enhance the efficacy and potency of this EC at TRPV1 (Huang *et al.*, 2002; Szolcsanyi, 2000; De Petrocellis *et al.*, 2001). Interestingly, elevation of AEA concentrations by pharmacological or genetic inhibition of FAAH reduced 2-AG levels via TRPV1 receptors (Maccarrone *et al.*, 2008). Similarly, direct stimulation of TRPV1 channels mimicked the effects of endogenous AEA on 2-AG levels through a glutathione-dependent pathway. Since AEA and 2-AG are considered the primary ECs for reducing glutamate and GABAergic inputs to striatal neurons (Gerdeman *et al.*, 2002; Gubellini *et al.*, 2002; Jung *et al.*, 2005), the ability of AEA to affect 2-AG levels via TRPV1 channels may represent a mechanism to integrate excitatory and inhibitory inputs in the basal ganglia.

Several cannabinoid compounds, including WIN55212-2, AEA, noladin ether and virodhamine, have been shown to activate PPAR receptors, which are characterized by a large ligand-binding domain and relative selectivity (Sun *et al.*, 2007). PPAR are ligand-activated transcription factors that form heterodimers with the retinoid X receptor and enhance the expression of several target genes. The three isoforms, α , β/δ and γ , are expressed in neuronal and glial cells of the PNS and CNS (Cimini *et al.*, 2005; Moreno *et al.*, 2004). In particular, PPAR α have been found in TH⁺ cells of the substantia nigra pars compacta and dorsal striatum (Galan-Rodriguez *et al.*, 2009). Low levels of PPAR γ expression have been detected in the ventral mesencephalon and striatum (Bredert *et al.*, 2002), although it is unclear whether this immunoreactivity co-localizes with neuronal or glial markers.

2. Endocannabinoid transmission in the basal ganglia: Relevance for PD

In the basal ganglia, pharmacological, neurochemical and electrophysiological data indicate that ECs act as retrograde signaling molecules at GABAergic and glutamatergic synapses, and promote depolarization-induced suppression of excitation (DSE) and inhibition (DSI) at striatal synapses (Adermark *et al.*, 2009; Gerdeman *et al.*, 2002; Gubellini *et al.*, 2002; Köfalvi *et al.*, 2005; Kreitzer and Malenka, 2007). Several lines of evidence also indicate the existence of a cross talk between the EC and dopaminergic systems. Indeed, ECs can affect dopamine release *in vivo* and modulate the firing activity of dopaminergic neurons by acting at TRPV1 or PPAR receptors (Cheer *et al.*, 2004; Price *et al.*, 2007; Solinas *et al.*, 2006; Melis *et al.*, 2008; de Lago *et al.*, 2004; Marinelli *et al.*, 2003). Also, stimulation of dopamine receptors has been shown to increase the levels of striatal AEA, which may serve as an inhibitory feedback signal countering dopamine-induced motor activity (Giuffrida *et al.*, 1999; Beltramo *et al.*, 2000; Ferrer *et al.*, 2003).

2.1. Cannabinoid effects in PD

The EC ability to modulate neurotransmission and synaptic plasticity in the basal ganglia circuitries has spurred interest to develop cannabinoid-based therapies to treat PD, a neurodegenerative disorder characterized by progressive loss of nigrostriatal neurons, maladaptive striatal plasticity and disabling motor disturbances (Dauer and Przedborski, 2003). Increased CB₁ mRNA and receptor binding have been reported in primate and rodent models of PD (Lastres-Becker *et al.*, 2001; Romero *et al.*, 2000). Although elevated EC levels have been found in the striatum of dopamine-depleted rats (Di Marzo *et al.*, 2000; Gubellini *et al.*, 2002), other studies carried out in rats treated with the neurotoxin 6-hydroxydopamine (6-OHDA) have shown decreased AEA tone (Ferrer *et al.*, 2003; Kreitzer and Malenka, 2007; Morgese *et al.*, 2007). In these animals, administration of levodopa, the mainstay treatment for PD, failed to elevate AEA levels (Ferrer *et al.*, 2003; Morgese *et al.*, 2007) and caused a further upregulation of striatal CB₁ receptors (Zeng *et al.*, 1999), suggesting that levodopa does not correct the EC abnormalities associated with nigro-striatal degeneration.

