

## Review Article

# Neuroleptics and Microglial Activation Associated with Neuropsychiatric Disorders

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## Special Issue on

## Neuropsychiatric Disorders and Microglia

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## Abstract

Microglial activation is one of common pathological findings in the lesions of many neurodegenerative diseases. In the 1980's immunohistochemical studies, using anti-major histocompatibility complex class II (MHCII) antibodies identified activated microglia in postmortem brains of neurodegenerative diseases. Microglial activation in the brains of patients with neurodegenerative diseases has been demonstrated since 2000 by positron emission tomography studies employing PK11195. Moreover, activated microglia have also recently been implicated in endogenous psychiatric disorders, such as schizophrenia and mood disorders, where common pathological findings had never before been identified. However, the exact functional states of microglial activation in neuropsychiatric diseases remain to be clarified, since an increase in expression of a microglial marker MHC II or PK11195 is not necessarily an indicator of classical inflammatory microglial activation. Accumulating evidence shows that both antidepressants and antipsychotics attenuate the classical activation of microglia, suggesting that such an action may be associated with their therapeutic effects. It is clearly desirable to establish reliable markers that would identify specific microglial activation states in neuropsychiatric diseases.

## Keywords

- Antidepressants
- Antipsychotics
- Classical activation
- Neuropsychiatric disorders
- Microglia

## ABBREVIATIONS

COX, cyclooxygenase; D2R, dopamine 2 receptor; EAE, experimental autoimmune encephalomyelitis; GFAP, glial fibrillary acidic protein; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MHC II, major histocompatibility complex class II; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NO, nitric oxide; PET, positron emission tomography; PHOX, NADPH oxidase; PKA, protein kinase A; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TNF, tumor necrosis factor

## INTRODUCTION

Microglial activation is a common pathological finding in lesions of a broad spectrum of neurodegenerative diseases. In the 1980's seminal studies by the McGeer group, using immunohistochemistry with anti-major histocompatibility complex class II (MHC II) antibodies, identified activated microglia in the postmortem brains of Alzheimer disease [1,2], Parkinson disease [2], multiple sclerosis [3] and amyotrophic lateral sclerosis [3]. From 2000 onward, the microglial activation in the brain of patients with various neurodegenerative diseases has been demonstrated by positron emission tomography (PET) studies employing PK11195, a tracer of peripheral

benzodiazepine receptors [4]. Moreover, activated microglial have also recently been implicated in endogenous psychiatric disorders, such as schizophrenia and mood disorders, where no common pathological findings had previously been identified. Immunohistochemical studies have shown an increase in MHCII expression in the postmortem brains with both schizophrenia and affective disorder [5,6], while PET studies have demonstrated increased binding of PK11195 in brains of schizophrenia patients [7,8]. In a way, these studies appear to verify "the macrophage theory" proposed by Smith in 1990's that argued that dysregulation of innate immune and inflammatory processes caused by activated macrophage/microglia may be involved in the pathogenesis of schizophrenia and major depression [9,10]. However, the exact functional states of microglial activation in neuropsychiatric diseases must still be clarified, since increases in expression of the microglial marker MHC II and PK11195 are not necessarily indicators of classical activation [11]. Accumulating evidence suggests that inhibitory effects on the classical inflammatory activation of microglia may be associated with therapeutic actions of psychoactive drugs, such as antidepressants (reviewed in [12-14]) and antipsychotics (reviewed in [15,16]). This mini-review discusses anti-inflammatory properties of the neuroleptics and nature of microglial activation associated with neuropsychiatric disorders.

## ACTIVATION STATES OF MICROGLIA AND NEUROPSYCHIATRIC DISORDERS

Recent studies imply that microglial response is heterogeneous and that microglial activation states are more complicated than originally described by Del Rio Hortega almost a century ago [11,17]. Del Rio Hortega defined "activation" of microglia based on their morphology, in which ramified microglia in the healthy brain are supposed to be in a resting state and, upon any potential danger signal, these cells morph into an amoeboid or macrophage-like shape [18,19]. It has now been suggested that there are, at least, three different states of microglial activation.

Conversion of microglia into the pro-inflammatory phase as an innate immune response is one of the initial functional outcomes of the activation process and has been defined as "classical activation". This microglial state is associated with the production and release of pro-inflammatory cytokines (e.g., tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, IL-1 $\beta$ ), proteases (e.g., matrix metalloproteinase-9), chemokines, superoxide anion, nitric oxide (NO) and reactive oxygen-nitrogen species [20-23]. Although cytoactive agents released during classical activation are aimed at tissue defense and the destruction of pathogens, they also have potency to induce inflammatotoxic response of host tissue [11].

