Microglial Cells as a Link between Cannabinoids and the Immune Hypothesis of Psychiatric Disorders

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Psychiatric disorders are one of the leading causes of disability worldwide. Although several therapeutic options are available, the exact mechanisms responsible for the genesis of these disorders remain to be fully elucidated. In the last decade, a body of evidence has supported the involvement of the immune system in the pathophysiology of these conditions. Microglial cells play a significant role in maintaining brain homeostasis and surveillance. Dysregulation of microglial functions has been associated with several psychiatric conditions. Cannabinoids regulate the brain–immune axis and inhibit microglial cell activation. Here, we summarized evidence supporting the hypothesis that microglial cells could be a target for cannabinoid influence on psychiatric disorders, such as anxiety, depression, schizophrenia, and stress-related disorders.

Keywords: microglia, glia, cannabinoids, anxiety, depression, schizophrenia

INTRODUCTION

Microglial Cells and Psychiatric Disorders

Over the last 20 years, both the innate and adaptive components of the immune system have been associated with the development of psychiatric disorders, such as depression (1) and schizophrenia (2). However, the mechanisms involved in this association are not altogether clear. Although a full review of these mechanisms would be out of the scope of this mini-review, recent evidence indicates that microglial cells could be important players in this complex puzzle and future targets for the treatment of these disorders (3).

Microglial cells are macrophage-like cells involved in immune surveillance of the central nervous system (CNS) and are a major source of inflammatory mediators in the brain (4). They originate from primitive myeloid progenitors before embryonic day 8 and from infiltrating myeloid cells during embryonic and postnatal development (5, 6). Microglia also contributes to CNS homeostasis and plasticity by removing redundant synapses and eliminating dying neurons; modulating neurotransmitter release and neurogenesis; and producing neurotrophic factors (7, 8).

During processes that challenge the brain milieu microglial cells proliferate and change their morphology from surveillance (ramified form) to executive and phagocytic state (amoeboid form, activated microglia) (9). Similar to peripheral macrophages, microglial cells assume at least two distinct states of polarization: M1, a profile that secretes proinflammatory cytokines, and M2, a pro-resolution state (4). The activated microglia releases proinflammatory mediators that, along with its phagocytic activity, may lead to brain damage and contribute to the development of psychiatric disorders (4).
Immune System, Microglia, Anxiety, and Stress-Related Disorders

Stressful experiences such as social defeat activate long-lasting peripheral and central immune response (10–12) and induce microglial activation, myelopoiesis in the bone marrow and spleen, infiltration of monocytes into the brain and neuroinflammation (12–14).

In humans, posttraumatic stress disorder (PTSD) patients present increased peripheral levels of cytokines, in basal and inflammatory conditions (15, 16). Also, although no longer classified as an anxiety disorder, alterations in the immune system of patients with obsessive-compulsive disorder have also been reported (17, 18).

The activation and morphological changes of microglial cells associated with neuroinflammatory states have been recently found to depend on changes induced by stress, including the engagement of glucocorticoids and β-adrenergic receptors (19).

Pharmacological strategies to suppress microglial activity support the involvement of these cells in the development of disease- or stress-induced neuroinflammation and behavioral alterations (20–22). Minocycline is a tetracycline-derived antibiotic with central anti-inflammatory properties that readily crosses the blood–brain barrier (23, 24). It attenuates microglial activation, neuroinflammation, synaptic plasticity, neurogenesis, and behavioral changes in animal models of stress-related disorders (19, 22, 25–27) and after systemic lipopolysaccharides (LPSs) administration (28, 29). The mechanisms of minocycline anti-inflammatory effects are not clear, but may involve facilitation of endocannabinoid (eCB) signaling, since they can be prevented by CB1 or CB2 receptor antagonists (30). However, its effects in patients with anxiety disorders are still unknown.

Propranolol, a β-adrenergic receptor antagonist, also attenuates anxiety-like behavior, stress-induced brain proinflammatory profile (including infiltration of peripheral macrophages into the brain and microglial activation) (31, 32), and the increase in bone marrow monocytes progenitors (33). These effects could be due to an inhibitory effect on stress-induced peripheral immune system activation (12). Anti-inflammatory effects have also been described for antidepressant drugs after clinical and preclinical studies (34–36).

