Mol Neurobiol
DOI 10.1007/s12035-016-9697-5

Role of the Endocannabinoid System in the Pathophysiology of Schizophrenia

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Received: 16 November 2015 / Accepted: 5 January 2016

Abstract The endocannabinoid system (ECS) is a group of neuromodulatory lipids, enzymes, and receptors involved in numerous behavioral and physiological processes such as mood, memory, and appetite. Recently, longitudinal and post-mortem studies have shown that the ECS might be involved in neuropsychiatric disorders like schizophrenia. However, despite the large amount of research, our knowledge of the ECS and its implication in this debilitating disorder is still largely limited. This review aims at providing a comprehensive overview of the current state of knowledge of the ECS in schizophrenia and presenting some potential antipsychotic compounds that modulate this system. Findings from animal and human studies, and their implications for pharmacotherapy, will be integrated and discussed in this paper. A closer look will be given at the roles of the cannabinoid receptors type 1 (CB_1) and type 2 (CB_2), as well as the endogenous ligand *N*-arachidonoylethanolamine (AEA) and 2-arachidonylglycerol (2-AG), in the development of psychotic and schizophrenia-like symptoms.

Keywords Antipsychotics · Cannabis · Cannabinoid receptor · Endocannabinoid · Psychosis · Schizophrenia

Introduction

The term "psychosis" is very broad and denotes a variety of mental disorders. Schizophrenia is a particular kind of psychosis and is associated with a myriad of signs including positive symptoms such as delusion and hallucination, negative symptoms such as lack of motivation and social withdrawal, and cognitive symptoms such as reduced attention and altered speech [1, 2]. This disorder, which typically emerges during late adolescence and early adulthood, affects approximately 1 % of the population worldwide [3]. One of the most enduring model of schizophrenia is the dopamine hypothesis, which speculates that the psychotic symptoms of this disorder are due to a hyperfunction of dopaminergic signaling in the brain [4, 5]. Evidence supporting this hypothesis comes from the observation that compounds that are effective in treating schizophrenia were found to block dopamine D2 receptors [4, 6]. Nowadays, antipsychotics are classified into two classes: the typical and atypical antipsychotics. In contrast to typical antipsychotics, atypical antipsychotics bind loosely to D2 receptors and exert part of their therapeutic effects by binding to serotonin type 2A ($5\text{-}HT_{2A}$) receptors [7]. Although being considered the cornerstone in the management of schizophrenia, antipsychotic drugs are associated with serious limitations. Treatment with typical antipsychotics is often linked with extrapyramidal side effects such as tremors, spasticity, and tardive dyskinesia [8, 9], whereas atypical antipsychotics are associated with severe complications such as sedation and weight gain [10, 11]. As a result, approximately half of patients with schizophrenia are non-adherent to antipsychotic medication and are more likely to experience symptoms of psychosis upon drug discontinuation [12, 13].

Until recently, the predominant focus of research concerning the biological basis of schizophrenia has been primarily centered on the role of neurotransmitters including dopamine, serotonin, norepinephrine, glutamate, and glutamate and γ-aminobutyric acid (GABA). However, given the limited efficiency of drugs that act on these neurotransmitters, researchers are now investigating the role of other potential

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Published online: 15 January 2016

neurotransmitter substrates in the pathophysiology of schizophrenia. One such substrate is the endocannabinoid system (ECS). The ECS is composed of cannabinoid receptors, endogenous cannabinoid ligands, and enzymes responsible for the biosynthesis and degradation of endocannabinoids [14]. This newly discovered system of neuromodulation participates in several physiological and behavioral processes such as pain [15], emotion [16], appetite [17], energy metabolism [18], mood [19], and memory [20]. Recent preclinical studies evaluating the levels of brain endocannabinoids in animal models of schizophrenia have suggested that the ECS could play a role in the pathophysiology of this disorder [21, 22]. Genetic and postmortem studies investigating the neurochemical changes in the brain of patients with schizophrenia provided additional evidence for the role of the ECS in psychotic and schizophrenia-like symptoms [1, 23]. However, despite the large amount of work devoted to this field of research, still more effort is needed to fully elucidate the role of the ECS in schizophrenia. More particularly, the mechanisms by which the ECS is associated with psychotic and schizophrenia-like symptoms remain to be determined in appropriate animal models.

The overarching goal of this review is to provide a better understanding of the contribution of the ECS in the pathophysiology of schizophrenia. This paper starts by describing some of the most recent studies investigating the link between cannabis use and psychosis and then provides an overview of evidences indicating a dysfunction of the ECS in schizophrenia. Finally, a closer look will be given at pharmacological tools that aimed at targeting the ECS for therapeutic purposes.

