European Archives of Psychiatry and Clinical Neuroscience (2018) 268:727–737
https://doi.org/10.1007/s00406-018-0874-6

INVITED REVIEW

Cannabinoids and glial cells: possible mechanism to understand schizophrenia

Valéria de Almeida[1] · **Daniel Martins-de-Souza**[1,2]

Received: 7 November 2017 / Accepted: 24 January 2018 / Published online: 1 February 2018

Abstract

Clinical and neurobiological findings have reported the involvement of endocannabinoid signaling in the pathophysiology of schizophrenia. This system modulates dopaminergic and glutamatergic neurotransmission that is associated with positive, negative, and cognitive symptoms of schizophrenia. Despite neurotransmitter impairments, increasing evidence points to a role of glial cells in schizophrenia pathobiology. Glial cells encompass three main groups: oligodendrocytes, microglia, and astrocytes. These cells promote several neurobiological functions, such as myelination of axons, metabolic and structural support, and immune response in the central nervous system. Impairments in glial cells lead to disruptions in communication and in the homeostasis of neurons that play role in pathobiology of disorders such as schizophrenia. Therefore, data suggest that glial cells may be a potential pharmacological tool to treat schizophrenia and other brain disorders. In this regard, glial cells express cannabinoid receptors and synthesize endocannabinoids, and cannabinoid drugs affect some functions of these cells that can be implicated in schizophrenia pathobiology. Thus, the aim of this review is to provide data about the glial changes observed in schizophrenia, and how cannabinoids could modulate these alterations.

Keywords Endocannabinoid system · Glia · Oligodendrocytes · Microglia · Astrocytes · *Cannabis sativa*

Abbreviations

Δ9-THC	Delta-9-tetrahydrocannabinol
2-AG	2-Arachidonoylglycerol
AEA	Anandamide
CB1	Type 1 cannabinoid receptor
CB2	Type 2 cannabinoid receptor
CNR1	Cannabinoid receptor type-1 gene
CNR2	Cannabinoid receptor type-2 gene
COX	Cyclooxygenase
DAGLα	Diacylglycerol lipase alpha
DAGLβ	Diacylglycerol lipase beta
DISC-1	Disrupted in schizophrenia-1
FAAH	Fatty acid amide hydrolase
GFAP	Glial fibrillary acid protein
GLAST	Glutamate aspartate transporter
GLT-1	Astrocytic glutamate transporter-1
GPR55	G protein-coupled receptor 55
IL-1	Interleukin 1
IL-6	Interleukin 6
KO	Knockout
LPS	Lipopolysaccharide
MAGL	Monoacylglycerol lipase
NAPE	*N*-Acyl-phosphatidylethanolamine-phospholipase
NMDA	*N*-Methyl-D-aspartate
OPCs	Oligodendrocyte precursor cells
PPARγ	Peroxisome proliferator-activated receptor
TNF-α	Tumor necrosis factor alpha
TRPV1	Transient receptor potential vanilloid 1

✉ Valéria de Almeida
dmsouza@unicamp.br

[1] Laboratory of Neuroproteomics, Department of Biochemistry and Tissue Biology, Institute of Biology, University of Campinas (UNICAMP), Rua Monteiro Lobato 255, Campinas, SP 13083-862, Brazil

[2] Instituto Nacional de Biomarcadores em Neuropsiquiatria (INBION), Conselho Nacional de Desenvolvimento Científico e Tecnológico, São Paulo, Brazil

Schizophrenia

Schizophrenia is a chronic mental disorder characterized by three main classes of symptoms: positive, negative, and cognitive. Clinical manifestation of schizophrenia usually occurs between late adolescence and early adulthood, which contributes to a high cost for public health care.

Schizophrenia is understood to be caused by genetic and environmental interactions that impair neurodevelopment [1]. Although the introduction of antipsychotics in the 1950s has had a great impact on the treatment of schizophrenia, these drugs have limited efficacy on the negative and cognitive symptoms, and present several side effects. Therefore, studies are required to better understand the pathophysiology of schizophrenia, which could lead to the development of new therapeutic compounds or the improvement of the current drugs.

The pathophysiology of schizophrenia has not yet been fully elucidated, but evidence suggest a dysfunction of dopaminergic neurotransmission [2] and a hypofunction of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors [3]. Moreover, studies reported that glial cells [4–7] can be involved in the pathobiology of schizophrenia. Finally, endocannabinoid signaling modulates neurotransmissions [8] and may be involved in the maintenance of physiological conditions in the central nervous system, through the regulation of glial cells [9, 10]. In this regard, a targeted modulation of the endocannabinoid system may contribute to understand the glial mechanisms and cannabinoid function that underlie the pathophysiology of schizophrenia.

Endocannabinoid system

Although *Cannabis sativa* is widely recognized as a recreational drug since ancient times, its compounds present several pharmacological uses in psychiatric disorders [11]. Interest in understanding the mechanisms of delta-9-tetrahydrocannabinol (Δ9-THC) in the brain led to the discovery of cannabinoid receptors [12]. Thereafter, endogenous ligands for cannabinoid receptors were identified [13]. Thus, the endocannabinoid system comprises the endocannabinoids (Fig. 1), such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG); the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), responsible for degradation; the synthesis enzymes *N*-acyl-phosphatidylethanolamine-phospholipase (NAPE) and diacylglycerol lipase alpha (DAGLα) and beta (DAGLβ); as well the type 1 (CB1) and 2 (CB2) cannabinoid receptors [13–16].