So far, studies on the effects of cannabinoid agonists and antagonists on PD motor symptoms have produced conflicting results, and there is no general consensus whether cannabinoid-based therapies might be beneficial in PD (Cao *et al.*, 2007; Meschler *et al.*, 2001; Mesnage *et al.*, 2004; Papa, 2008; van der Stelt *et al.*, 2005). These discrepancies are possibly due to species-specific differences across PD models and/or to the specific physiological state of the animals at the time of the experiments, which may both affect EC transmission. Nevertheless, cannabinoid drugs may delay PD progression and the underlying neuroinflammatory process by modulating cell-mediated inflammatory and brain immune responses via cannabinoid receptor-dependent and -independent mechanisms (Molina-

Holgado *et al.*, 2003; Price *et al.*, 2009; Ramirez *et al.*, 2005; Sancho *et al.*, 2003; Walter and Stella, 2004).

Interestingly, chronic stimulation of CB₂ receptors has been shown to protect against MPTP-induced nigrostriatal degeneration by inhibiting microglial activation infiltration, whereas CB₂ genetic ablation exacerbated MPTP systemic toxicity (Price *et al.*, 2009). These observations confirm previous reports in 6-OHDA-treated rats showing CB₁-independent neuroprotective effects of cannabinoids (Garcia-Arencibia *et al.*, 2007; Lastres-Becker *et al.*, 2005). They also suggest that, unlike other neurodegenerative conditions, such as cerebral ischemia and brain trauma, activation of CB₂, rather than CB₁ receptors may be a more effective pharmacological strategy to slow down or halt nigrostriatal degeneration (Marsicano *et al.*, 2003; Nagayama *et al.*, 1999; Panikashvili *et al.*, 2001).

Cannabinoids can also exert neuroprotective actions via their anti-oxidant properties, or by encouraging the proliferation and differentiation of progenitor cells in neurogenic areas (Marsicano *et al.*, 2002; Lastres-Becker *et al.*, 2005; Galve-Roperh *et al.*, 2007).

Recent data point to MAGL as a metabolic node controlling brain prostaglandin production in neuroinflammatory states (Nomura *et al.*, 2011). Specifically, MAGL inhibition has been shown to suppress the inflammatory cascade associated with MPTP toxicity in a CB₁/CB₂-independent manner, and to protect against dopaminergic neuronal loss possibly by preventing 2-AG conversion into pro-inflammatory prostaglandins (Nomura *et al.*, 2011). If confirmed in clinical settings, this approach appears particularly promising, as MAGL inhibitors do not show the gastrointestinal toxicity generally associated with other anti-inflammatory drugs, such as COX1 inhibitors. Long-term administration of MAGL inhibitors, however, may lead to CB₁ desensitization and impair EC-dependent synaptic plasticity, which in turn may limit their application in the clinic (Stella, 2011).

2.2 Studies on levodopa-induced dyskinesias

In addition to their possible use as adjunctive therapy in PD, cannabinoid drugs are emerging as promising antidyskinetic agents, given their ability to reduce levodopa-induced abnormal involuntary movements (AIMs) in rodent and primate models (Morgese *et al.*, 2007; Walsh *et al.*, 2010; Cao *et al.*, 2007). This beneficial effect may result from a combination of multiple downstream actions, including: 1) normalization of aberrant neurotransmission and synaptic plasticity (Chevalleyre *et al.*, 2007; Kreitzer and Malenka, 2007; Mato *et al.*, 2008; Morgese *et al.*, 2009; Picconi *et al.*, 2003); and 2) inhibition of levodopa-induced activation of cAMP/DARPP32 signaling, which is overactive in dyskinetic animals (Martinez *et al.*, 2011; Picconi *et al.*, 2003; Santini *et al.*, 2008). Interestingly, inhibition of presynaptic PKA activity is required for EC-mediated long-term depression in rat midbrain dopamine neurons (Haj-Dahmane and Shen, 2010). Thus, given the deficient AEA production observed in dyskinetic 6-OHDA-treated rats, activation of CB₁ receptors could rebalance the striatal maladaptive plasticity by inhibiting levodopa-induced PKA hyperactivity and reducing glutamatergic input at striatal synapses, which is increased in dyskinetic animals (Gubellini *et al.*, 2002).

