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# Glia: An Important Target for Anti-Inflammatory and Antidepressant Activity

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**Abstract:** Activated glial cells are capable of generating various inflammatory mediators, including cytokines, nitric oxide and reactive oxygen species. These potentially neurotoxic molecules have been suggested to play a role in the etiology and development of depression. Accumulating evidence indicates that antidepressants have inhibitory effects on inflammatory activation of glial cells and confer neuroprotection under neuropathological conditions. Such efficacy of antidepressants appears to depend on suppressing microglial production of inflammatory substances and up-regulating both astrocytic secretion of neurotrophins and astrocytic glutamine synthase, which converts neurotoxic glutamate into non-toxic glutamine. Therefore, glial cells, both as source and target of inflammatory molecules, may represent a potential promising target involved in the pathophysiology of depression. Moreover, antidepressants have the possibility to be useful treatment, not only for depression, but for a broad spectrum of neuroinflammatory and neurodegenerative disorders where the pathogenesis is associated with glial activation.

**Keywords:** Antidepressants, anti-inflammatory effect, astrocyte; cytokine, depression, microglia, nitric oxide, reactive oxygen species

## INTRODUCTION

The WHO estimates that more than 350 million people suffer from depression in the world [1]. Almost one million people commit suicide every year and a large proportion of them are supposed to have experienced depression [1]. Antidepressant drugs are the first line treatment for various forms of depression, especially for moderate-severe depression. Despite their widespread use, there has thus far been no all-encompassing hypothesis for how these remedies actually work in the brain microenvironment to exert antidepressant effects. Indeed, treatments for depression are still based on empirical data, not mechanisms of drug action [2]. Their ability to increase synaptic concentrations of monoamine led to the monoamine theory of depression in 1960s [3, 4]. For five decades, the monoamine theory has been predominant and has guided research into the etiology of depression. However, it seems unlikely that every phenomenon caused by antidepressants can be attributed to intrasynaptic monoamine levels. For instance, the monoamine theory does not address the fact that drug-induced rise in synaptic monoamine occurs immediately, while their clinical effects take 2-4 weeks to become evident [4]. It also could not be a good reason why 20% to 40% of patients in a depressive episode show either partial response or no response to antidepressants [5].

Chronic inflammatory processes in the brain are typical findings in the development of various neurodegenerative diseases, including Alzheimer disease and Parkinson disease [6]. There is growing evidence that inflammation in the periphery and brain are also associated with some cases of depression [7-10]. Although contemporary investigations have still not come to a firm conclusion about whether the suppression of inflammation *per se* ameliorates depressive symptoms, increasing evidence indicates that antidepressant drugs possess anti-inflammatory properties [9, 11, 12]. Intriguingly, an anti-inflammatory drug such as the cyclooxygenase (COX)-2 inhibitor celecoxib, which crosses the human blood brain barrier [13], has been shown to have antidepressant efficacy [14]. Anti-inflammatory effects of antidepressants were established originally in the peripheral immune system, as shown by the limited extent of rat paw edema caused by different chemicals [15], by antagonized prostaglandin E2 in the rat mesenteric vascular bed [16], and by decreased human plasma or serum levels of inflammatory markers [17-19]. More recently, seminal studies have revealed that antidepressants also inhibit inflammatory responses by activated glial cells [20, 21].

Glial cells are the resident and principal innate immune cells in the brain [22]. Unlike neurons and other types of glia that stem from ectoderm, microglia are mesodermal in origin and are characterized by a very low threshold of activation leading to immunological functions [23]. Astrocytes are complex, highly differentiated and the most abundant glial cells [24]. Astrocytes play essential roles to maintain the brain homeostasis and neuronal functions [25], and also mediate innate immunity and inflammatory responses in the brain [22, 25]. Activated glia (also referred to as gliosis) produce excessive amount of inflammatory molecules, such as cytokines, chemokines, nitric oxide (NO) and reactive oxygen species (ROS) [26-28]. These molecules have been implicated in the pathophysiology of depression [29, 30].