Cannabis Use and Psychosis: Towards a "Cannabinoid Hypothesis" of Schizophrenia

Cannabis is considered one of the most frequently used illicit drugs, and most consumers first experiment it during adolescence [24, 25]. Psychotic disorders such as schizophrenia are strongly associated with the regular consumption of cannabis, especially when consumed during adolescence and young adulthood [26]. Among consumers of cannabis, only individuals who are genetically vulnerable to its psychotomimetic effect will develop the symptoms of psychosis [27]. Adolescents are generally more affected by the long-term effects of cannabis because their brain is still in a phase of development and is therefore more vulnerable to environmental insults [24, 28].

Among all the chemical constituents of cannabis, delta-9-tetrahydrocanabinol (THC) is by far the most studied and is responsible for the majority of the psychotropic effects of cannabis. THC exerts its action in the brain by binding to cannabinoid receptors type 1 (CB_1) and type 2 (CB_2) [29, 30]. Continuous exposure to THC has been shown to upregulate the ECS, leading to long-lasting neurobiological changes in various regions of the brain [31]. By acting on cannabinoid receptors, THC also influences the release of neurotransmitters involved in the pathophysiology of schizophrenia, including dopamine and glutamate [32]. As a result, heavy consumption of cannabis most often has harmful effects on an individual's health and can lead to the development of psychosis and schizophrenic-like symptoms [24, 33].

In the past decades, longitudinal studies investigating cannabis use in psychosis have prompted debates as to whether the ECS might be involved in the pathogenesis of schizophrenia. Even though the first observation between cannabis and schizophrenia was made almost 60 years ago [34], it was not until 1987 that the first longitudinal study provided empirical evidence of the increased risk of schizophrenia among cannabis users [35]. Since then, several other reports, which are summarized in Table 1, have shown similar risk and prevalence data. The results from these studies, along with other evidences from neuroimaging and postmortem analysis [46, 47], have led to the formulation of the "cannabinoid hypothesis," which speculates that hyperactivity of the ECS may be associated with increased risk of developing symptoms of schizophrenia, mainly by increasing dopamine neurotransmission in the brain. In accordance with this hypothesis, several reports have observed high levels of cannabinoid receptors and endocannabinoid ligands in animal models of schizophrenia and psychotic patients. However, despite the large amount of research, the exact role of the ECS in schizophrenia has eluded the scientific community and remains to be characterized.

The Endocannabinoid System: Discovery and Characterization

Since the discovery and isolation of THC 50 years ago [48], researchers were interested in understanding how this compound and other known cannabinoids work in the brain. However, progress in this field of research was hindered by the lack of identified receptors for these molecules. It is only in 1988 that the pharmacological characterization of a cannabinoid receptor was reported in the central nervous system [49], and in 1990, the CB_1 receptor was successfully cloned [50]. The CB_1 receptor is the most prevalent cannabinoid receptor in the brain and is primarily located in the cerebellum, hippocampus, and prefrontal cortex [51]. This receptor plays key roles in modulating the level of excitatory and inhibitory neurotransmitters, including acetylcholine, noradrenaline, and dopamine [51, 52]. CB_1 receptors also act as inhibitory neuromodulators for the release of GABA, especially in the prefrontal cortex, where glutamate and GABA

Table 1 Representation of 12 longitudinal studies showing the relationship between cannabis use and psychosis and/or schizophrenia

Country	Individuals	Follow-up period	Odds ratio	Outcome	Study
Sweden	50,465 adult conscripts	15 years	2.4 (cannabis use by age 18 years)	Schizophrenia	[35]
USA	4994 adults	5 years	1.30 (daily users of cannabis)	Psychotic symptoms	[36]
Netherland	4104 adults	3 years	2.76 (weekly users of cannabis)	Psychotic symptoms	[37]
New Zealand	Birth cohort of 759 individuals	26 years	4.5 (by age 15 years), 1.65 (by age 18 years) (cannabis use ≥3 times by age 15 years)	Schizophrenia or schizophreniform disorder	[28]
Sweden	50,087 individuals aged 18–20 years	27 years	1.9 (cannabis use more than once), 6.7 (cannabis use >50 times)	Schizophrenia	[38]
New Zealand	Birth cohort of 1265 individual	18–21 years	3.7 at age 18 years and 2.3 at age 21 years (individuals meeting criteria for cannabis dependence)	Psychotic symptoms	[39]
Israel	50,413 male 16–17 years	5–11 years	2.02 (individuals meeting criteria for cannabis dependence)	Schizophrenia	[40]
Greece	Birth cohort of 3500 individuals	19 years	4.3 (cannabis use by age 19 years)	Negative and positive psychotic symptoms	[41]
Germany	2437 individuals aged 14–24 years	4 years	1.69 (cannabis use ≥5 times) 2.23 (daily cannabis use)	Psychotic symptoms	[42]
Netherland	1580 individuals aged 4–6 years	14 years	2.81 (cannabis use >5 times)	Psychotic symptoms	[43]
UK	8580 adults aged 16–74 years	18 months	1.47 (individuals meeting criteria for cannabis dependence)	Psychotic symptoms	[44]
Finland	Birth cohort of 6440 individuals	15–16 years	2.23 (lifetime cannabis use)	Psychotic symptoms	[45]