Although some reports have shown that even CB₁ antagonists can reduce levodopa-induced dyskinesias in reserpine-treated rats and MPTP-treated marmosets (Segovia *et al.*, 2003; van der Stelt *et al.*, 2005), these results have not been confirmed in other animal models of PD (Cao *et al.*, 2007; Martinez *et al.*, 2011; Walsh *et al.*, 2010). Similarly, the observation that DARPP-32 activation (which implies the phosphorylation of this protein at threonine 34) is required for the expression of cannabinoid-mediated motor effects (Andersson *et al.*, 2005), has not been confirmed in dyskinetic 6-OHDA-treated rats. In these animals, indeed, the cannabinoid agonist WIN55212-2 significantly reduced levodopa-induced AIMs via

activation of CB₁ receptors, but reversed levodopa-induced DARPP-32 phosphorylation at Thr34 through a mechanism that was not fully reversed by CB₁ antagonism (Martinez *et al.*, 2011). Interestingly, Polissidis *et al.* (2010) observed that the dose of WIN55,212-2 used in the study of Martinez and co-workers (1 mg/kg, i.p.) induced opposite changes in striatal Thr-34 phosphorylation in different rat strains. The reasons for these discrepancies require further investigation, and reveal some limitations in generalizing cannabinoid function/effects across different animal species, which in turn may complicate the translation of these findings into therapeutic interventions.

In this context, a double-blind, placebo-controlled trial carried out in 19 PD patients failed to recognize any antidyskinetic effect of oral cannabis extracts (Carroll *et al.*, 2004). This assessment, however, was based on data reported from patients, which are often inaccurate in identifying symptoms (Vitale *et al.*, 2001). It is also important to point out that cannabis has a more complex pharmacological profile than synthetic cannabinoid agonists, as well as highly variable pharmacokinetics and pharmacodynamics, which may account for the lack of effect in the study of Carroll and co-workers.

Inhibition of the AEA degrading enzyme FAAH, a pharmacological approach that limits the activation of CB₁ receptors to those brain areas where EC production and release occurs, failed to produce anti-dyskinetic effects in 6-OHDA-treated rats (Morgese *et al.*, 2007). These findings suggest that AEA elevation is not sufficient to attenuate levodopa-induced dyskinesias, possibly because of its concomitant action at TRPV1 receptors (Ross, 2003). In support of this hypothesis, systemic administration of the FAAH inhibitor URB597 in combination with the TRPV1 antagonist capsazepine produced a significant anti-dyskinetic effect, suggesting that the beneficial actions of CB₁ stimulation may be counteracted by TRPV1 agonism. These data, however, differ from those reported by Lee *et al.* (2006), which showed that administration of URB597 alone, or stimulation of TRPV1 receptors by capsaicin, can attenuate levodopa-induced hyperactivity in reserpine-treated rats. As previously mentioned, these discrepancies may be attributed to differences in the biological and pathological aspects of PD reproduced by different animal models, and/or to the use of behavioral outcomes (i.e., vertical motor activity) that model stereotypies rather than dyskinesias (Cenci *et al.*, 2002).

3. Endocannabinoid transmission in schizophrenia

Schizophrenia is a severe mental illness characterized by three main types of symptoms: positive (e.g., hallucinations, delusions), negative (e.g., social withdrawal, anhedonia), and cognitive deficits (e.g., impaired working memory and attention).

Since THC produced perceptual alterations similar to those observed in psychotic patients, Emrich and co-workers proposed that abnormalities in the EC system might contribute to the pathogenesis of schizophrenia, at least in a subgroup of patients (Emrich *et al.*, 1997). This “cannabinoid hypothesis” of schizophrenia is consistent with the commonly accepted view that cannabis exposure has a negative impact on the course and expression of psychoses (D’Souza, 2007; Sewell *et al.*, 2009).