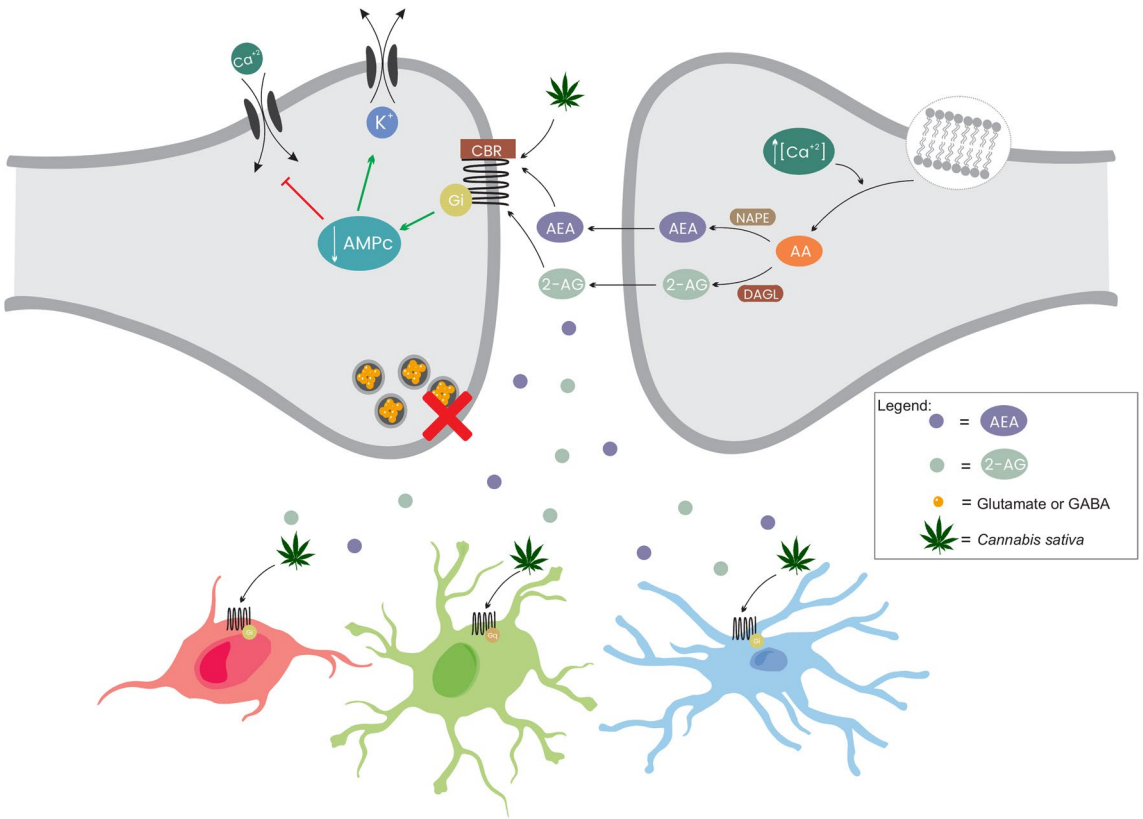

Fig. 1 Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are synthesized from arachidonic acid (AA) on post-synaptic neuron or glia cells. Once released by post-synaptic neurons, endocannabinoids act in retrograde signaling at presynaptic neuron. Cannabinoid receptors (CB1 and CB2) are $G_{i/0}$ protein coupled, except in astrocytes that it is coupled to $G_{q/11}$. Intracellular mechanism cannabinoid receptors comprise inhibition of adenylate cyclase, increasing K^+ currents, and inhibition of Ca^{2+} channels, that decrease neurotransmitter release. Exogenous cannabinoids (e.g., compounds of *Cannabis sativa*) can activate cannabinoid receptor in neurons or glial cells

It was originally believed that CB1 is widely expressed in the central nervous system [12], while CB2 is abundant in peripheral immune cells [17]. However, CB2 expression has also been found in the brain [18, 19]. Additionally, other candidates for endocannabinoid binding, such as G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid 1 (TRPV1) receptors [20–22] have been described. Cannabinoid receptors are localized mainly at presynaptic membranes [15], where they are responsible for modulating neurotransmitter release. The activation of cannabinoid receptors at presynaptic neurons results in decreased neurotransmitter release [23–25]. Despite the primarily presynaptic localization, cannabinoid receptors are still expressed on the membranes of post-synaptic neurons [15, 26]. The cannabinoid-induced psychotomimetic effects are mediated mainly through CB1 activation in neurons. Moreover, cannabinoid receptor expression has been shown in mitochondria [27, 28] and glial cells [9], but their functions are not totally understood. Thus, findings suggest that the effects of cannabinoids on glial cells may provide a new approach to treat certain brain disorders [29].

Schizophrenia and endocannabinoid system

The first evidence of the endocannabinoid system being involved in the pathophysiology of schizophrenia was based on high prevalence of *Cannabis sativa* abuse [30, 31]. Studies showed that cannabis abuse worsens the symptoms of schizophrenia patients [32, 33], and increases the risk for schizophrenia development in vulnerable individuals [34]. Moreover, studies have shown increased AEA levels in the cerebrospinal fluid [35, 36] and plasma [37, 38] of schizophrenia patients. Additionally, regulation in CB1 receptor density in some brain areas of schizophrenia patients was observed [39–45]. In this regard, a pre-clinical study reported that increased CB1 levels in some brain areas by antipsychotics could be prevented by high-fat diet [46], suggesting a confounding factor for changes observed in CB1 levels in schizophrenia.

Genetic studies also support the cannabinoid hypothesis of schizophrenia. Cannabinoid receptor type-1 gene (CNR1) polymorphism has been associated with schizophrenia and hebephrenic schizophrenia [47–50]. In addition, CNR2 polymorphism has also been observed in schizophrenia [51]. Together, these studies have shown that CNR1 and CNR2 polymorphisms are involved in susceptibility of schizophrenia, symptom outcomes, and treatment response. Interestingly, Ho et al. [52] found the association of CNR1 polymorphism with variations in white matter volume in schizophrenia.

Finally, investigations have pointed to cannabinoid drugs as potential tools to treat schizophrenia. Studies have shown that CB1 agonists lead to schizophrenia-like behaviors [53–57], while CB1 antagonists may have antipsychotic properties [58, 59] in animal models. The antipsychotic effects of AEA have been also reported [53]. Additional evidence has reinforced the antipsychotic properties of cannabidiol in animal models of schizophrenia [60]. Study has shown preventive effects of cannabidiol in schizophrenia [61].

However, limited clinical studies have reported the effects of cannabinoid drugs. Cannabidiol seems to be the most promising cannabinoid in schizophrenia treatment. The first evidence of the antipsychotic effects of cannabidiol came from a case study [62]. Leweke and colleagues [63] then confirmed the antipsychotic properties of cannabidiol. Recently, a randomized, controlled trial reported the antipsychotic effects of cannabidiol in schizophrenia patients [64].

Therefore, consistent findings have shown the involvement of this system in the pathobiology of schizophrenia. However, fewer studies have investigated the implications of cannabinoids on glial cells in schizophrenia, which are further described in the following section.

Glial cells and schizophrenia

Recent findings suggest the importance of glial cell functions in schizophrenia. Several neurobiological functions have been attributed to these cells. Oligodendrocytes are responsible for myelinating axons, ensuring efficient neuronal impulse conduction; microglia cells are involved with the immune response in the central nervous system; and astrocytes provide metabolic and structural support for neurons and play a role in some neuronal signaling. Increasing evidence has shown abnormalities in all three types of glial cells in schizophrenia.

Glial cells express cannabinoid receptors and synthesize endocannabinoids, and effects of cannabinoid drugs on these cells have been demonstrated [29] (Fig. 1). As such, interactions between the endocannabinoid system and glia may point to evidence for understanding schizophrenia pathobiology and contribute to the development of pharmacological tools. Some dysfunction observed in glial cells may be treated by cannabinoids, alleviating white matter deficits, damage caused by neuroinflammatory or glutamate excitotoxicity, and other pathological pathways observed in schizophrenia.

Oligodendrocytes, schizophrenia, and cannabinoids

Magnetic resonance imaging studies showed decrease of white matter in schizophrenia patients [65–67]. Other imaging studies using white matter fractional anisotropy, a measure of integrity of axons and myelin, demonstrated disrupted

white matter in schizophrenia, suggesting a possible reduced myelin [68, 69]. Interestingly, these data reported that the disruption of white matter was correlated with the severity of schizophrenia symptoms. Following this, white matter deficits can lead to a disconnect between brain regions, contributing to schizophrenia pathobiology [70]. Particularly, oligodendrocytes play a role in this context, as these glial cells are the most abundant cell type in white matter.

Postmortem investigations have shown a decrease in density and morphological disturbances in oligodendrocyte cells of schizophrenia patients compared to healthy individuals, indicating alterations in metabolism and energy [70–73]. Moreover, proteomic investigations have reported differential expression of myelin- and oligodendrocyte-associated proteins in schizophrenia [70]. Study using cuprizone, a model of demyelinating process, reported that quetiapine attenuated the schizophrenia-like behaviors and protected myelin integrity [74]. In addition, it was shown in human oligodendrocyte cell culture that MK-801 treatment promoted alterations in proteins involved in energy metabolism, and clozapine reversed some of these alterations [75].

Another interesting point is the role of oligodendrogenesis in schizophrenia. This process takes place during brain development and following myelin injuries. In adult brains, oligodendrocyte precursor cells (OPCs) can migrate to damaged areas, differentiate into mature oligodendrocytes, and remyelinate the local injury. As aforementioned, white matter deficit seems to be involved in schizophrenia pathobiology, and oligodendrocytes play a crucial role in this process. Study showed that antipsychotic drugs can improve myelin integrity in drug-responder schizophrenia patients [76]. However, no data reported the specific effects of antipsychotics on OPCs. Conversely, animal and in vitro studies have been performed in this field. In vitro studies showed that antipsychotics promote changes in the migration, proliferation, and differentiation of OPCs [77–79]. Another study have reported effects of antipsychotics on glycolysis process in oligodendrocytes [80]. Thus, the modulation of OPCs and mature oligodendrocytes by drugs can comprise an interesting approach to investigate schizophrenia pathobiological and treatment.