The odds ratio is defined as the risk of developing symptoms of psychosis and/or schizophrenia for cannabis consumers relative to non-consumers. Data from this table show that adolescents are in general more vulnerable than adults to the harmful effect of cannabis consumption

neurotransmissions are crucial for cognitive functions [53–55]. Another cannabinoid receptor, which shares amino acid sequence similarities with CB_1, was discovered later and designated as the CB_2 receptor [56]. Although CB_2 receptors are primarily found in endothelial and immune cells, they are also present in different brain regions such as the hippocampus, striatum, amygdala, and cerebellum [51, 57, 58].

The discovery and subsequent characterization of cannabinoid receptors immediately raised the possibility of endogenous molecules that could bind and act on these receptors. The search for potential endogenous ligands led to the isolation and discovery of *N*-arachidonoylethanolamine (AEA) in 1992, an arachidonic acid derivative also termed anandamide [59]. AEA is an endogenous cannabinoid neurotransmitter and is considered a full agonist of CB_1 receptor and a partial agonist of CB_2 receptor [51, 60]. It is implicated in a variety of functions in the central nervous system, including sleep regulation, memory, and reward [61–63]. 2-Arachidonylglycerol (2-AG) is the second endogenous ligand of the ECS to be discovered [64] and, unlike AEA, is a full agonist of both CB_1 and CB_2 receptors [51, 65]. It is also found in relatively higher concentration than AEA in various brain regions including the anterior cingulate cortex (ACC), the hippocampus, and the prefrontal cortex (PFC) [66]. Although several other natural and synthetic endocannabinoid ligands have been discovered and developed, AEA and 2-AG remain the most widely studied [60, 67].

AEA and 2-AG act as retrograde messengers at specific synapses; they are synthesized and secreted from postsynaptic cells, and they bind to receptors located on pre-synaptic neurons (Fig. 1). These endogenous ligands are found in different brain regions, particularly in the brainstem, medulla, limbic forebrain, striatum, and hippocampus [69]. After being synthesized and released from postsynaptic cells, AEA and 2-AG