Overall, these results suggest that modulation of microglial proinflammatory profile, either centrally or by interference with peripheral sympathetic activity, could induce anxiolytic and antistress effects.

Immune System, Microglia, and Depression

Patients with mood disorders exhibit an activated inflammatory status (37–39), characterized by increases in the number of circulating lymphocytes and macrophages and proinflammatory cytokines (40). Treatment of inflammatory conditions with interferon-α induces depressive symptoms and decreases serotonin levels in the prefrontal cortex of patients (41). These effects could be related to central activation of the enzyme indoleamine 2,3-dioxygenase (IDO) (42, 43). Proinflammatory cytokines are proposed to activate IDO that, by interfering with tryptophan/kynurenine metabolism, decreases serotonin levels and facilitates the production of quinolinic acid, an N-methyl-d-aspartate (NMDA) receptor agonist (40, 44). Microglial and astrocyte cells control IDO activity. Moreover, activated microglia and infiltrated macrophages have a high capacity for synthesizing quinolinic acid (45). Victims of suicide with the history of affective disorder have increased density of activated phagocytes in the ventral prefrontal white matter (46) and upregulation of the gene IBA1, associated with phenotypic changes in microglia, and MCP-1, a chemokine responsible for attracting monocytes, in the dorsal anterior cingulate (47, 48). Besides the increased number of activated microglial cells are reported in the hippocampus of bipolar patients (49).

Antidepressant drugs are reported to inhibit IL-6 (50, 51) and TNF-α production (52). Antidepressants inhibit LPS-stimulated microglia (36). Moreover, fluoroxetine prevents IκB-α degradation and NF-κB nuclear translocation (53), while lithium decreases LPS-induced microglial activation through the PI3K/Akt/FoxO1 signaling pathway (54). Corroborating these findings, studies suggest that anti-inflammatory drugs as add-on therapy to antidepressant medication may boost depression treatment (55–57).

Stressful experiences are highly associated with predisposition for both depression episodes and immune dysfunction (58, 59). Stress activates microglia in the prefrontal cortex, amygdala, and hippocampus of mice (60) and impairs synaptic plasticity by reducing neuronal activity and decreasing dendritic spine density (61). The high levels of proinflammatory cytokines secreted by microglia downregulate neurotrophic factors, intracellular growth pathways, and neurogenesis (61, 62), in which mechanisms believe to be downregulated in depressive states.

Immune System, Microglia, and Schizophrenia

Increased expression of inflammatory markers in blood and brain tissues (63–65) and changes in genes that control the expression of immune system components have been described in schizophrenia patients (66). Prenatal exposure to inflammatory agents increases the risk for schizophrenia development (67) and meta-analyses indicate the potential use of anti-inflammatory drugs as adjunct treatment in schizophrenia (68).

Postmortem brains of schizophrenia patients present activation and increased cellular density of microglia (69–71). The latter finding has been confirmed by positron emission tomography studies using in vivo markers of activated microglia (72–74). Additionally, elevated microglial activity is also observed in people at ultra high risk of psychosis and is associated with symptom severity, suggesting a link between microglial activation and the risk of psychosis (74). Increased microglial activation is also observed in animal models of schizophrenia (75, 76). Although it is unclear how changes in microglial activity result in schizophrenia symptoms, there seems to be an association between microglial activation and negative and cognitive symptoms (77, 78). In line with this proposition, minocycline improved negative symptoms and cognitive function as an add-on treatment in schizophrenia patients (77, 79, 80). Antipsychotic-like effects of minocycline have also been observed in preclinical studies (81, 82). Together, these results suggest that inhibition of microglial activation may improve schizophrenia symptoms.
CANNABINOIDS AS IMMUNOMODULATORS IN THE CENTRAL NERVOUS SYSTEM

The eCB system was initially described in the late 1980s after the identification of specific receptors (83). It now comprises the cannabinoid receptor types 1 (CB1) and 2 (CB2), their endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and the enzymes responsible for their synthesis and degradation (84–86).