Study demonstrated CB1 receptor expression in oligodendrocytes from postnatal and adult rats, as well as in oligodendrocyte culture [81]. This same study also reported that CB1/CB2 agonists WIN55,212-2 and HU211 protected OPCs from apoptosis induced by deprivation of trophic support. Furthermore, another study found an oligodendrogliogenetic effect of WIN55,212-2 in an animal model of multiple sclerosis [82], which shares some degenerative process with schizophrenia. Another group using a model of cerebral ischemia reported that WIN55,212-2 induced OPCs' differentiation and remyelination through the activation of CB1 [83]. Concordantly, differentiation of OPCs by WIN55,212-2 was demonstrated by in vitro studies [84, 85]. Taken together, these studies provide evidence that cannabinoid agonists can modulate OPCs' differentiation, and remyelination process [69]. Although these studies do not represent schizophrenia pathobiology, the findings point to potential effects in mature oligodendrocytes and OPCs which may benefit schizophrenia white matter deficits.

Despite the beneficial effects on oligodendrocytes, WIN55,212-2 induces psychotic behavioral similar to Δ9-THC [53–56]. However, low doses of WIN55,212-2 improve behavioral-like symptoms in animal model of schizophrenia [53, 54]. Another promising cannabinoid in schizophrenia treatment, cannabidiol, displays effects on OPCs. Studies have shown a protective role of cannabidiol against oxidative stress by decreasing the production of reactive oxygen species in OPCs [86, 87]. Redox disturbance has been implicated in schizophrenia [88, 89], and oligodendrocytes seem to be widely affected by oxidative stress in schizophrenia [88], giving strength to this hypothesis. Additionally, there are reports that apoptosis induced by lipopolysaccharide (LPS) and endoplasmic reticulum stress in OPCs were attenuated by cannabidiol [86].

In vivo study showed that cannabidiol decreases inflammation, demyelination, axonal damage, and inflammatory cytokine levels in an animal model of multiple sclerosis [89]. However, cannabidiol exhibits cytotoxicity in oligodendrocytes of the optic nerve by increasing intracellular Ca^{2+} levels [90]. These controversial findings can result from varying stages of the disease or different sources of cells. However, the dosage range also could be responsible for these different effects, since biphasic effects have been shown in behavioral data from multiple sources as mentioned in a previous study [53]. Thus, investigations about cannabidiol effects on oligodendrocytes are required to understand the mechanism, clinical usefulness, and the suitable dose for treatment.

As mentioned, MAGL is the main enzyme responsible for hydrolysis of 2-AG in the brain, producing arachidonic acid and glycerol [91]. Studies have suggested two important results of blocking MAGL. First, data showed the involvement of 2-AG in neuroprotection [92]; second, anti-inflammatory properties of blocking MAGL have been demonstrated, via a decrease in cyclooxygenase (COX) precursors, and a subsequent decrease in prostaglandin synthesis [93–95]. Study reported that the MAGL inhibitor reduced cytotoxicity in oligodendrocytes, as well as reduced demyelination, inflammation, and clinical severity in an animal model of encephalomyelitis [96], suggesting the role of 2-AG enhancement in oligodendrocyte protection and demyelination process. In agreement with this, inhibition of DAGL disrupted oligodendrocyte maturation, suggesting that 2-AG plays a key role in oligodendrocyte differentiation [97]. Therefore, the neuroprotective effects of blocking

MAGL are a potential pharmacological tool to treat disorders with neuroinflammation, such as schizophrenia.

Astrocytes, schizophrenia, and cannabinoids

Similar to oligodendrocytes, astrocytes have been investigated in the schizophrenia pathobiology. Studies have shown impairments of these cells in schizophrenia. Contradictory results of expression have been shown (for example, increase, decrease, or no change) for glial fibrillary acid protein (GFAP), an astrocytic marker [98]. These discrepancies may be related to techniques used, brain areas analyzed, or the stage of disorder. Despite this inconclusive data, a gene set analysis found that astrocyte genetic alterations are associated with an increased risk for schizophrenia [99], strengthening the hypotheses suggesting an astrocytic role in this disorder.

Astrocytes are the most abundant glial cells in the brain and they present several physiological functions, such as maintaining homeostasis, providing energy support for neurons, and assisting with immune system functionality [100]. Moreover, communication has been proposed between astrocytes and pre- and post-synaptic neurons, namely tripartite synapses [101]. Recently, a study reviewed the tripartite synapse and suggested that astrocytic signaling and gliotransmission present different functions depending on brain region [102]. Additionally, this review reported bidirectional signaling between astrocytes and glutamate transmission pathways.

Unlike neurons, astrocytes are not electrically excitable; signaling occurs by altering levels of intracellular calcium [103], which stimulates the release of gliotransmitters (e.g., glutamate and D-serine). Also, astrocytes play an important role in extracellular glutamate uptake in synapses through the astrocytic glutamate transporter-1 (GLT-1) and glutamate aspartate transporter (GLAST) [98]. These transporters remove glutamate from the synaptic cleft, preventing excitotoxicity in neurons.

Another physiological function of astrocytes is related to synaptic plasticity, including pruning and assisting in the formation of synapses [104, 105]. Studies have shown the expression of protein disrupted in schizophrenia-1 (DISC-1) in astrocytes. A study demonstrated that a mutant astrocytic DISC-1 protein was associated with decrease in D-serine, a co-ligand of NMDA receptors [106]. In addition, a mutant DISC-1 expressed in astrocytes, co-cultured with neurons resulted in an impairment of dendritic and synaptic maturation, both of which were counteracted by D-serine treatment [107]. Interestingly, clozapine, but not haloperidol, activated astrocytes and increased D-serine levels [108]. These findings suggest that astrocytes may be a target of drugs to treat schizophrenia.

The role of astrocytes in tripartite synapses has been demonstrated, and the endocannabinoid system presents an interesting contribution to this interaction [109]. CB1 and CB2 expression, and their function in astrocytes, is under controversial debate; but in vivo and in situ studies have reported cannabinoid receptor expression in astrocytes [9, 110, 111]. Enzymes related to endocannabinoid synthesis (NAPE and DAGL) and degradation (FAAH and MAGL) were also found in astrocytes [112]. Studies have shown that astrocytes produce AEA, 2-AG, homo-gamma-linolenylethanolamide, and docosatetraenylethanolamide in a calcium-dependent manner [10, 111, 113–115]. Moreover, astrocytes are responsive to exogenous cannabinoids [116–118].

The main effects of cannabinoids on astrocytes occur through the activation of CB1. In astrocytes, CB1 is coupled to $G_{q/11}$ which activates phospholipase C and increases intracellular Ca^{2+} levels [115, 117]. This alteration in Ca^{2+} levels stimulates the release of glutamate which can in turn activate NMDA receptors in neurons [115]. Study using mutant mice lacking type-1 cannabinoid receptors in astroglial cells (GFAP-CB1-KO) showed that memory impairment induced by Δ9-THC was abolished in this animal [118]. This study also reported that heavy cannabinoid treatment elicited glutamate release through the activation of astroglial CB1 [118]. Additionally, the CB1 activation increases glutamate levels by inhibition of its uptake by GLT-1 and GLAST [115–119]. Thus, cannabinoid and astrocyte interaction could affect glutamatergic neurotransmission, shown to be changed in schizophrenia, and further investigations can contribute to understand this hypothesis.