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Furthermore, postmortem brain studies have revealed the existence of activated microglia in some cases of depression [31-33]. Given that such glial activation-mediated neuroinflammation may play a role in depression, the anti-inflammatory actions of antidepressants on glial cells may compensate insufficiency of the monoamine theory.

In order to illuminate the possibility that glial cells may be as new targets of antidepressant treatment, we attempt to provide an overview of studies on influence of antidepressants on inflammatory activation of glial cells. Also, we will briefly discuss the relevance of glia-derived inflammatory molecules in the etiology of depression.

## EFFECTS OF ANTIDEPRESSANTS ON GLIAL ACTIVATION-MEDIATED NEUROINFLAMMATION *IN VIVO*

Animal studies have shown the efficacy of antidepressants in the inflamed brain induced by various stimuli, including lipopolysaccharide (LPS), an endotoxic glycolipid located in the outer membrane of Gram-negative bacteria. LPS is often used as a potent activator of microglia *in vitro* [34, 35] and also induces depression-like "sickness behavior" in rodents [36]. LPS injection leads to glial activation and increased amount of ROS, NO and proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, in the rodent brain [37-39]. Administration of desipramine, a tricyclic antidepressant (TCA), just before LPS injection prevents the increase in mRNA expression of IL-1β, TNF-α, inducible nitric oxide synthase (iNOS) and the microglial activation markers CD11b and CD40 in the rat cortex [39]. Desipramine also diminishes the cortical activity of the inflammatory transcription factor nuclear factor-κB (NF-κB) [39]. The reduced mRNA expression of proinflammatory cytokines seems to be due to attenuated activity of microglia to a certain extent, even though astrocytes and infiltrated peripheral immune cells may also be involved in the LPS-induced cortex inflammation.

Antidepressants have recently been shown to confer neuroprotection presumably through suppressing glial production of potentially neurotoxic inflammatory substances. Administration of the selective serotonin reuptake inhibitor (SSRI) fluoxetine before and after LPS injection reduces the increased microglial expression of iNOS, NADPH oxidase and its product ROS, and prevents degeneration of dopaminergic neurons in the rat substantia nigra [38]. In contrast, the atypical TCA tianeptine, which selectively enhances serotonin reuptake, does not change the elevated mRNA levels of TNF-α, IL-6 and IL-10 in the brain of LPS-injected rats [37].

Anti-inflammatory effects of antidepressants have been established in the rodent brain inflammation induced by stimulants other than LPS. 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and kainetic acid (KA) are experimental reagents which elicit pathological characteristics similar to Parkinson disease and epilepsy, respectively. Injection of these reagents to mice results in enhanced glial production of ROS, NO and proinflammatory cytokines, and neuronal death in damaged areas. Jin's group showed that two SSRIs, paroxetine [40] and fluoxetine [41], reduced the MPTP-caused neuronal death, oxidative damage of DNA and iNOS expression in the murine substantia nigra. These remedies also decreased the microglial expression of NADPH oxidase, ROS, TNF-α and IL-1β, and microglial immunoreactivity for MAC-1 in the murine substantia nigra. In addition, paroxetine also suppressed up-regulated immunoreactivity for myeloperoxidase and glial fibrillary acidic protein (GFAP) of MPTP-activated astrocytes in the murine substantia nigra [41]. These antidepressants were administrated to mice after MPTP injections, suggesting that the drugs are effective on existing glial activation. Both paroxetine and fluoxetine ameliorated the MPTP-elicited motor dysfunctions [40, 41]. Preemptive administration of fluoxetine has been demonstrated to inhibit the increase in mRNAs for IL-1β, TNF-α and COX-2, and both microgliosis and astrogliosis in the hippocampus of KA-injected mice [42]. Moreover, fluoxetine prevents the KA-caused neuronal death in the hippocampus and remarkably improves the KA-induced memory impairment [42].