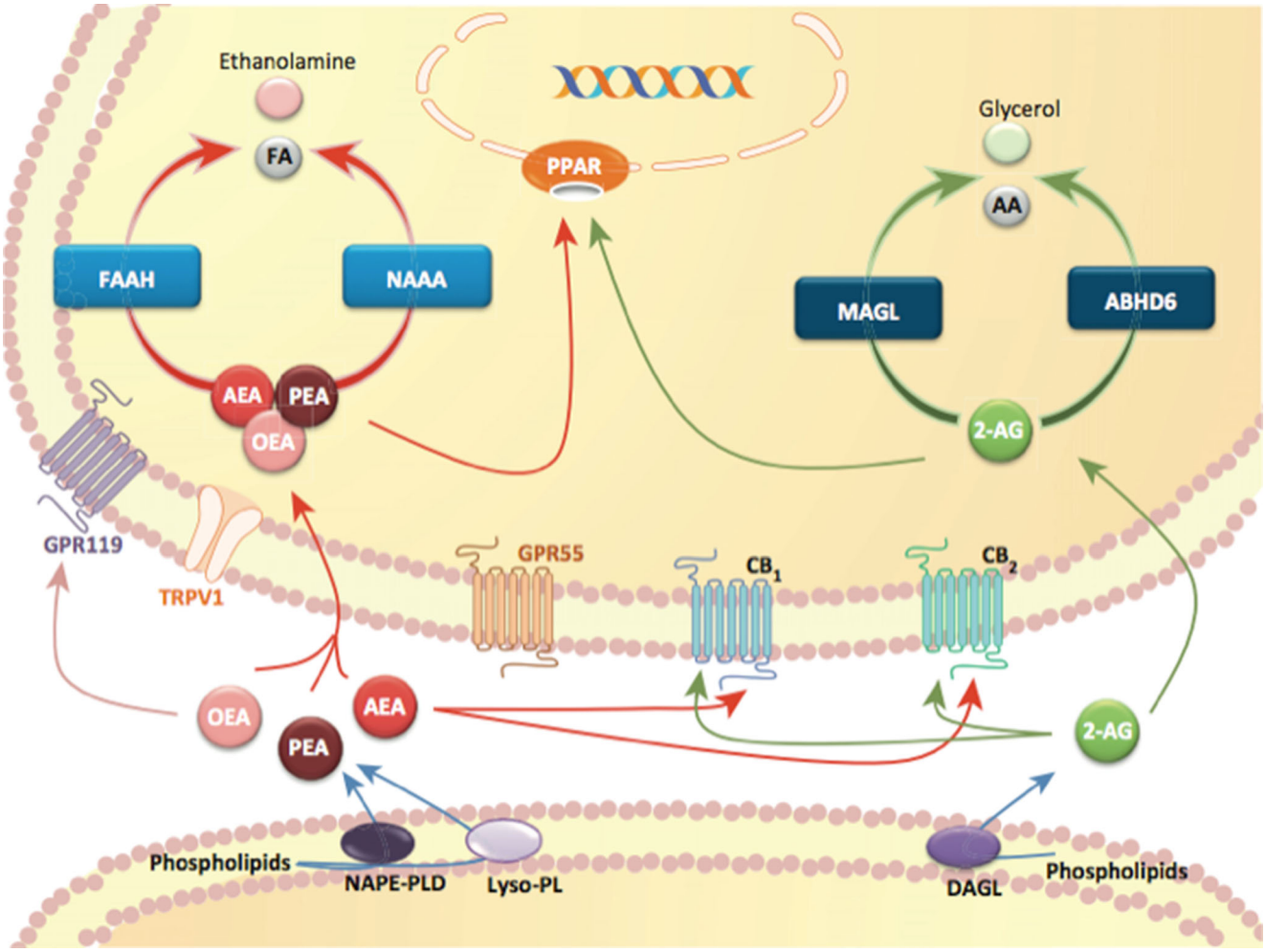

Fig. 1 The major players of the ECS. The ECS comprises of cannabinoid receptors, endogenous ligands, and hydrolytic enzymes. AEA and 2-AG are endogenous bioactive lipids that bind to and activate the cannabinoid receptors CB_1 and CB_2 located on presynaptic terminals. FAAH and MAGL are the main hydrolytic enzymes responsible for the degradation of AEA and 2-AG, respectively. *NAE N*-acylethanolamines, *PEA N*-palmitoylethanolamine, *OEA N*-oleoylethanolamine, *NAPE-PLD N*-acylphosphatidylethanolamine selective phospholipase D, *Lyso-PL* lysophospholipase, *DAGL* diacylglycerol lipase, *GPR119* G protein-coupled receptor 119, *GPR55* G protein-coupled receptor 55, *TRPV1* transient receptor potential vanilloide 1, PPARs peroxisome proliferator-activated receptors, *NAAA* cysteine amidase, *ABHD6* monoacylglycerol lipase, *FA* fatty acids. Taken with permission from [68]

are taken up by specific transport proteins, and once inside pre-synaptic cells, they get rapidly inactivated by enzymatic hydrolysis. AEA is mainly degraded by the fatty acid amid hydrolase (FAAH) and the *N*-acylethanolamine acid amide hydrolase (NAAA) (Fig. 1). FAAH, which was discovered as the first enzyme responsible for AEA hydrolysis, is an integral protein widely distributed throughout the brain [70]. FAAH and NAAA terminate AEA signaling by converting the ligand into ethanolamine and arachidonic acid [71, 72]. On the other hand, 2-AG is mainly degraded by the enzyme monoacylglycerol lipase (MAGL) and, during the process, gets converted into glycerol and arachidonic acid (AA) [68, 73]. Although 2-AG degradation is mainly mediated by the enzymatic activity of MAGL, it is also influenced by the activity of other serine proteases, including ABHD6 and ABHD12 [74].

Cannabinoid Receptors in Schizophrenia

Insights from Pre-clinical and Clinical Studies

Evidence demonstrating the involvement of cannabinoid receptors in schizophrenia first originated from studies using animal models [21, 22]. Results from these studies have consistently demonstrated a reduction of CB_1 receptor levels in various brain regions in schizophrenia [22, 75] and were in contrast with what was observed in schizophrenic patients. This may be due to cytoarchitectural differences in cortical regions between animals and humans and by the fact that animal models for schizophrenia are only efficient in mimicking some but not all aspects of the disease [75].