Another role of astrocytes in the pathobiology of schizophrenia may involve a neuroinflammatory process, since these cells modulate inflammatory response and tissue repair [120]. In vitro studies have reported that CB1/CB2 agonists attenuated the release of proinflammatory cytokines by astrocytes [121–126], suggesting that cannabinoids may have the potential to modulate neuroinflammation. In addition, cannabidiol attenuated neuroinflammation in astrocytes through peroxisome proliferator-activated receptor gamma (PPARγ) activation [127]. In this regard, the activation of PPARs has been proposed as a potential treatment for schizophrenia [128].

As previously mentioned, the inhibition of MAGL results in neuroprotection. It was found that MAGL had high levels of expression in astrocytes [129] suggesting that these cells may be responsible, at least in part, for the metabolism of 2-AG in the brain. Study using an animal model with the deletion of MAGL in astrocytes reported that, expressed in astrocytes, this enzyme has the main responsibility for the availability of arachidonic acid for prostaglandin synthesis, which is involved in neuroinflammation [130]. However, activation of CB1 by 2-AG may result in psychotomimetic effects, since this cannabinoid is a full agonist of CB1

receptors. In agreement, genetic deletion of MAGL in mice resulted in decreased levels of arachidonic acid and prostaglandin levels when the animals were treated with LPS [94]. Interestingly, one study demonstrated that astrocytic deletion of MAGL did not promote psychotomimetic effects or desensitization of cannabinoid receptors [131], which are both common effects of exogenous CB1 agonists, such as Δ9-THC. Moreover, a potent inhibitor of MAGL, KML29, presented anti-inflammatory properties without promoting cannabimimetic effects in mice, depending on the dose [132, 133]. As a whole, these data suggest that the inhibition of MAGL activity represents a promising pharmacological tool to treat disorders with neuroinflammatory processes, such as schizophrenia, but the dosage range should be carefully considered to avoid psychotomimetic side effects.

Microglia, schizophrenia, and cannabinoids

Microglia play an important role in immune-mediated response in the brain, and modulate neuronal plasticity. Resting microglia present motile protrusions that detect alterations in the local environment. Once a cell is activated, protrusions are retracted and the cell body becomes enlarged. Activated microglia are classified as being in M1 or M2 states, which are associated with a proinflammatory or anti-inflammatory response, respectively. Evidence from pathobiological investigations points to immune-related changes in schizophrenia [134]. Inflammatory biomarkers and clinical findings [135] have been reported in schizophrenia, suggesting that neuroinflammation may contribute to the pathogenesis of this disorder. Studies found increased levels of interleukin 1 and 6 (IL-1 and IL-6), C-reactive protein, and tumor necrosis factor alpha (TNF-α) in schizophrenia patients [136, 137]. These cytokines lead to several branches of the inflammatory response, among these being the activation of microglia, the primary immune cells of the central nervous system.

Once activated, microglial cells can play a key role in causing damage to the brain, through the release of proinflammatory mediators such as IL-1, IL-6, interferon gamma (IFN-γ), and TNF-α; an increase in COX-2 expression and activation; an increase of reactive oxygen species; and the activation of astrocytes [138]. Interestingly, postmortem studies have demonstrated higher activation and increased microglia density in schizophrenia [139]. Moreover, positron emission tomography studies have reported increased microglial activation in patients with schizophrenia and in patients with ultra-high risk for psychosis [140, 141]. However, recent studies did not support the inflammation role in schizophrenia [142] or microglial activation in first episode psychosis [143].

The use of pharmacological agents such as minocycline which counteract microglia hyperactivation can be an interesting tool to treat schizophrenia [144, 145]. Relevantly, studies have shown improvement of negative and cognitive symptoms of patients when minocycline is used as an add-on treatment with antipsychotic drugs [146, 147]. Animal studies have also reported an improvement of behavioral-like schizophrenia symptoms by minocycline [144, 148]. Finally, antipsychotics alleviate microglia overactivation and modulate cytokine levels in both in vivo and in vitro studies [149, 150]. In contrast, another group reported the increased density of microglia in brain of rats treated with antipsychotics [151].

Data have shown that cannabinoid drugs modulate microglia activation. CB1 and CB2 expressions have been shown in microglia under physiological conditions [9, 152]. The increasing in CB2 expression has been found in pathological processes of neurodegenerative disorders [153] and in microglia cultures [9]. The 2-AG and AEA are synthesized on-demand by microglia [154], and these synthesis may be 20-fold more than what is produced by neurons or astrocytes in vitro [10]. Once synthesized, endocannabinoids act as autocrine signalers by CB1 and CB2 activation, resulting in a display of the M2 phenotype. Activated M2 microglia are associated with anti-inflammatory processes, tissue repair, and immune regulation [155]. Endocannabinoids synthesized by microglia may act as paracrine mediators in neurons or other glial cells. Therefore, activated microglia have a key role in endocannabinoid synthesis and release, mainly in neuroinflammatory processes. However, there are no reports of the contribution of microglia in endocannabinoid synthesis in schizophrenia. To note, AEA presents protective and antipsychotic properties in schizophrenia patients [156–158] and animal models [53, 159, 160]. Thus, alterations in AEA synthesis by microglia could have implications for schizophrenia.

Despite protection of the brain by microglia, overactivation of these cells leads to damage to the brain, and drugs that have been shown to mediate the damage play a role in schizophrenia treatment. CB1 and CB2 agonists have proven to decrease microglia activation [161, 162]. Moreover, a CB2 agonist inhibited the release of reactive oxygen species by microglia cells treated with LPS [163]. In addition, studies of Alzheimer's disease reported a decrease in proinflammatory cytokines in microglial culture, brought on by a CB2 agonist [164]. Therefore, schizophrenia could be benefited with these anti-inflammatory and antioxidant effects. Although the mechanisms underlying these properties are not fully understood, the decrease in intracellular Ca^{2+} levels seem to be involved [165].

On the other hand, sub-chronic administration of Δ9-THC leads to microglial activation and an increase of proinflammatory markers in mice; and these effects are a result of down-regulation of CB1 receptors, which was correlated with cerebellar deficits [166]. While sub-chronic Δ9-THC

administration leads to a pro-inflammatory profile, cannabidiol presents opposite effects in several conditions. Data reported that cannabidiol, like clozapine, attenuated the schizophrenia-like behavior induced by MK-801, and this effect was correlated with a decrease in microglia reactivity, suggesting that the antipsychotic effects of cannabidiol may involve microglia [167]. Cannabidiol and dimethylheptyl-cannabidiol (a synthetic derivative of cannabidiol) attenuated LPS-induced inflammatory pathways in BV-2 microglial cells [168, 169]. Cannabidiol also prevented microglial activation by decreasing intracellular Ca^{2+} levels [165]. These data point to potential mechanism of cannabidiol in microglial activation observed in schizophrenia.

Microglia overactivation has been also implicated in oligodendrocytes' damage [170]. Study showed that second-generation antipsychotics, but not first ones, can protect oligodendrocytes by modulating microglial activation [171]. Moreover, activated microglia induces reactive astrocytes, which may impair neuronal support and contribute to the death of neurons and oligodendrocytes [172]. In this regard, modulating of microglial response by cannabinoids can protect other glial cells from damage.