In animal models of other neurological diseases associated with neuroinflammation, antidepressants have also been shown to attenuate gliosis and expression of inflammatory mediators and to ameliorate neurological symptoms. Even after occlusion of the middle cerebral artery, fluoxetine treatment inhibits the rise in mRNA levels of COX-2, IL-1β and TNF-α in the rat brain of an ischemia model [43]. Fluoxetine also reduces the microgliosis with increased immunoreactivity for IBA-1 and Mac2, and the neutrophil infiltration shown by enhanced immunoreactivity for myeloperoxidase [43]. Moreover, fluoxetine decreases the NF-κB activity and infarct volumes in the post ischemic brain. The effectiveness of fluoxetine is accompanied by improvement of motor impairment and neurological deficits [43]. Preemptive and postonset administration of the serotonin-noradrenaline reuptake inhibitor (SNRI), venlafaxine, suppresses the elevated mRNA expression of GFAP, the proinflammatory cytokines, interferon (IFN)-γ and TNF-α, and the inflammatory chemokine, monocyte chemotactic protein-1 (MCP-1, also known as CCL2), in the spinal cord of mice with experimental autoimmune encephalomyelitis (EAE) [44]. On the other hand, venlafaxine increases the mRNA expression of brain-derived neurotrophic factor (BDNF) and improves multiple sclerosis-like EAE symptoms [44]. Postsurgery administration of mirtazapine, a tetracyclic antidepressant, after L5 spinal nerve transection decreases the surgery-caused rise in protein levels of IL-1β and TNF-α, and in GFAP immunoreactivity in the hippocampus of rats with neuropathic pain [45]. Furthermore, mirtazapine shows significant antinociceptive effects in the operated rats [45].

The studies mentioned above show that antidepressant treatment reduces the increased levels of inflammatory molecules and gliosis in lesions. In order 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 glial activation, in spite of the fact that glial cells are main source of inflammatory mediators in the brain. Under pathological conditions peripheral immune cells, which could produce various inflammatory substances, infiltrate the brain [22]. Antidepressants have been demonstrated to suppress the production of proinflammatory cytokines in peripheral immune cells [46, 47].

In contrast to their inhibitory effects on astrogliosis in the inflamed brain, antidepressants may activate astrocytes in the normal brain [48]. *In vivo* studies using rodents without chemical stimulation have reported that fluoxetine increases protein levels of S100B, an astrocyte-derived neurotrophic factor, in the rat hippocampus [49] and that paroxetine raises mRNA expression of GFAP in the murine hippocampus [50].

## EFFECTS OF ANTIDEPRESSANTS ON INFLAMMATORY ACTIVATION OF MICROGLIA *IN VITRO*

It is evident that antidepressants have the potency to inhibit microglial activation with respect to the expression of various types of inflammatory molecules and exertion of neurotoxicity *in vitro*. A few studies imply that antidepressants do not affect or even increase microglial expression of inflammatory mediators [44, 51]. However, most studies on this subject have demonstrated that treatment of cultured microglia with a variety of antidepressants before stimulation with LPS or IFN-γ results in reduced microglial expression of IL-1β, IL-6 and TNF-α, at both mRNA and protein levels, indicating that antidepressants are able to prevent microglia from getting activated [20, 52-55]. Such drug efficacy is also observed when antidepressants and stimuli are simultaneously added to microglial cultures [43, 56, 57]. In addition to proinflammatory cytokines, antidepressants diminish LPS-induced microglial generation of ROS [55].

Similar to the aforementioned *in vivo* studies, *in vitro* studies in microglia-neuron co-cultures have clarified that antidepressants confer neuroprotection against LPS- or 1-methyl-4-phenyl-pyridinium-caused microglial neurotoxicity [41, 53, 55]. Interestingly, the antidepressants-induced neuroprotection is not observed in astrocyte-neuron co-cultures or neuron-enriched cultures [41, 55].