3.1 Studies on CB₁ receptors

Recent investigations have established an association between some CB₁ receptor gene polymorphisms and the hebephrenic type of schizophrenia (Chavarria-Siles *et al.*, 2008; Ujike and Morita, 2004). By using radioactive cannabinoid agonists ([³H]CP55,940) or antagonists ([³H]SR141716A), post-mortem studies have shown increased CB₁ binding in prefrontal cortex areas of schizophrenic patients (Dalton *et al.*, 2011; Dean *et al.*, 2001; Newell *et al.*, 2006; Zavitsanou *et al.*, 2004). Although these reports support the

“cannabinoid hypothesis” of schizophrenia, new experimental evidence has challenged these findings and suggested that CB₁ abnormalities may be related, at best, to specific disease subtypes, or result from the chronic use of antipsychotic medications (Dalton *et al.*, 2011; Zuardi *et al.*, 2011; Uriguen *et al.*, 2009). In addition, direct measurements of CB₁ mRNA and protein have not confirmed the CB₁ up-regulation in the anterior cingulate cortex (Koethe *et al.*, 2007), but found decreased CB₁ density in the dorsolateral prefrontal cortex (areas 9 and 46) (Eggan *et al.*, 2008). Finally, a recent PET imaging study has suggested that CB₁ binding increases with the severity of positive symptoms, but is inversely correlated to negative symptoms (Wong *et al.*, 2010). These observations indicate that future clinical investigations should be ideally carried out in better-defined, and possibly drug-free, groups of subjects with similar symptom severity.

3.2 Endocannabinoid levels and schizophrenic symptoms

Several studies have reported increased AEA levels in the blood and cerebrospinal fluid (CSF) of schizophrenic patients (Leweke *et al.*, 1999; De Marchi *et al.*, 2003; Giuffrida *et al.*, 2004), and clinical remission induced by the atypical antipsychotic olanzapine has been associated with a significant drop in circulating AEA (De Marchi *et al.*, 2003). In other studies, patients treated with typical antipsychotics did not show elevated CSF AEA, whereas those receiving atypical antipsychotics (including olanzapine) had increased levels similar to those observed in drug-naïve schizophrenics (Giuffrida *et al.*, 2004). Nevertheless, since these studies were carried out in acute paranoid schizophrenics, a patient population showing the highest CB₁ density in the dorsolateral prefrontal cortex (Dalton *et al.*, 2011), it is unclear whether these changes in AEA levels can be generalized to other subgroups of schizophrenic patients.

Surprisingly, the elevation of CSF AEA in drug-naïve schizophrenics has been negatively correlated to the severity of negative symptoms (Giuffrida *et al.*, 2004; Leweke *et al.*, 2007). Thus, the idea that AEA might play a possible anti-psychotic role contrasts with the assumptions of the “cannabinoid hypothesis” of schizophrenia, and suggests that the association between cannabinoids and mental disorders is more complex than originally postulated.

3.3 Studies in animal models

So far, a limited number of animal models of schizophrenia have been used to clarify the contribution of EC dysfunction to schizophrenic symptoms. The psychostimulant phencyclidine (PCP) is known to produce behavior abnormalities that are almost indistinguishable from those observed in schizophrenia (Murray, 2002; Steinpreis, 1996). Thus, PCP administration in rodents has been proposed as a valuable pharmacological approach to induce behavioral phenotypes modeling the three main categories of schizophrenic symptoms (Enomoto *et al.*, 2007; Jentsch and Roth, 1999). The psychotogenic effects of PCP, however, vary greatly according to the treatment regimen, and only chronic exposure to the drug produces schizophrenia-like behavioral deficits and neurochemical changes (Jentsch and Roth, 1999). Moreover, as PCP-induced symptoms persist for several weeks after drug discontinuation (Murray, 2002; Qiao *et al.*, 2001), it is preferable to add a washout period after chronic PCP to avoid possible interactions with the drugs to be tested. By using this approach, Giuffrida and Seillier (2009) showed that sub-chronic PCP administration (5 mg/kg, b.i.d., i.p., for 7 days, followed by a 7-day washout) produced not only a behavioral phenotype reminiscent of negative (social withdrawal) and positive (enhanced amphetamine-induced hyperactivity) symptoms, but also the characteristic cognitive deficit (impaired working memory) observed in the disease. In line with the clinical observations, several studies have also shown that atypical antipsychotics reverse

social withdrawal and cognitive deficits in this model (Qiao *et al.*, 2001; Grayson *et al.*, 2007; Hashimoto *et al.*, 2005; McLean *et al.*, 2008).