Conclusion

Alterations in neurotransmitters have been proposed as the main mechanism in schizophrenia pathobiology, but consistent findings have reported the role of glial cells in schizophrenia, suggesting a glial hypothesis for the pathophysiology of this disorder. Glial cells present CB1 and CB2 receptors, and can produce and metabolize endocannabinoids. Thus, the modulation of endocannabinoid signaling in glial cells can result in pharmacological tools to treat and prevent white matter deficits, neuroinflammatory response, and other pathological mechanisms observed in schizophrenia. On the other hand, some cannabinoid agonists can worsen positive symptoms of schizophrenia depending on the dose, mainly via CB1 receptors, limiting the use of CB1 agonists in treating this disorder. However, selective CB2 drugs may present advantages compared to CB1 agonists, and findings suggest that CB2 is an important modulator in neuroinflammatory conditions. Moreover, pharmacological tools to increase endocannabinoid levels seem to be interesting to treat schizophrenia, since AEA and 2-AG can be protective for some brain cells. Finally, cannabidiol—a potential antipsychotic treatment—modulates key role in glial cells. However, fewer studies have shown the implications of cannabinoid modulators in glial cells for the treatment of schizophrenia. Notwithstanding, investigation about the contribution of glial cells on psychotomimetic effects of chronic or acute cannabis abuse can increase the knowledge about interplay between endocannabinoid system and glial cells. Thus, further studies are needed to better understand the schizophrenia pathobiology as well as the discovery of novel approaches to treat this disorder.

Acknowledgements This work was supported by Grant from the 'Fundação de Amparo à Pesquisa do Estado de São Paulo' (FAPESP Grant number 2013/08711-3 and 2014/10068-4), 'Coordenação de Aperfeiçoamento de Pessoal de Nível Superior' (Capes Grant number 1656470), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq Grant 460289/2014-4). DMS is also supported by Instituto Serrapilheira, Brazil (grant G-1709-16349).

Author contributions AV conceived the study, designed, and wrote the first draft and final version of manuscript. MSD conceived, supervised, and finalized the manuscript.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Owen MJ, Sawa A, Mortensen PB (2016) Schizophrenia. Lancet 388(10039):86–97
2. Howes OD, Kapur S (2009) The Dopamine hypothesis of schizophrenia: version III—the final common pathway. Schizophr Bull 35(3):549–562
3. Kantrowitz J, Javitt D (2012) Glutamatergic transmission in schizophrenia: from basic research to clinical practice. Curr Opin Psychiatry 25(2):96–102
4. Do KQ, Cabungcal JH, Frank A, Steullet P, Cuenod M (2009) Redox dysregulation, neurodevelopment, and schizophrenia. Curr Opin Neurobiol 19:220–230
5. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH (2010) Mechanisms underlying inflammation in neurodegeneration. Cell 140(6):918–934
6. van Kesteren CF et al (2017) Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl Psychiatry 7(3):e1075
7. Bernstein HG, Steiner J, Guest PC, Dobrowolny H, Bogerts B (2015) Glial cells as key players in schizophrenia pathology: recent insights and concepts of therapy. Schizophr Res 161(1):4–18
8. Fernandez-Espejo E, Viveros MP, Nunez L, Ellenbroek BA, Rodriguez De Fonseca, F (2009) Role of cannabis and endocannabinoids in the genesis of schizophrenia. Psychopharmacology (Berlin) 206:531–549
9. Stella N (2009) Endocannabinoid signaling in microglial cells. Neuropharmacology 56(1):244–253
10. Walter L, Stella N (2003) Endothelin-1 increases 2-arachidonoyl glycerol (2-AG) production in astrocytes. Glia 44(1):85–90
11. Mechoulam R, Parker LA (2013) The endocannabinoid system and the brain. Annu Rev Psychol 64:21–47
12. Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC (1988) Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 34:605–613
13. Devane WA et al (1992) Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258:1946–1949

14. Bisogno T et al (2003) Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signalling in the brain. J Cell Biol 163:463–468
15. Piomelli D (2003) The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 4(11):873–884
16. Pertwee RG (2006) The pharmacology of cannabinoid receptors and their ligands: an overview. Int J Obes (Lond) 30(1):S13-8
17. Munro S, Thomas KL, Abu-ShaarM (1993) Molecular characterization of a peripheral receptor for cannabinoids. Nature 365(6441):61–65
18. Brusco A, Tagliaferro P, Saez T, Onaivi ES (2008) Postsynaptic localization of CB2 cannabinoid receptors in the rat hippocampus. Synapse 62:944–949
19. Onaivi ES, Ishiguro H, Gu S, Liu QR (2012) CNS effects of CB2 cannabinoid receptors: beyond neuro-immuno-cannabinoid activity. J Psychopharmacol 26(1):92–103
20. Nevalainen T, Irving AJ (2010) GPR55, a lysophosphatidylinositol receptor with cannabinoid sensitivity? Curr Top Med Chem 10(8):799–813
21. Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, Moriello AS et al (2001) Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 134:845–852
22. Zygmunt PM et al (1999) Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 400(6743):452–457
23. De Petrocellis L, Cascio MG, Di Marzo V (2004) The endocannabinoid system: a general view and latest additions. Br J Pharmacol 141:765–774
24. Di Marzo V, De Petrocellis L (2012) Why do cannabinoid receptors have more than one endogenous ligand? Philos Trans R Soc Lond B Biol Sci 367(1607):3216–3228
25. Wilson RI, Nicoll RA (2002) Endocannabinoid signaling in the brain. Science 296:678–682
26. Bacci A, Huguenard JR, Prince DA (2004) Long-lasting self-inhibition of neocortical interneurons mediated by endocannabinoids. Nature 431(7006):312–316
27. Bénard G et al (2012) Mitochondrial CB(1) receptors regulate neuronal energy metabolism. Nat Neurosci 15:558–564
28. Hebert-Chatelain E et al (2014) Cannabinoid control of brain bioenergetics: exploring the subcellular localization of the CB1 receptor. Mol Metab 3(4):495–504
29. Scheller A, Kirchhoff F (2016) Endocannabinoids and heterogeneity of glial cells in brain function. Front Integr Neurosci 10:24. https://doi.org/10.3389/fnint.2016.00024.eCollection2016
30. Bersani G, Orlandi V, Kotzalidis GD, Pancheri P (2002) Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes. Eur Arch Psychiatry Clin Neurosci 252(2):86–92
31. Barnett JH, Werners U, Secher SM (2007) Substance use in a population based clinic sample of people with first-episode psychosis. Br J Psychiatry 190:515–520
32. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE (2002) Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 325(7374):1212–1213
33. Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, van Os J (2005) Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ 330:11
34. Ksir C, Hart CL (2016) Cannabis and psychosis: a critical overview of the relationship. Curr Psychiatry Rep.18(2):12. https://doi.org/10.1007/s11920-015-0657-y
35. Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D (1999) Elevated endogenous cannabinoids in schizophrenia. Neuroreport 10:1665–1669
36. Reuter AR et al (2016) Association of anandamide with altered binocular depth inversion illusion in schizophrenia. World J Biol Psychiatry 11:1–6 **(Epub ahead of print)**
37. DeMarchi N et al (2003) Endocannabinoid signalling in the blood of patients with schizophrenia. Lipids Health Dis 2:5
38. Potvin S, Stip E, Lipp O, Roy MA, Demers MF, Bouchard RH, Gendron A (2008) Anhedonia and social adaptation predict substance abuse evolution in dual diagnosis schizophrenia. Am J Drug Alcohol Abuse 34(1):75–82
39. Ceccarini J et al (2010) In vivo PET imaging of cerebral type 1 cannabinoid receptor availability in patients with schizophrenia. Schizophr Res 117:70
40. Dalton VS, Long LE, Weickert CS, Zavitsanou K (2011) Paranoid schizophrenia is characterized by increased CB1 receptor binding in the dorsolateral prefrontal cortex. Neuropsychopharmacology 36:1620–1630
41. Dean B, Sundram S, Bradbury R, Scarr E, Copolov D (2001) Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neuroscience 103:9–15
42. Eggan SM, Stoyak SR, Verrico CD, Lewis DA (2010) Cannabinoid CB1 receptor immunoreactivity in the prefrontal cortex: comparison of schizophrenia and major depressive disorder. Neuropsychopharmacology 35(10):2060–2071
43. Urigüen L et al (2009) Immunodensity and mRNA expression of A2A adenosine, D2 dopamine, and CB1 cannabinoid receptors in postmortem frontal cortex of subjects with schizophrenia: effect of antipsychotic treatment. Psychopharmacol Berl 206(2):313e324
44. Wong DF et al (2010) Quantification of cerebral cannabinoid receptors subtype 1 (CB1) in healthy subjects and schizophrenia by the novel PET radioligand [11C]OMAR. Neuroimage 52:1505–1513
45. Zavitsanou K, Garrick T, Huang XF (2004) Selective antagonist [3H]SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 28:355–360
46. Delis F, Rosko L, Shroff A, Leonard KE, Thanos PK (2017) Oral haloperidol or olanzapine intake produces distinct and region-specific increase in cannabinoid receptor levels that is prevented by high fat diet. Prog Neuropsychopharmacol Biol Psychiatry 79(Pt B):268–280. https://doi.org/10.1016/j.pnpbp.2017.06.005
47. Chavarría-Siles I et al (2008) Cannabinoid receptor 1 gene (CNR1) and susceptibility to a quantitative phenotype for hebephrenic schizophrenia. Am J Med Genet B Neuropsychiatr Genet 147(3):279–284
48. Martínez-Gras I et al (2006) (AAT)n repeat in the cannabinoid receptor gene, CNR1: association with schizophrenia in a Spanish population. Eur Arch Psychiatry Clin Neurosci 256(7):437–441
49. Suárez-Pinilla P et al (2015) Brain structural and clinical changes after first episode psychosis: Focus on cannabinoid receptor 1 polymorphisms. Psychiatry Res 233(2):112–119. https://doi.org/10.1016/j.pscychresns.2015.05.005
50. Ujike H et al (2002) CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. Mol Psychiatry 7(5):515–518
51. Ishiguro H et al (2010) Brain cannabinoid CB2 receptor in schizophrenia. Biol Psychiatry 67:974–982
52. Ho BC, Wassink TH, Ziebell S, Andreasen NC (2011) Cannabinoid receptor 1 gene polymorphisms and marijuana misuse interactions on white matter and cognitive deficits in schizophrenia. Schizophr Res 128:66–75