Molecular targets in microglia for anti-inflammatory actions of antidepressants are yet to be verified. However, the cAMP-dependent PKA pathway is suggested as mediating the anti-inflammatory events [20, 57] and seems to be one of the most plausible for the following reasons:

1) Antidepressants have been considered to exert their therapeutic effects *via* activation of the cAMP-PKA cascade [58].
2) Various antidepressants have been shown to up-regulate adenylate cyclase activity through enhancing coupling between the stimulatory α-subunit of the G protein Gs and adenylate cyclase, resulting in elevated levels of cellular cAMP in C6 glioma cells [59, 60].
3) In a number of cell types, the up-regulated cAMP/PKA pathway has been shown to inhibit the activity of NF-κB [61], whose up-regulation induces the gene expression of iNOS and a wide range of proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α [62]. In fact, fluoxetine [43, 55, 56] and the TCAs imipramine and clomiparmine [53] have been shown to attenuate the LPS-induced NF-κB activation in cultured rodent microglia. These drugs have also been demonstrated to inhibit LPS-evoked phosphorylation of p38, a key upstream regulator of NF-κB [53, 56].

The purinergic $P2X_7$ receptor is another potential target in microglia for antidepressants. Since $P2X_7$ receptor knockout mice exhibit anti-depressant-like profile in behavior tests and show high responsibility to a subefficacious dose of imipramine [63], the antagonism of $P2X_7$ receptor may be useful for treatment of depression.

## EFFECTS OF ANTIDEPRESSANTS ON INFLAMMATORY ACTIVATION OF ASTROCYTES *IN VITRO*

To date, few studies have been made on the influences of antidepressants on the inflammatory activation of purified astrocytes *in vitro*. Tianeptine, an atypical TCA and a selective serotonin reuptake enhancer, suppresses the increased expression of iNOS and NO in human astroglioma cells activated by glycoprotein 120 of human immunodeficiency virus [64]. Additionally, tianeptine enhances the astrocytic activity of glutamine synthase, which converts neurotoxic glutamate into non-toxic glutamine, and interferes with the glycoprotein 120-activated NF-κB signaling [64]. Imipramine and clomipramine decrease LPS- or LPS plus IFN-γ-induced NO production in primary murine astrocytes [53]. Imipramine also diminishes the release of CXC chemokine ligand 1 (CXCL1) from primary rat astrocytes exposed to TNF-α by suppression of the NF-κB-mediated CXCL1 promoter [65]. Thus, imipramine blocks CXCL1-caused migration of murine microglial cells, which highly express CXCL1 receptor, to the astrocytes [65].

In contrast to a relative paucity of information with regard to the relationship between antidepressants and astrocytic production of inflammatory molecules, antidepressants-elicited astrocytic expression of neurotrophins has been well documented. Different classes of antidepressants, not antipsychotics, increase the production of glial cell line-derived neurotrophic factor (GDNF) in human astrocytes and in rat astrocytes at both the mRNA and protein levels [66, 67]. Expression of another neurotrophin, BDNF, is also up-regulated in rodent astrocytes treated with antidepressants, including fluoxetine [68] and imipramine [69, 70]. The imipramine-induced expression of BDNF is blocked by the PKA inhibitor 14-22 amide [70]. Intriguingly, astrocyte-derived GDNF has recently been established as a potent inhibitor of microglial activation [71]. In addition, BDNF itself has been indicated to possess anti-inflammatory properties [11]. For instance, BDNF reduces the mRNA expression of TNF-α and IFN-γ, as well as the inflammatory adhesion molecules, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, in the brain of EAE mice [72]. Antidepressants therefore appear to exert anti-inflammatory actions on astrocytes in relatively indirect fashions, unlike their anti-inflammatory impacts on microglia.

## ANTIDEPRESSANTS AND MICROGLIA-ASTROCYTE INTERACTION

Microglia-astrocyte interaction plays a crucial role in neuroinflammatory responses [73]. It is becoming widely accepted that activated microglia act as immunoregulators of astrocytic activation, and *vice versa* [73, 74]. The significant influence of microglia on astrogliosis has been validated in animal studies showing that suppression of astrogliosis can be achieved by minocycline-induced inhibition of microglial

activation [75, 76]. In the pathological brain, microglial activation tends to precede astrocytic activation [73, 74, 77]. Activated microglia secret IL-1β, IL-6 and TNF-α, which could induce or promote astrocytic activation in a paracrine manner [73, 74]. In fact, the receptors for these cytokines have been identified on astrocytes [74]. Also, such microglia-derived proinflammatory cytokines could further microgliosis in an autocrine manner. Microglia-generated ROS is critical for regulation of microglial activation [78] and is implicated in triggering the activation of neighboring astrocytes [77]. Activated astrocytes are likely to maintain neuroinflammation and to regulate distant microglial activities by secreting chemokines, including CXCL1 and CX3CL1 (also known as fractalkine) [65, 77]. Astrocyte-derived chemokines may induce microglial chemotaxis in inflamed regions.