Classical activation is followed rapidly by an anti-inflammatory and repair phase that ideally leads to wound healing and the return of tissue homeostasis, the ultimate outcome of a successful innate immune response [11]. This anti-inflammatory and repair function of microglial activation includes "alternative activation" and "acquired deactivation" [24,25]. When stimulated with IL-4 and/or IL-13, microglia demonstrate alternative activation, with decreased expression of pro-inflammatory mediators, including inducible nitric oxide synthase (iNOS) and TNF- $\alpha$  mRNA, and an increased expression of repair genes, such as arginase I and mannose receptor [26,27]. Acquired deactivation is induced by exposure to IL-10, transforming growth factor- $\beta$  and/or apoptotic cells [25,28-30]. After engulfment of the apoptotic phospholipid phosphatidylserine, microglia reduces their generation and release of superoxide anion, NO and TNF- $\alpha$  [31, 32]. Alternative activation and acquired deactivation both down-regulate innate immune responses and show similar, but not identical, gene profiles, even though many investigators mix them up [17].

Several antigenic markers have commonly been established to indicate microglial activation states. For example, CD45/MHCII and mannose receptor/CD163 are conventionally used as typical markers for classical activation and for alternative activation, respectively [17,22]. However, recent studies have revealed that CD45 expression represents a down-regulation of pro-inflammatory and neurotoxic activation of microglia [33,34] and that increased expression of MHCII is also observed in alternative activated microglia [11]. Although microglial activation in brain of patients with neuropsychiatric disorders has been demonstrated by PET studies using PK11195, the mechanism by which the mitochondrial peripheral benzodiazepine receptor directly regulates classical microglial activation is unknown. Therefore, it is obvious that single microglial marker cannot provide enough information to identify the specific activation states of microglia, and that microglial activation states in lesions of neuropsychiatric diseases have yet to be elucidated. It is likely

that lesions contain heterogeneous activation states of microglia in various neuropsychiatric disorders, since Wynn et al. [35] defined chronic inflammation as the coexpression of alternative activation and classical activation. Although the exact states of microglial activation associated with neuropsychiatric diseases are still unknown, growing evidence indicates that the common antidepressants and antipsychotics have inhibitory effects on the classical inflammatory activation of microglia.

## EFFECTS OF ANTIDEPRESSANTS ON CLASSICAL ACTIVATION OF MICROGLIA

Animal studies have established the ability of antidepressants to suppress the classical activation of microglia in inflamed brain. Desipramine, a tricyclic antidepressant (TCA), prevents the increase in mRNA expression of the microglial activation markers CD11b and CD40, and proinflammatory mediators IL-1 $\beta$ , TNF- $\alpha$ , iNOS in the cortex of lipopolysaccharide (LPS)-injected rats [36]. Desipramine also diminishes the cortical activity of the inflammatory transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B) [36]. The reduced mRNA expression of proinflammatory molecules seems to be at least partially due to attenuated activity of microglia, but astrocytes and infiltrated peripheral immune cells may also be involved in the LPS-induced cortex inflammation. Post-injury intraperitoneal administration of the TCA amitriptyline attenuates spinal nerve ligation-induced increase in CD11b immunoreactivity and thermal hypersensitivity, but does not inhibit up-regulation of immunoreactivity of the astrocytic marker glial fibrillary acidic protein (GFAP) or mechanical hypersensitivity [37]. Intrathecal pretreatment with amitriptyline plus post-injury intraperitoneal injection of the same agent suppresses not only CD11b immunoreactivity and thermal hypersensitivity, but also GFAP immunoreactivity and mechanical hypersensitivity [37]. Preemptive administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), inhibits the increase in the mRNAs for IL-1 $\beta$ , TNF- $\alpha$  and cyclooxygenase (COX)-2, and in the immunoreactivities of the microglial marker IBA-1 and GFAP in the hippocampus of kainic acid-injected mice [38]. These findings suggest that fluoxetine has some power to reduce the inflammatory activation of microglia and astrocytes in the pathological brain of an epilepsy model. Interestingly, fluoxetine also prevents the kainic acid-caused neuronal death in the hippocampus and markedly improves kainic acid-induced memory impairment [38]. Even after occlusion of the middle cerebral artery, fluoxetine treatment inhibits the rise in mRNA levels of COX-2, IL-1 $\beta$  and TNF- $\alpha$  in the rat brain of an ischemia model [39]. Fluoxetine also attenuates the microglial activation, quantified by immunoreactivity for IBA-1 and Mac2, and reduces the neutrophil infiltration, shown by enhanced immunoreactivity for myeloperoxidase [39]. Moreover, fluoxetine decreases the NF- $\kappa$ B activity and infarct volumes in the post ischemic brain. The effectiveness of fluoxetine is accompanied by improvement of motor impairment and neurological deficits [39]. The *in vivo* studies mentioned above demonstrate that antidepressant treatment reduces the increased levels of inflammatory molecules and activated microglia in lesions. To interpret the data appropriately, it should be noted that the antidepressant-reduced levels of inflammatory mediators may not be exclusively due to inhibition of microglial activation, in spite of the fact that