In phencyclidine (PCP)-treated rats, an animal model for the positive and negative symptoms of schizophrenia,

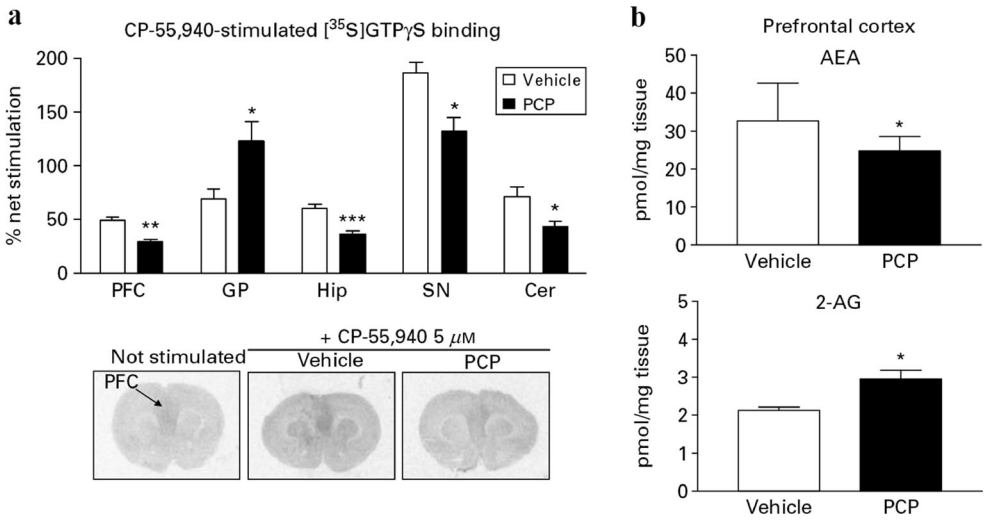

Fig. 2 Alteration of CB_1 receptor and endocannabinoid levels in PCP-treated rats. **a** CB_1 receptor level using [3H] CP 55 940 binding density expressed in % net stimulation in various regions of the brain in vehicle and PCP-treated rats. **b** AEA and 2-AG levels in the PFC of vehicle and PCP-treated rats. Each group was compared with the vehicle using Student's *t* test (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). Data are expressed as the mean ± S.E.M. *GP* globus pallidus, *Hip* hippocampus, *SN* substantia nigra, *Cer* cerebellum. Taken with permission from [22]

levels of CB_1 receptors were found to be decreased in the PFC, hippocampus, substantia nigra, and cerebellum (Fig. 2a) [22]. Moreover, downregulation of CB_1 receptors in the brain has been shown to correlate with impairment in fear memory specificity and GABA-mediated transmission, which are known to be implicated in schizophrenia [76, 77]. Similar to CB_1 receptors, accumulating evidence points to the involvement of CB_2 receptors in the behavioral and functional deficits observed in schizophrenia. Decreased peripheral level of CB_2 receptor was found in non-treated patients with first-episode psychosis [78] and in acute schizophrenia patients treated with antipsychotics [79]. Moreover, administration of a CB_2 receptor antagonist in mice resulted in schizophrenia-like phenotypes, including increased locomotor activity and deficits in pre-pulse inhibition (PPI), which is defined by the ability to filter out non-relevant sensory stimuli [23].

Taken together, the aforementioned studies indicate that altered cannabinoid functioning leads to increased susceptibility to schizophrenia. Such alterations appear to mediate their psychotomimetic effect by interacting with factors that are already observed in schizophrenia, including changes in glutamate and GABA neurotransmission. However, due to discrepancies in the results from several studies, still more work is needed to fully elucidate the role of cannabinoid receptors in schizophrenia. More specifically, future research needs to explore whether alterations in cannabinoid receptors are directly related to the pathology of schizophrenia or if they arise in response to an imbalance of neurotransmitters in the brain such as glutamate and GABA.

Insights from Genetic Studies

Most of the genetic evidences supporting the cannabinoid hypothesis of schizophrenia come from studies investigating the role of cannabinoid receptor genes. However, the majority of these studies have reported controversial findings, and still more work is needed prior to drawing any reliable conclusions.