As described above, a variety of antidepressants have been shown to modulate both microgliosis and astrogliosis as well as glia interactions in the pathological brain. In addition to the attenuation of microglial production of inflammatory substances, antidepressants induce astrocytic expression of potentially anti-inflammatory factors, such as the neurotrophins BDNF and GDNF. Therefore, antidepressants appear to be immunosuppressive and anti-inflammatory by inhibiting gliosis existing in lesions or preventing a glial shift from the resting state to activated state. Furthermore, antidepressants are likely to exhibit antineurodegenerative effects by suppressing microglial production of inflammatory/potentially neurotoxic molecules and by up-regulating both astrocytic secretion of neurotrophins and astrocytic glutamine synthase, that metabolizes glutamate into non-toxic glutamine. Indeed, human neuroimaging studies have shown that depressed patients have decreased volumes of specific brain regions, such as prefrontal cortex, amygdala and hippocampus [79-81], suggesting that either progressive neurodegeneration or reduced neurogenesis are involved in the etiology of depression. The presumed molecular events elicited by antidepressants are shown in (Fig. **1**).

## INFLAMMATORY MOLECULES AND DEPRESSION: GLIAL CELLS ASSOCIATED WITH NEUROINFLAMMATION AS TARGET OF ANTIDEPRESSANT ACTION

Although increasing evidence indicates that inflammation associated with activation of innate immune cells, including microglia and astrocytes, plays a role in depression, it should be noted that depression is characterized by hyperactivity of hypothalamic-pituitary-adrenal axis and increased release of cortisol, one of the most potent anti-inflammatory hormone in the body [82]. This apparent contradiction is resolved by the finding that glucocorticoid signaling is disturbed in patients with depression [83].