microglia are the main source of inflammatory mediators in the central nervous system. Under pathological conditions peripheral immune cells, which could produce various inflammatory substances, infiltrate the brain [40]. *Ex vivo* studies have shown that antidepressants decrease the production of proinflammatory cytokines in peripheral immune cells [41,42].

In line with *in vivo* studies, a number of *in vitro* studies have also demonstrated that various types of antidepressants attenuate classical microglial activation which leads to the production of inflammatory molecules and neurotoxicity. Although a few *in vitro* studies imply that antidepressants do not affect or even increase microglial expression of inflammatory mediators [36, 43], the majority of studies on this subject show that treatment of cultured microglia with TCA, SSRI or serotonin-noradrenaline reuptake inhibitor before stimulation with LPS or interferon (IFN)- $\gamma$  results in reduced microglial expression of proinflammatory cytokines, including IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , at both mRNA and protein levels [44-48]. Such drug efficacy is also observed when antidepressants and stimuli are simultaneously added to microglial cultures [39, 49, 50]. In addition to proinflammatory cytokines, antidepressants diminish LPS or IFN- $\gamma$ -induced microglial generation of free radicals, such as nitric oxide and reactive oxygen species [44-46,48-50]. *In vitro* studies using microglia-neuron cocultures demonstrate that antidepressants confer neuroprotection against LPS- or 1-methyl-4-phenyl-pyridinium-induced microglial neurotoxicity [46,48,51]. Interestingly, the antidepressant-induced neuroprotection is not observed in astrocyte-neuron cocultures or neuron-enriched cultures [48,51]. Glutamate and D-serine, which acts as a co-agonist with glutamate on N-methyl-D-aspartate receptors, are secreted from activated microglia and supposed to lead excitatory neurotoxicity. The SSRIs fluoxetine and citalopram decrease the release of glutamate and D-serine from LPS-activated microglia to promote cortical neuronal viability [52]. Calcium signaling is implicated in microglial activation [53]. A recent calcium imaging study has revealed that SSRIs suppress the amplitude of the IFN- $\gamma$ -induced increase in the intracellular calcium concentration ( $[Ca^{2+}]_i$ ) of 6-3 murine microglial cells [45]. On the other hand, neither the noradrenaline-dopamine reuptake inhibitor bupropion, nor the noradrenaline-dopamine disinhibitor agomelatine, reduces the IFN- $\gamma$ -induced  $[Ca^{2+}]_i$  elevation in 6-3 cells [45].

Molecular targets for the inhibitory effects of antidepressants on the classical activation of microglia are yet to be clarified. However, the cAMP-dependent protein kinase A (PKA) pathway has been suggested as mediating the anti-inflammatory events [44,50] and seems to be one of the most plausible for the following reasons:

- 1) Antidepressants have been thought to exert their therapeutic effects via activation of the cAMP-PKA cascade [54].
- 2) Various antidepressants have been shown to up-regulate adenylate cyclase activity through enhancing coupling between the stimulatory  $\alpha$ -subunit of the G protein Gs and adenylate cyclase, resulting in elevated levels of cellular cAMP in C6 glioma cells [55,56].
- 3) In a number of cell types, the up-regulated cAMP/PKA pathway has been shown to inhibit the activity of NF- $\kappa$ B [57],

whose up-regulation induces the gene expression of iNOS and a wide range of proinflammatory cytokines, such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$  [58]. In fact, fluoxetine [39,48,49] and the TCAs imipramine and clomipramine [46] have been shown to attenuate the LPS-induced NF- $\kappa$ B activation in cultured rodent microglia. These drugs have also been demonstrated to inhibit LPS-evoked phosphorylation of p38, a key upstream regulator of NF- $\kappa$ B [46,49].