CB_1 receptors are encoded by the CNR1 gene, which is located in a schizophrenia susceptibility locus designated by Schizophrenia 5 (SCZ5, OMIM 603175) [80]. CNR1 variants have been linked with schizophrenia and a variety of other mental disorders. More particularly, polymorphism of the (AAT)n trinucleotide repeat (AL136096), located in the promotor region of CNR1, was shown to be associated with schizophrenia or subtypes of this disorder [80–82]. In contrast with these findings, other studies failed to report an association between the AAT repeat polymorphism of CNR1 and schizophrenia, probably due to limited size sample and the lack of subtype classification [83, 84]. Three other polymorphisms of CNR1 (rs12720071-G-allele carriers, rs7766029-C homozygotes, and rs9450898-C homozygotes) were identified in patients with schizophrenia and were shown to influence the phenotypic features of the disease in patients that were consuming cannabis [85]. Schizophrenic patients with cannabis dependence were shown to have greater white matter volume deficits and cognitive impairment than patients without heavy cannabis use, confirming the multifactorial nature of the disease, namely that gene-environment interactions play an important role in the development of schizophrenia-like phenotype [85].

Similarly, findings from genetic studies also suggest a link between altered CB_2 receptor function and increased susceptibility to schizophrenia-like symptoms. Polymorphisms of CNR2, the gene encoding CB_2 receptors, are frequently observed in schizophrenia patients [23], and deletion of this gene induces schizophrenia-related behaviors in mice [86].

Taken together, these observations support the notion that cannabinoid receptors participate in the development of schizophrenia. However, to date, very few studies have evaluated the role of CNR1 and CNR2 in the development of psychosis and schizophrenia-like symptoms. Future research should focus on studying other polymorphisms in cannabinoid receptor gene that may be relevant for schizophrenia and that could help strengthen our understanding of the genetic etiology of this disorder.

Insights from Postmortem and Neuroimaging Studies

The potential involvement of cannabinoid receptors in the pathophysiology of schizophrenia has also been supported by postmortem and neuroimaging studies. Although not much is known about CB_2 receptor brain levels in patients with schizophrenia, recent evidences have revealed increased radioligand binding for CB_1 receptors in the dorsolateral prefrontal cortex (DLPC) (Fig. 3a) [52, 87, 88], the posterior anterior cortex [89], and the ACC [90] of patients with schizophrenia. The changes observed in CB_1 receptor binding, which were independent of previous cannabis use and exposure to antipsychotic drugs, further support a role of these receptors in schizophrenia, particularly in working memory processes, which depends on the circuitry of the DLPC as well as in motivation, attention, and emotional responses, which are modulated by the ACC. Similarly, studies using neuroimaging techniques such as positron emission tomography (PET) have reported elevated CB_1 receptor binding in the nucleus accumbens [91] and in the pons [92] of patients with schizophrenia.

In summary, postmortem and neuroimaging studies clearly show that patients with schizophrenia have elevated levels of CB_1 receptors in various parts of the brain. However, the results of these studies appear at odds with findings showing unaltered CB_1 receptor mRNA expression in the DLPC of schizophrenic patients [52, 93, 94]. The discrepancies observed at the protein and mRNA levels might be explained by the different methodological approaches used for the quantification of CB_1 receptors (immunohistochemistry versus autoradiography). In addition, increased radioligand binding for CB_1 receptors could reflect differences other than the amount of receptor present, such as changes in the affinity of the ligand to its binding site [93]. Finally, the increase in CB_1 receptor binding sites without a similar change in mRNA (Fig. 3b) could be due to differences in posttranslational processes between schizophrenic and healthy individuals [52].

Endogenous Cannabinoid Ligands in Schizophrenia

AEA Level in Schizophrenia

There are plenty of evidences pointing to the involvement of AEA in psychotic-like symptoms. Recent reports indicate that AEA levels are higher in the plasma [95] and whole blood [79] of schizophrenic patients compared to healthy individuals, suggesting that this endocannabinoid may play a beneficial role in psychosis homeostasis. Consistent with these results, AEA is found in relatively high concentration in the CSF of individuals with schizophrenia [96, 97] and acute