In the CNS, eCBs modulate synaptic function and act as a homeostatic mechanism on HPA axis (87). During stressful or threatening situations, eCBs favor HPA axis activation through the amygdala. Glucocorticoids, by enhancing the production of eCB, modulate glutamatergic and GABAergic neurotransmission via CB1 receptors (87). These receptors are highly expressed in presynaptic terminals and their activation suppresses the release of several neurotransmitters, such as glutamate, GABA, and serotonin (88). CB1 is also expressed in astrocytes (89), oligodendrocytes (90), and neural precursor cells, which also expresses CB2 receptors (91). In addition to CB1, CB2 receptors are constitutively expressed in microglia cells (92) and its expression increases in inflammatory conditions (93). These receptors have been proposed as key regulators of the immune functions, including microglial activation (94–96). They are overexpressed during neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis, conditions in which activated microglia is observed (97). Recently, Mecha et al. (98) demonstrate that the eCB system, by activating CB2 receptors, not only influences the migration, proliferation, and release of proinflammatory mediators of microglial cells but also affects their phagocytic function and drive these glial cells to the M2 state.

2-Arachidonoylglycerol can protect neurons exposed to harmful insults by acting as an endogenous inhibitor of cyclooxygenase-2 (COX-2) (99), whereas AEA inhibits TNF-α-induced NF-κB activation by direct inhibition of the IκB kinase (100). Pharmacological inhibition of AEA hydrolysis reduces microglial activation, nitric oxide levels, and the production of inflammatory mediators (101). Under pathological conditions, microglia cells produce large amounts of eCBs, which could facilitate an anti-inflammatory phenotype of microglia (92). Enzymes controlling eCB tone also play an important neuroprotective role during neuroinflammatory process (97). Supporting the involvement of eCBs in immune modulation, the neuroprotective effect and inhibition of microglial activation induced by minocycline were prevented by CB1 and CB2 receptor antagonists in a rodent model of traumatic brain injury (30).

Exogenous cannabinoids can also modulate microglia activation (97, 102, 103). They reduce the binding of transcription factors to CRE and NF-κB in immune cells (104) and inhibit cytokine and chemokine production (105). WIN55,212-2, a mixed CB1/CB2 receptor agonist, reduced brain mRNA expression of proinflammatory cytokines, such as TNF-α and IL-6, in a viral model of multiple sclerosis (106) and in the Alzheimer's disease model of Aβ amyloid injection (107, 108). Moreover, WIN55,212-2 also decreased the number of activated microglia related to Aβ administration (107) or the aging process in rats (102).

Cannabinoids, Microglia, and Anxiety Disorder

Overexpression of CB1 and CB2 receptors, or their acute pharmacological activation, promotes anxiolytic-like effects (109, 110), whereas their genetic deletion or pharmacological blockade causes opposite results (111, 112). These receptors also attenuate the increased proinflammatory profile observed in the frontal cortex after subchronic stress in mice (113, 114), reducing microglial activation and proliferation (95, 115–117).

Cannabinoids could also attenuate anxiety by modulating the release of IL-1ra, the endogenous antagonist of IL-1β, by glial cells in response to glutamate (118), and by interfering with the HPA axis (119). In the latter case, glucocorticoids modulate microglial activation induced by stressors (120, 121) and suppress hippocampal and amygdala eCB signaling (122).

Cannabinoids, Microglia, and Depression

Lipopolysaccharide induces "sickness behavior" in rodents, a syndrome that shows some similarity with depressive symptoms and depends on prolonged cytokines release and microglial activation (123, 124). Accordingly, using LPS as inflammatory stimulus, cannabinoids reduced the number of circulating lymphocyte, corticosterone levels (125), and the release of IL-1β, TNF-α, and iNOS expression in vitro (126). Moreover, the long-lasting behavioral deficits induced by LPS are prevented by the administration of THC (127) or cannabidiol (CBD) (108). As discussed above, in addition to interfere with HPA axis (119), cannabinoids can directly decrease microglial activation and attenuate stress-induced neuroinflammatory states (108, 125, 126).