53. Almeida V et al (2014) Effects of cannabinoid and vanilloid drugs on positive and negative-like symptoms on an animal model of schizophrenia: the SHR strain. Schizophr Res 153(1–3):150–159
54. Levin R et al (2014) Effects of cannabinoid drugs on the deficit of prepulse inhibition of startle in an animal model of schizophrenia: the SHR strain. Front Pharmacol 6:5:10
55. Malone DT, Taylor DA (2006) The effect of delta9-tetrahydrocannabinol on sensorimotor gating in socially isolated rats. Behav Brain Res 166(1):101–109
56. Schneider M, Koch M (2002) The cannabinoid agonist WIN 55,212-2 reduces sensorimotor gating and recognition memory in rats. Behav Pharmacol 13:29–37
57. Wegener N, Kuhnert S, Thuns A, Roese R, Koch M (2008) Effects of acute systemic and intra-cerebral stimulation of cannabinoid receptors on sensorimotor gating, locomotion and spatial memory in rats. Psychopharmacology (Berlin) 198:375–385
58. Ballmaier M et al (2007) Cannabinoid receptor antagonists counteract sensorimotor gating deficits in the phencyclidine model of psychosis. Neuropsychopharmacology 32(10):2098–2107
59. Levin R et al (2012) Antipsychotic profile of cannabidiol and rimonabant in an animal model of emotional context processing in schizophrenia. Curr Pharm Des 18(32):4960–4965
60. Campos AC et al (2017) Plastic and Neuroprotective mechanisms involved in the therapeutic effects of cannabidiol in psychiatric disorders. Front Pharmacol 8:269. https://doi.org/10.3389/fphar.2017.00269.eCollection2017
61. Peres FF et al (2016) Peripubertal treatment with cannabidiol prevents the emergence of psychosis in an animal model of schizophrenia. Schizophr Res 172(1–3):220–221
62. Zuardi AW, Morais SL, Guimarães FS, Mechoulam R (1995) Anti-psychotic effect of cannabidiol. J Clin Psychiatry 56:485–486
63. Leweke FM et al (2012) Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry 2:e94. https://doi.org/10.1038/tp.2012.15
64. McGuire P et al (2017) Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry. https://doi.org/10.1176/appi.ajp.2017.17030325
65. Bora E et al (2011) Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr Res 127(1–3):46–57
66. Breier A et al (1992) Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. Arch Gen Psychiatry 49(12):921–926
67. Sigmundsson T et al (2001) Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms. Am J Psychiatry 158(2):234–243
68. Fujino J et al (2014) Impaired empathic abilities and reduced white matter integrity in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 48:117–123
69. Holleran L et al (2014) Altered interhemispheric and temporal lobe white matter microstructural organization in severe chronic schizophrenia. Neuropsychopharmacology 39(4):944–954
70. Cassoli JS et al (2015) Disturbed macro-connectivity in schizophrenia linked to oligodendrocyte dysfunction: from structural findings to molecules. NPJ Schizophr 1:15034
71. Falkai P et al (2016) Decreased oligodendrocyte and neuron number in anterior hippocampal areas and the entire hippocampus in schizophrenia: a stereological postmortem study. Schizophr Bull 42(Suppl 1):S4-S12. https://doi.org/10.1093/schbul/sbv157
72. Uranova NA, Vikhreva OV, Rachmanova VI, Orlovskaya DD (2011) Ultrastructural alterations of myelinated fibers and oligodendrocytes in the prefrontal cortex in schizophrenia: a postmortem morphometric study. Schizophr Res Treat. 325789. https://doi.org/10.1155/2011/325789
73. Vikhreva OV, Rakhmanova VI, Orlovskaya DD, Uranova NA (2016) Ultrastructural alterations of oligodendrocytes in prefrontal white matter in schizophrenia: a post-mortem morphometric study. Schizophr Res 177(1–3):28–36
74. Wang HN et al. (2015) Quetiapine ameliorates schizophrenia-like behaviors and protects myelin integrity in cuprizone intoxicated mice: the involvement of notch signaling pathway. Int J Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyv088
75. Cassoli JS et al (2016) Effect of MK-801 and clozapine on the proteome of cultured human oligodendrocytes. Front Cell Neurosci 10:52
76. Garver DL, Holcomb JA, Christensen JD (2008) Compromised myelin integrity during psychosis with repair during remission in drug-responding schizophrenia. Int J Neuropsychopharmacol 11:49–61
77. Kimoto S et al (2011) Olanzapine stimulates proliferation but inhibits differentiation in rat oligodendrocyte precursor cell cultures. Prog Neuropsychopharmacol Biol Psychiatry 35(8):1950–1956
78. Niu J et al (2010) Haloperidol promotes proliferation but inhibits differentiation in rat oligodendrocyte progenitor cell cultures. Biochem Cell Biol 88(4):611–620
79. Xu H, Yang HJ, Li XM (2014) Differential effects of antipsychotics on the development of rat oligodendrocyte precursor cells exposed to cuprizone. Eur Arch Psychiatry Clin Neurosci 264(2):121–129
80. Steiner J et al (2014) Clozapine promotes glycolysis and myelin lipid synthesis in cultured oligodendrocytes. Front Cell Neurosci 8:384
81. Molina-Holgado E et al (2002) Cannabinoids promote oligodendrocyte progenitor survival: involvement of cannabinoid receptors and phosphatidylinositol-3 kinase/Akt signaling. JNeurosci 22:9742–9753
82. Solbrig MV, Fan Y, Hermanowicz N, Morgese MG, Giuffrida A (2010) A synthetic cannabinoid agonist promotes oligodendrogliogenesis during viral encephalitis in rats. Exp Neurol 226:231–241
83. Sun J,et al (2013) WIN55, 212-2 promotes differentiation of oligodendrocyte precursor cells and improve remyelination through regulation of the phosphorylation level of the ERK 1/2 via cannabinoid receptor 1 after stroke-induced demyelination. Brain Res 1491:225–235
84. Gomez O et al (2011) Cannabinoid receptor agonists modulate oligodendrocyte differentiation by activating PI3K/Akt and the mammalian target of rapamycin (mTOR) pathways. Br J Pharmacol 163:1520–1532
85. Tomas-Roig J, Wirths O, Salinas-Riester G, Havemann-Reinecke U (2016) The cannabinoid CB1/CB2 agonist WIN55212.2 promotes oligodendrocyte differentiation in vitro and neuroprotection during the cuprizone-induced central nervous system demyelination. CNS Neurosci Ther 22(5):387–395
86. Mecha M et al (2012) Cannabidiol protects oligodendrocyte progenitor cells from inflammation-induced apoptosis by attenuating endoplasmic reticulum stress. Cell Death Dis 28(3):e331
87. Barron H, Hafizi S, Andreazza AC, Mizrahi R (2017) Neuroinflammation and oxidative stress in psychosis and psychosis risk. Int J Mol Sci 18(3):651
88. Steullet P et al (2016) Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A "central hub" in schizophrenia pathophysiology? Schizophr Res 176(1):41–51
89. Rahimi A et al (2015) Interaction between the protective effects of cannabidiol and palmitoylethanolamide in experimental model of multiple sclerosis in C57BL/6 mice. Neuroscience 290:279–287