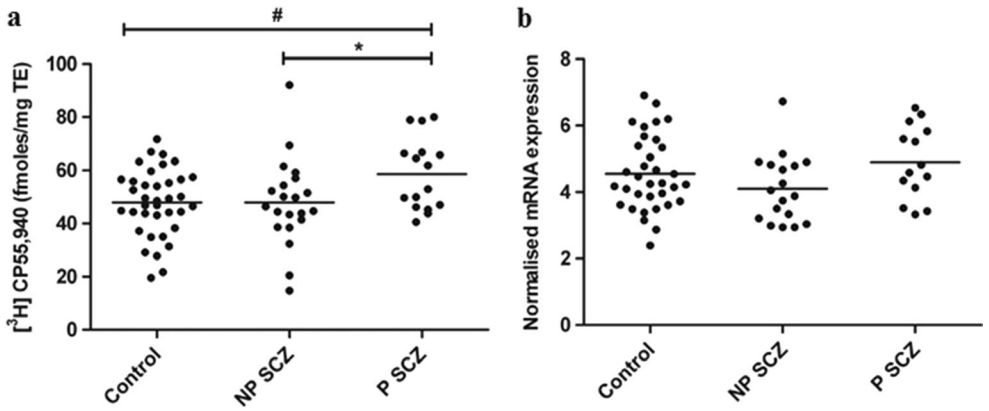

Fig. 3 CB_1 receptor levels were measured in the DLPC of control individuals and in patients with non-paranoid (*NP*) and paranoid (*P*) schizophrenia (*SCZ*). **a** [3H] CP 55 940 binding density expressed in fmoles/mg of tissue equivalent (*TE*). **b** CB_1 mRNA expression normalized to the geometric mean of four housekeeping genes. Statistical comparison between each group was carried out using a one-way analysis of variance (ANOVA) and covariance (ANCORA) followed by post hoc Bonferroni tests to account for multiple comparisons. The increase in CB_1 receptor density in the P SCZ group was statistically significant when compared with controls using ANOVA (#) and when compared with the NP SCZ group using ANCOVA (*). Taken with permission from [52]

paranoid schizophrenia [98]. However, its level is reduced in the PFC of PCP-treated rats [22] (Fig. 2b) and in the hippocampus and cerebellum of schizophrenic patients postmortem [1]. Although these findings appear at odds with previous reports showing increased AEA level in schizophrenia, taken together, the aforementioned studies highlight a striking opposite phenomenon, namely that the concentration of AEA is elevated in the plasma and CSF of schizophrenic patients, but reduced in various regions of the brain. As such, elevated levels of AEA in the CSF, but not in the brain, might play a protective role during the early stages of schizophrenia and could serve as an adaptive mechanism countering hyperdopaminergia [98].

2-AG Level in Schizophrenia

There are clear evidences indicating that 2-AG is implicated in psychotic disorders such as schizophrenia [14]. Studies using PCP-induced animal models of schizophrenia found a significant increase in the level of 2-AG in the PFC [22, 99]. Such increase is most likely the result of glutamatergic-related cognitive deficits in schizophrenia [22]. 2-AG is known to reduce glutamate release in the brain [100, 101], as such, a higher level of 2-AG in certain brain regions could represent an adaptive mechanism aimed at counteracting glutamatergic hyperactivity in schizophrenia. Interestingly, differences in 2-AG level were only found in the PFC but not in the hippocampus of PCP-treated animal [22], suggesting that cognitive processes and glutamate neurotransmission are most likely subserved by the activity of the PFC. The notion that 2-AG is involved in the cognitive deficits associated with negative schizophrenia symptoms is also supported by a postmortem brain tissue analysis indicating a significant increase in the level of 2-AG in the PFC of schizophrenic subjects [1].

Although the aforementioned studies have reported altered brain level of 2-AG in schizophrenia, other studies have failed to demonstrate any changes in the plasma or CSF of schizophrenic subjects [95, 96], probably due to altered peripheral immune response in schizophrenia that do not reflect the changes occurring in the central nervous system [1, 79]. Clearly, more work is needed to better characterize the fluctuations of 2-AG in schizophrenia, both in patients and animal models.

Implications for Pharmacotherapy

Cannabinoid Receptor Antagonists/Inverse Agonists

The search of effective antipsychotic agents for the treatment of schizophrenia is hindered by the multifactorial nature of the disease. Since THC and other cannabinoid receptor agonists contribute to the development of psychotic states, molecules that counteract their psychotomimetic effects have been investigated for therapeutic applications [70, 102]. More particularly, a lot of interest is given to cannabinoid receptor antagonists and inverse agonists because of their ability to inhibit THC-induced hyperactivity of the ECS. Among them, cannabidiol (CBD), a non-psychotropic component of cannabis, was recently suggested as a promising antipsychotic agent. Findings from animal and human studies have shown that CBD behaves as an inverse agonist of CB_1 and CB_2 receptors, and could be effectively used to block THC-induced psychosis [29, 103]. CBD also exerts its antipsychotic properties by inhibiting FAAH activity, leading to increased AEA level in the brain [70]. Unlike most antipsychotic agents, CBD is able to inhibit the hyperlocomotion induced by psychotomimetic drugs in rodents without causing catalepsy or motor impairment [104]. In addition, human studies investigating the safety of chronic CBD administration for the treatment of schizophrenia have reported few undesirable side effects and low toxicity compared to currently used antipsychotics [70, 105].