Although the specific contribution of CB1 and CB2 receptors for the aforementioned anti-inflammatory effects is still unclear, the neuroprotective effects of CB2 agonists are associated with a decrease in the number of activated microglial cells (107). In vitro studies indicate that these receptors, located at microglial cells, facilitate the production of anti-inflammatory mediators (128). Considering the pieces of evidence suggesting that depression could be a "microglial disease," these results point to CB2 receptors located at this cells as possible targets for future antidepressant treatments.

Cannabinoids, Microglia, and Schizophrenia

Adolescent cannabis exposure represents a risk factor for developing schizophrenia later in life (129). Besides the long-lasting changes in neuronal activity induced by adolescent cannabinoid exposure (76, 130), increased microglial activation in the prefrontal cortex (131) and hippocampus of adult rats have also been observed (132). Moreover, ibudilast (AV411), a non-selective phosphodiesterase inhibitor that suppresses glial cell activation (133), prevents the development of behavioral changes induced by adolescent THC exposure (131).

Unlike THC, CBD is a phytocannabinoid devoid of psychotomimetic activity that present antipsychotic activity (134). The mechanism of action involved in this effect is not entirely understood. However, the anti-inflammatory and neuroprotective effects of this drug (135) may contribute to its beneficial effects in...
schizophrenia. Repeated treatment with CBD-attenuated behavioral deficits and the percentage of Iba-1-positive microglial cells with a reactive phenotype in the medial prefrontal cortex and dorsal hippocampus of mice chronically treated with the NMDA receptor antagonist MK-801 (136). CBD treatment also attenuated the decreased number of GABAergic parvalbumin-positive cells in the medial prefrontal cortex, which could, by reducing inhibitory tonus in this region, facilitate glutamate release and lead to microglial activation (137). Interestingly, schizophrenia patients with a higher inflammatory state had more deficits in GABAergic neuron-related mRNAs, including GAD67 and parvalbumin (138).

Regarding the eCB system, whereas higher levels of 2-AG have been observed in the prefrontal cortex, hippocampus, and cerebellum of schizophrenia patients, AEA levels are lower (139). Moreover, increased AEA levels in the cerebrospinal fluid correlate negatively with psychotic symptoms (140) and the antipsychotic effect of CBD was associated with increased AEA serum levels. This latter effect likely reflects CBD inhibition of the FAAH enzyme, responsible for AEA degradation (141). Increases in eCBs may contribute to defense mechanisms through accumulation of anti-inflammatory microglia phenotype (92). Thus, the pharmacological inhibition of eCB hydrolysis may be a useful approach in the schizophrenia treatment.

As aforementioned, CB2 receptors are expressed on microglia and its expression is strongly upregulated when these cells are activated. Schizophrenia has been associated with single nucleotide polymorphisms in the CB2 receptor gene that reduce its expression and functionality (142). Decreased expression of CB2 receptors in isolated peripheral blood mononuclear cells is found during first-episode psychosis (143). However, no study has evaluated changes on CB2 receptor expression in microglia cells in the brain of schizophrenia patients. In rodents, pharmacological or genetic CB2 receptor blockade increases susceptibility for developing schizophrenia-like symptoms (111, 142). Additionally, a CB2 receptor agonist reversed sensorimotor gating deficits in mice induced by MK-801 (144). However, the involvement of microglial CB2 receptors in these effects is unknown.

CONCLUSION

A large body of evidence supports the involvement of neuroinflammatory mechanisms, including microglial activation, in the pathophysiology of psychiatric disorders. Drugs that interfere with these mechanisms, such as cannabinoids, could be a novel and important new pathway for the treatment of these disorders (Figure 1). Despite these pieces of evidence, few studies have yet directly investigated if interference with microglial cell activation is essential for the therapeutic effects of cannabinoids in psychiatric disorders. Additional studies, therefore, are needed to test this hypothesis.

AUTHOR CONTRIBUTIONS

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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