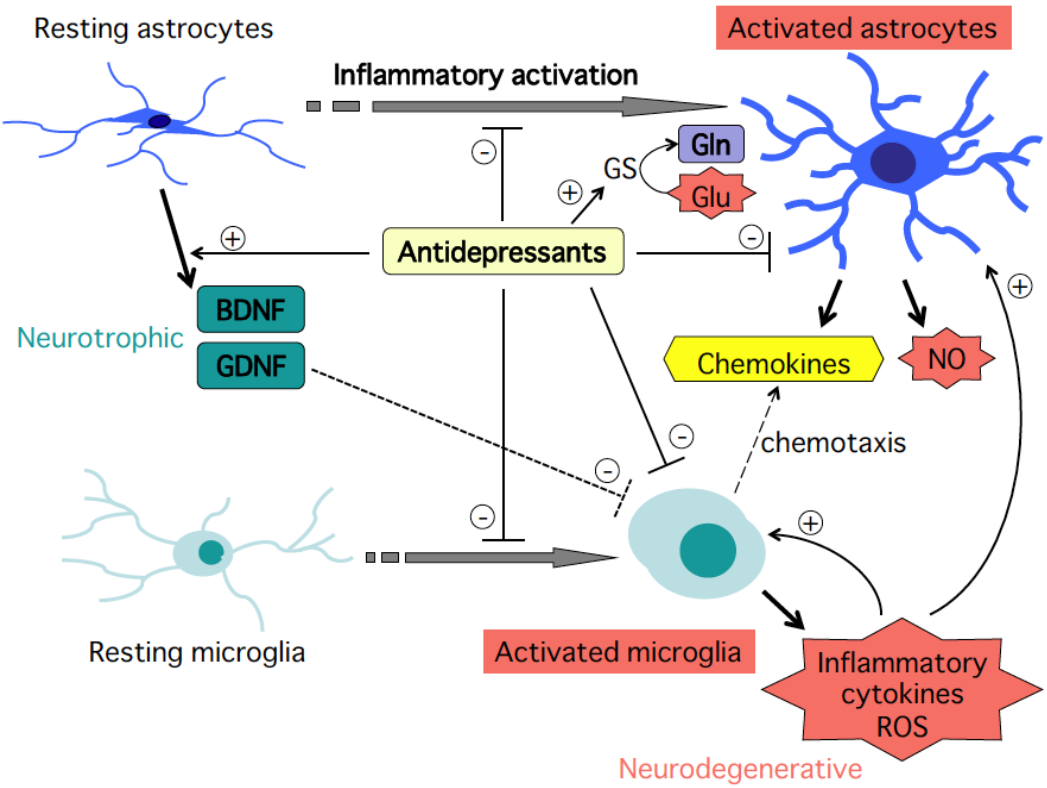


**Fig. (1). Scheme for presumed molecular events elicited by antidepressants.** Antidepressants may exert anti-inflammatory effects in the inflamed brain through inhibiting existing gliosis or preventing a glial shift from the resting state to activated state. Antidepressants may also exhibit antineurodegenerative effects by suppressing microglial production of inflammatory/neurotoxic molecules and by up-regulating both astrocytic secretion of neurotrophins and astrocytic GS metabolizing neurotoxic glutamate into non-toxic glutamine. GS, glutamine synthase; Gln, glutamine; Glu, glutamate; NO, nitric oxide; ROS, reactive oxygen species.

It has been shown that hippocampal volume is decreased in depression and that chronic treatment with various antidepressants enhances neurogenesis in adult hippocampus [84]. Anti-inflammatory properties of antidepressants may contribute to the development of neurogenesis since the inflammation associated with LPS-activated microglia has been demonstrated to suppress hippocampal neurogenesis in adult rats [85].

In addition to through direct influences on glial cells, antidepressants may control brain inflammation *via* neuronal regulation of inflammatory activities of glial cells. The neurotransmitters acetylcholine and noradrenaline have been shown to inhibit the expression of proinflammatory genes in microglia and astrocytes [86]. Furthermore, both microglia and astrocytes express acetylcholine receptors and noradrenaline receptors [86]. Accordingly, antidepressants-induced increase in such amine neurotransmitters released from neurons may be involved in the anti-inflammatory mechanism of the drugs.

Activated glial cells are capable of generating various inflammatory mediators such as proinflammatory cytokines, ROS and NO, all of which have been suggested to play a role in the pathophysiology and development of depression. Patients with depression have been found to show higher serum/plasma levels of IL-6, TNF-α [87] and the markers of oxidative damage to DNA (e.g., 8-hydroxy-2'-deoxyguanosine) and to lipid (e.g., malondialdehyde) [88-90] as compared to normal individuals. Proinflammatory cytokines are beleived to interact with many pathophysiological systems that characterize depression, namely metabolism of monoamine neurotransmitters and neuropeptides, neuroendocrine function and synaptic plasticity [30]. These interactions may be initiated or enhanced by psychological and physical stressors, including organic inflammatory diseases [30]. Extensive production of ROS causes lipid peroxidation and thus leads to neuronal damages with membrane destruction. This results in impaired functions of monoamine receptors on neuronal cell membrane and disturbed monoamine-receptor interactions [91]. Although NO has not been reported to increase in the plasma of depressed patients, NO could participate in the pathogenesis of depression by up-regulating guanylatecyclase. NO is known to activate soluble guanylatecyclase which converts GTP to cGMP. Excessive cGMP is suggested to cause depression-like state in the forced swimming test in rats [92].

Taken together, these findings support the view that glial cells, both as source and target of inflammatory products, may represent a potential promising target involved in the pathophysiology of depression. Antidepressant drugs were not originally developed to target glial cells. Nevertheless, their anti-inflammatory and antioxidant properties on glial cells could confer neuroprotection in the inflamed brain and open up new possibilities for them as a useful treatment, not only for depression, but for a broad spectrum of neuroinflammatory and neurodegenerative disorders associated with glial activation.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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