90. Mato S, Victoria Sanchez-Gomez M, Matute C (2010) Cannabidiol induces intracellular calcium elevation and cytotoxicity in oligodendrocytes. Glia 58:1739–1747
91. Blankman JL, Simon GM, Cravatt BF (2009) A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. Chem Phys Lipids 14:1347–1356
92. Panikashvili D et al (2001) An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature 413(6855):527–531
93. Chen R et al (2012) Monoacylglycerol lipase is a therapeutic target for Alzheimer's disease. Cell Rep 2:1329–1339
94. Nomura DK et al (2011) Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science 334:809–813
95. Piro JR et al (2012) A dysregulated endocannabinoid-eicosanoid network supports pathogenesis in a mouse model of Alzheimer's disease. Cell Rep 1:617–623
96. Bernal-Chico A et al (2015) Blockade of monoacylglycerol lipase inhibits oligodendrocyte excitotoxicity and prevents demyelination in vivo. Glia 63(1):163–176
97. Gomez O et al (2010) The constitutive production of the endocannabinoid 2-arachidonoylglycerol participates in oligodendrocyte differentiation. Glia 58(16):1913–1927
98. Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP (2016) Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol Psychiatry 21(8):1009–1026
99. Goudriaan A et al. (2014) Specific glial functions contribute to schizophrenia susceptibility. Schizophr Bull. 40(4):925–935
100. Sofroniew MV, Vinters HV (2010) Astrocytes: biology and pathology. Acta Neuropathol 119(1):7–35
101. Araque A, Parpura V, Sanzgiri RP, Haydon PG (1999) Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci 22:208–215
102. Araque A et al (2014) Gliotransmitters travel in time and space. Neuron 81(4):728–739
103. Perea G, Navarrete M, Araque A (2009) Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci 32:421–431
104. Bernardinelli Y et al (2014) Activity-dependent structural plasticity of perisynaptic astrocytic domains promotes excitatory synapse stability. Curr Biol 24:1679–1688
105. Perez-Alvarez A, Navarrete M, Covelo A, Martin ED, Araque A (2014) Structural and functional plasticity of astrocyte processes and dendritic spine interactions. J Neurosci 34:12738–12744
106. Ma TM et al (2013) Pathogenic disruption of DISC1-serine racemase binding elicits schizophrenia-like behavior via D-serine depletion. Mol Psychiatry 18:557–567
107. Xia M, Zhu S, Shevelkin A, Ross CA, Pletnikov M (2016) DISC1, astrocytes and neuronal maturation: a possible mechanistic link with implications for mental disorders. J Neurochem 138(4):518–524
108. Tanahashi S, Yamamura S, Nakagawa M, Motomura E, Okada M (2012) Clozapine, but not haloperidol, enhances glial D-serine and L-glutamate release in rat frontal cortex and primary cultured astrocytes. Br J Pharmacol 165:1543–1555
109. Oliveira da Cruz JF, Robin LM, Drago F, Marsicano G, Metna-Laurent M (2016) Astroglial type-1 cannabinoid receptor (CB1): a new player in the tripartite synapse. Neuroscience 323:35–42
110. Metna-Laurent M, Marsicano G (2015) Rising stars: modulation of brain functions by astroglial type-1 cannabinoid receptors. Glia 63(3):353–364
111. Navarrete M, Díez A, Araque A (2014) Astrocytes in endocannabinoid signalling. Philos Trans R Soc Lond B Biol Sci 369(1654):20130599
112. Suárez J et al (2010) Endocannabinoid system in the adult rat circumventricular areas: an immunohistochemical study. J Comp Neurol 518(15):3065–3085
113. Walter L, Franklin A, Witting A, Moller T, Stella N (2002) Astrocytes in culture produce anandamide and other acylethanolamides. J Biol Chem 277(23):20869–20876
114. Min R, Nevian T (2012) Astrocyte signaling controls spike timing-dependent depression at neocortical synapses. Nat Neurosci 15:746–753
115. Navarrete M, Araque A (2008) Endocannabinoids mediate neuron–astrocyte communication. Neuron 57:883–893
116. Navarrete M, Araque A (2010) Endocannabinoids potentiate synaptic transmission through stimulation of astrocytes. Neuron 68:113–126
117. Navarrete M et al (2013) Astrocyte calcium signal and gliotransmission in human brain tissue. Cereb Cortex 23:1240–1246
118. Han J et al (2012) Acute cannabinoids impair working memory through astroglial CB1 receptor modulation of hippocampal LTD. Cell Mar 148(5):1039–1050
119. Shivachar AC (2007) Cannabinoids inhibit sodium-dependent, high-affinity excitatory amino acid transport in cultured rat cortical astrocytes. Biochem Pharmacol 73(12):2004–2011
120. Farina C, Aloisi F, Meinl E (2007) Astrocytes are active players in cerebral innate immunity. Trends Immunol 28:138–145
121. Aguirre-Rueda D et al (2015) WIN 55,212-2, agonist of cannabinoid receptors, prevents amyloid β1–42 effects on astrocytes in primary culture. PLoS One 10(4):e0122843
122. Froger N et al (2009) Cannabinoids prevent the opposite regulation of astroglial connexin43 hemichannels and gap junction channels induced by pro-inflammatory treatments. J Neurochem 111(6):1383–1397
123. Gajardo-Gómez R et al (2017) Cannabinoids prevent the amyloid β-induced activation of astroglial hemichannels: a neuroprotective mechanism. Glia 65(1):122–137
124. Molina-Holgado F, Molina-Holgado E, Guaza C, Rothwell NJ (2002) Role of CB1 and CB2 receptors in the inhibitory effects of cannabinoids on lipopolysaccharide-induced nitric oxide release in astrocyte cultures. J Neurosci Res 67:829–836
125. Ortega-Gutierrez S, Molina-Holgado E, Guaza C (2005) Effect of anandamide uptake inhibition in the production of nitric oxide and in the release of cytokines in astrocyte cultures. Glia 52:163–168
126. Sheng WS et al (2005) Synthetic cannabinoid WIN55,212-2 inhibits generation of inflammatory mediators by IL-1beta-stimulated human astrocytes. Glia 49:211–219
127. Esposito G et al (2011) Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement. PLoS One 6(12):e28668
128. Rolland B et al (2013) Therapeutic prospects of PPARs in psychiatric disorders: a comprehensive review. Curr Drug Targets 14(7):724–732
129. Walter L, Dinh T, Stella N (2004) ATP induces a rapid and pronounced increase in 2-arachidonoylglycerol production by astrocytes, a response limited by monoacylglycerol lipase. J Neurosci 24:8068–8074
130. Grabner GF et al (2016) Deletion of monoglyceride lipase in astrocytes attenuates lipopolysaccharide-induced neuroinflammation. J Biol Chem 291(2):913–923
131. Viader A et al (2015) Metabolic interplay between astrocytes and neurons regulates endocannabinoid action. Cell Rep 12(5):798–808
132. Ignatowska-Jankowska et al (2014) In vivo characterization of the highly selective monoacylglycerol lipase inhibitor KML29: antinociceptive activity without cannabimimetic side effects. Br J Pharmacol 171:1392–1407