Globally, repeated PCP administration did not alter CB₁ receptor expression in brain areas relevant to schizophrenia, such as the medial prefrontal cortex, anterior cingulate cortex, caudate-putamen, nucleus accumbens, hippocampus, and ventral tegmental area (VTA) (Seillier *et al.*, 2010). In the latter region, Vigano *et al.* (2009) and Guidali *et al.* (2011) found increased CB₁ expression using a different PCP regimen (2.58 mg/kg, once daily followed by a 72h-washout period), which does not produce social withdrawal (Egerton *et al.*, 2008).

In PCP-treated rats, no changes in CSF or brain AEA levels were observed, with the exception of an increase of AEA in the nucleus accumbens (Seillier *et al.*, 2010; Guidali *et al.*, 2011; Vigano *et al.*, 2009). The discrepancy between the EC levels measured in the PCP rat model versus drug-naïve paranoid schizophrenics, in which CSF AEA is elevated, might reflect a specific feature of this patient subgroup, or depend on the different end-points used in these studies. Specifically, the human samples were obtained immediately after the first psychotic episode, which is accompanied by striatal hyperdopaminergia (Laruelle *et al.*, 2003) and may lead in turn to increased AEA production (Giuffrida *et al.*, 1999). On the other hand, the rat samples were collected from animals resting in their home cages, a condition that is unlikely to affect AEA levels, as EC release occurs in response to neuronal activity (Piomelli, 2003). In support of this observation, other studies have reported 2-AG elevation in the prefrontal cortex of PCP-treated rats sacrificed immediately after a memory test (Guidali *et al.*, 2011; Vigano *et al.*, 2009), thus stressing the importance of the physiological state of the animal at the time of EC measurements.

As suggested by the inverse correlation between CSF AEA and the negative symptoms of schizophrenia (Giuffrida *et al.*, 2004), elevation of AEA tone via administration of URB597 reversed social withdrawal in PCP-treated rats (Seillier *et al.*, 2010). The same drug, however, decreased social interaction in control rats to an extent comparable to that observed after PCP treatment (Seillier *et al.*, 2010). In agreement with these observations, Spano *et al.* (2010) showed that WIN55,212-2 self-administration attenuated PCP-induced deficits in sociability, but caused social withdrawal in saline-treated controls, strengthening the idea of a beneficial action of cannabinoids only in pathological conditions.

From this picture, it appears that the role played by the EC system in schizophrenia greatly varies depending on the type of symptoms (positive versus negative) and/or diagnosis (paranoid versus hebephrenic). In addition, the exposure to cannabinoid drugs produces clearly different effects in healthy versus pathological subjects. Therefore, further investigations in preclinical models, as well as in clinical settings, are still needed to understand the precise contributions of the EC system to psychoses.

Concluding remarks—Given their ability to modulate dopamine transmission and affect synaptic plasticity in cortico-striatal and limbic circuits, cannabinoid-based pharmacotherapies represent a promising treatment for psychomotor disorders, such as PD and schizophrenia. In addition, as cannabinoid drugs have clear anti-inflammatory properties and promote adult neuro- and gliogenesis (Solbrig *et al.*, 2010), they may find possible applications in neurodegenerative syndromes, including NeuroAIDS and diseases of aging.

While it is still unclear what could be the net effect produced by stimulation of cannabinoid receptors on PD motor symptoms, direct cannabinoid agonists have shown anti-dyskinetic properties in preclinical studies, and manipulation of AEA levels has produced antipsychotic-like effects in animal models of schizophrenia.

Further work is required to explore the therapeutic potentials of targets other than traditional CB₁/CB₂ receptors, such as TRP channels, PPAR receptors and EC degrading enzymes, which may offer an opportunity for more specific pharmacological interventions than those provided by direct-acting cannabimimetics.

Acknowledgments

This work was supported by the National Institute of Health, NS050401-07 and MH9113001-A1 to A.G.

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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Highlights

- Cannabinoid receptors are a promising pharmacological target for anti-dyskinetic and neuroprotective therapies in Parkinson's disease
- Animal models suggest the existence of disturbed endocannabinoid transmission in schizophrenia
- In humans, altered endocannabinoid transmission may occur in specific schizophrenia subtypes.