Besides CBD, other cannabinoid receptor antagonists are currently being investigated as potential therapeutic approaches. SR141716, clinically known as rimonabant, is the first selective CB_1 receptor inverse agonist to be developed. Although it has been shown to effectively block the acute effects of THC [106], studies investigating its use in schizophrenia have reported mixed results. Poncelet et al. (1999) showed that SR141716 at doses of 0.3–3 mg/kg was able to efficiently suppress the increased locomotor activity induced by psychostimulants in habituated gerbils [107], whereas in another study, administration of SR141716 at doses of 0.1, 5, and 10 mg/kg in rats had no effect on PPI and failed to reverse *d*-amphetamine-mediated increases in hyperactivity [108]. Similarly, AVE1625 (Drinabant), a CB_1 receptor antagonist, was shown to be inefficient in attenuating the positive symptoms of schizophrenia in rodents [109]. Although AVE1625 was able to improve working memory in rats, it did not attenuate amphetamine-induced disruption of latent inhibition and failed to reverse amphetamine-induced disrupted gating [109]. These data are in line with a previous report showing that administration of AM251, another CB_1 receptor antagonist, fails to reverse the positive and negative symptoms of schizophrenia in PCP-treated rats, suggesting that blockade of CB_1 receptors with selective antagonists may have limited therapeutic potential [21].

Endocannabinoid Signaling

Regulating the tone of endocannabinoids in the brain could be done by affecting their cellular uptake or by targeting the enzymes responsible of their hydrolysis [14]. FAAH and MAGL inhibitors are currently viewed as attractive targets for the development of antipsychotic drugs because of their ability to regulate brain levels of AEA and 2-AG, respectively

[70, 72]. Studies in rodents have shown that JZL184, a recently developed and highly selective MAGL inhibitor, could prevent impairments in induced long-term depression [110] and prolong the depolarization-induced suppression of excitation (DSE) in hippocampal slices [111], suggesting a possible role in the regulation of cognitive functions such as memory. On the other hand, enhancement of AEA level with URB597, a selective FAAH inhibitor, was shown to be associated with increased social interaction in PCP-treated rats [21, 112].

AEA reuptake inhibitors such as AM404 are also being extensively studied as potential therapeutic approaches. Administration of AM40 in spontaneously hypertensive rats (SHR), an animal model of schizophrenia, resulted in reduced locomotor activity [113] and increased social interaction [114], supporting the role of AEA in the regulation of psychomotor activity. However, in opposition to these studies, administration of AM404 at a concentration of 1, 5, or 10 mg/kg failed to reverse the deficits in PPI in SHR [115] and was associated with psychomimetic effects when administered in mice with a dose of 5 mg/kg [116]. Although differences in the behavioral paradigms and animal strains could account for the variable effects of AM404 on PPI, it still remains to determine whether inhibition of FAAH could effectively dampen the symptoms of schizophrenia.

Conclusion

The discovery of cannabinoid receptors and endocannabinoids has given us a new understanding of the behavioral and physiological roles of the ECS in the brain. This prominent signaling system mediates a variety of cellular and homeostatic functions involved in neuronal development, neurotransmission, and energy metabolism. Evidence from animal and human studies show that CB_1 and CB_2 receptor function, as well as AEA and 2-AG levels, are most likely to be involved in the pathophysiology of schizophrenia. These studies have opened exciting new perspectives for designing antipsychotic therapies that could modulate the level of cannabinoid receptors and/or endocannabinoids in the brain. Given the increasing interest in the therapeutic applications of the ECS, novel antipsychotics that target this system are likely to emerge in the not too distant future. Among all potential pharmacological agents targeting the ECS, CBD shows superior antipsychotic efficacy and holds therapeutic promise in patients with schizophrenia. Nonetheless, the mechanisms underlying its antipsychotic effects are still not clearly understood and need to be better characterized. This field of research would clearly benefit from the use of appropriate neurodevelopmental models of schizophrenia that could help better explore the role of the ECS in this disorder and promote the development of more efficient antipsychotic medications.

Acknowledgments The author acknowledges the financial support from the Natural Sciences and Engineering Research Council (NSERC) of Canada and would like to thank Dr. Giovanni Hernandez for providing critical reviews of early versions of the manuscript.

Compliance with Ethical Standards For this type of study, formal consent is not required.

Conflict of Interest The author declares that he has no competing interests.

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