133. Pasquarelli N et al (2015) Neuropharmacology. Comparative biochemical characterization of the monoacylglycerol lipase inhibitor KML29 in brain, spinal cord, liver, spleen, fat and muscle tissue. Neuropharmacology 91:148–156
134. Howes OD, McCutcheon R (2017) Inflammation and the neural diathesis-stress hypothesis of schizophrenia: a reconceptualization. Transl Psychiatry 7(2):e1024. https://doi.org/10.1038/tp.2016.278
135. Pasternak O, Kubicki M, Shenton ME (2015) In vivo imaging of neuroinflammation in schizophrenia. Schizophr Res 41:85–93
136. Fernandes BS et al (2016) C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry 21(4):554–564
137. Kunz M et al (2011) Serum levels of IL-6, IL-10 and TNF-α in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. Rev Bras Psiquiatr 33(3):268–274
138. Watkins CC, Andrews SR (2016) Clinical studies of neuroinflammatory mechanisms in schizophrenia. Schizophr Res 176(1):14–22
139. Bayer TA, Buslei R, Havas L, Falkai P (1999) Evidence for activation of microglia in patients with psychiatric illnesses. Neurosci Lett 271:126–128
140. Bloomfield PS et al (2016) Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [C]PBR28 PET Brain Imaging Study. Am J Psychiatry 173:44–52
141. van Berckel BN et al (2008) Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biol Psychiatry 64:820–822
142. Notter T et al (2017) Translational evaluation of translocator protein as a marker of neuroinflammation in schizophrenia. Mol Psychiatry 23:323–334
143. Hafizi S et al (2017) Imaging microglial activation in untreated first-episode psychosis: a PET study with [18F]FEPPA. Am J Psychiatry 174(2):118–124
144. Mattei D et al (2014) Minocycline rescues decrease in neurogenesis, increase in microglia cytokines and deficits in sensorimotor gating in an animal model of schizophrenia. Brain Behav Immun 38:175–184
145. Müller N et al (2010) Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. Schizophr Res 121(1–3):118 124
146. Chaudhry IB et al (2012) Minocycline benefits negative symptoms in early schizophre-nia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J Psychopharmacol 26:1185–1193
147. Kelly DL et al (2015) Adjunctive minocycline in clozapine-treated schizophrenia patients with persistent symptoms. J Clin Psychopharmacol 35:374–381
148. Fujita Y et al (2008) Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the antibiotic drug minocycline. Prog Neuropsychopharmacol Biol Psychiatry 32:336–339
149. Ribeiro BM et al (2013) Evidences for a progressive microglial activation and increase in iNOS expression in rats submitted to a neurodevelopmental model of schizophrenia: reversal by clozapine. Schizophr Res 151(1–3):12–19
150. Hu X et al (2012) Clozapine protects dopaminergic neurons from inflammation-induced damage by inhibiting microglial overactivation. J Neuroimmune Pharmacol 7(1):187–201
151. Cotel MC et al (2015) Microglial activation in the rat brain following chronic antipsychotic treatment at clinically relevant doses. Eur Neuropsychopharmacol 25(11):2098–2107
152. Ehrhart J et al (2005) Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation. J Neuroinflamm 2:29
153. Fernández-Ruiz J et al (2007) Cannabinoid CB2 receptor: a new target for the control of neural cell survival? Trends Pharmacol Sci 28:39–45
154. Mecha M et al (2015) Endocannabinoids drive the acquisition of an alternative phenotype in microglia. Brain Behav Immun 49:233–245
155. Mecha M, Carrillo-Salinas FJ, Feliú A, Mestre L, Guaza C (2016) Microglia activation states and cannabinoid system: therapeutic implications. Pharmacol Ther 166:40–55
156. Leweke FM (2012) Anandamide dysfunction in prodromal and established psychosis. Curr Pharm Des 18:5188–5193
157. Giuffrida A et al (2004) Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacology 29:2108–2114
158. Koethe D et al (2009) Anandamide elevation in cerebrospinal fluid in initial prodromal states of psychosis. Br J Psychiatry 194:371–372
159. Seillier A, Advani T, Cassano T, Hensler JG, Giuffrida A (2010) Inhibition of fatty- acid amide hydrolase and CB1 receptor antagonism differentially affect behavioural responses in normal and PCP-treated rats. Int J Neuropsychopharmacol 13:373–386
160. Beltramo M et al (2000) Reversal of dopamine D(2) receptor responses by an anandamide transport inhibitor. J Neurosci 20:3401–3407
161. Amenta PS, Jallo JI, Tuma RF, Elliott MB (2012) A cannabinoid type 2 receptor agonist attenuates blood-brain barrier damage and neurodegeneration in a murine model of traumatic brain injury. J Neurosci Res 90(12):2293–2305
162. Walter L et al (2003) Nonpsychotropic cannabinoid receptors regulate microglial cell migration. J Neurosci 23:1398–1405
163. Malek N, Popiolek-Barczyk K, Mika J, Przewlocka B, Starowicz K (2015) Anandamide, acting via CB2 receptors, alleviates LPS-induced neuroinflammation in rat primary microglial cultures. Neural Plast 2015:130639
164. Aso E, Ferrer I (2016) CB2 cannabinoid receptor as potential target against Alzheimer's disease. Front Neurosci 10:243
165. Martín-Moreno AM et al (2011) Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease. Mol Pharmacol 79(6):964–973
166. Cutando L et al (2013) Microglial activation underlies cerebellar deficits produced by repeated cannabis exposure. J Clin Invest 123(7):2816–2831
167. Gomes FV et al (2015) Decreased glial reactivity could be involved in the antipsychotic-like effect of cannabidiol. Schizophr Res 164(1–3):155–163
168. Kozela E et al (2010) Cannabinoids Δ9-tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-κB and interferon-β/STAT proinflammatory pathways in BV-2 microglial cells. J Biol Chem 285:1616–1626
169. Juknat A, Kozela E, Kaushansky N, Mechoulam R, Vogel Z (2016) Anti-inflammatory effects of the cannabidiol derivative dimethylheptyl-cannabidiol—studies in BV-2 microglia and encephalitogenic T cells. J Basic Clin Physiol Pharmacol 27(3):289–296
170. Chew LJ, Fusar-Poli P, Schmitz T (2013) Oligodendroglial alterations and the role of microglia in white matter injury: relevance to schizophrenia. Dev Neurosci 35(2–3):102–129
171. Seki Y et al (2013) Pretreatment of aripiprazole and minocycline, but not haloperidol, suppresses oligodendrocyte damage from interferon-γ-stimulated microglia in co-culture model. Schizophr Res 151(1–3):20–28
172. Liddelow SA et al (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541(7638):481–487