## EFFECTS OF ANTIPSYCHOTICS ON CLASSICAL ACTIVATION OF MICROGLIA

Increasing evidence shows that antipsychotics also attenuate the classical activation of microglia *in vitro*. With regard to conventional antipsychotics, flupentixol and trifluoperidol reduce the secretion of TNF- $\alpha$  and NO from LPS-activated rat microglia [59]. Flupentixol, trifluoperidol, chlorpromazine and loxapine reduce IL-1 $\beta$  and IL-2 release from LPS-activated microglia [60, 61]. The typical antipsychotics spiperone also reduces the release of NO and pro-inflammatory cytokines such as IL-1 $\beta$  and TNF- $\alpha$  from LPS-activated microglia [62]. Moreover, spiperone has been shown to attenuate microglial neurotoxicity in the microglia/neuroblastoma cell coculture [62].

Increasing evidence also shows pharmacological actions of atypical antipsychotics on the inflammatory activation of microglia. Olanzapine treatment of murine microglia inhibits LPS-induced NO production, but haloperidol and clozapine do not reduce the NO production [63]. Risperidone, one of the common atypical antipsychotics, decreases the secretion of NO and pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  from the IFN- $\gamma$ -activated microglia to greater extent than does haloperidol, a typical antipsychotic drug [64]. The atypical antipsychotics perospirone and quetiapine also have inhibitory effects on IFN- $\gamma$ -induced classical activation of microglia. Perospirone, quetiapine and ziprasidone significantly inhibit the NO release. Quetiapine and perospirone decrease the TNF- $\alpha$  release, whereas ziprasidone increases the TNF- $\alpha$  secretion [64]. Clozapine exerts neuroprotective effects via inhibition of classical activation of microglia [65]. Clozapine attenuates NADPH oxidase (PHOX)-generated ROS production, as well as production of NO and TNF- $\alpha$  in LPS-activated microglia [65]. All of above-mentioned antipsychotics are antagonist of dopamine 2 receptor (D2R), while aripiprazole, a novel unique atypical antipsychotic drug, is a D2R partial agonist [66]. Aripiprazole has inhibitory effects on the generation of NO and TNF- $\alpha$  in IFN- $\gamma$ -activated microglia and suppresses the microglial toxicity to oligodendrocytes [67], while quinpirole, a D2R full agonist, has no efficacy [68].

Compared to the number of *in vitro* studies, fewer *in vivo* studies have shown inhibitory effects of antipsychotics on the classical activation of microglia. Ziprasidone, an atypical antipsychotic drug, reduces microglial IBA-1 intensity and prevents severe loss of neural marker intensity in the infarction cortical area caused by middle cerebral artery occlusion in rats [69]. Quetiapine decreases the accumulation of activated microglia shown by CD11b immunoreactivity and alleviates white matter pathology in sites of cuprizone-induced demyelination in the mouse brain [70]. Quetiapine diminishes the accumulation of microglial cells which are CD11b-positive or CD68-positive, and reduces infiltration of T cells in the spinal cord of mouse

with experimental autoimmune encephalomyelitis (EAE) [71]. Intriguingly, antipsychotic quetiapine dramatically attenuates the severity of EAE symptoms and diminishes demyelination [71].

It should be noted that certain animal studies demonstrate little or no effect of antipsychotics on microglia or even adverse effects on the brain. An animal study demonstrates that haloperidol prevents neither ketamine- nor phencyclidine-induced microglial activation quantified by immunoreactivity for CD11b in the adult rat cortex [72]. Chronic treatment of haloperidol at both low and high doses induces degeneration of striatal neurons and myelin, scarcity of microglial macrophages, expansion of nuclear intermembranous space, degenerated mitochondria, and vacuoles in guinea pigs [73].

Although microglia have various receptors of neurotransmitters including D2R [74], the pharmacological basis for anti-inflammatory effects of antipsychotics appears not to be related to the conventional neurotransmitter receptors. Clozapine may inhibit microglial activation of PHOX via inhibiting phosphoinositide 3-kinase pathway [65]. Spiperone has been shown to repress microglial up-regulation of NF- $\kappa$ B and p38 mitogen-activated protein kinase [62]. A full agonist of D2R quinpirole has been demonstrated to have no anti-inflammatory effects, while aripiprazole has anti-inflammatory effects with inhibition of microglial  $[Ca^{2+}]_i$  elevation [68]. Accordingly, it is suggested that these antipsychotics exert their anti-inflammatory effects on microglia in a dopamine receptor-independent manner.

## CONCLUSION

It is evident that both antidepressants and antipsychotics inhibit classical activation of microglia and exert anti-neuroinflammatory effects through suppressing microglial expression of inflammatory mediators. While the exact states of microglial activation associated with neuropsychiatric diseases must still be elucidated, it is clearly desirable to establish reliable markers that would identify specific microglial activation states in neuropsychiatric diseases in order to learn more of the pathogenesis of neuropsychiatric diseases and as a guide in developing new therapeutic agents.

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