Antidepressants and Neuroinflammation: Can Antidepressants Calm Glial Rage Down?

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Abstract: Neuroinflammation is traditionally defined as the brain's innate immune response and is also considered to be a glial-cell propagated inflammation. Increasing evidence indicates that neuroinflammation plays an important role in some cases of major depression and also that antidepressants possess anti-neuroinflammatory properties. Inhibition of neuroinflammation may represent a novel mechanism of action of antidepressant treatment. *In vivo* studies with animal models of neurological conditions have shown that various types of antidepressants exert inhibitory effects on the expression of inflammatory mediators, including cytokines, as well as on both microgliosis and astrogliosis in the inflamed CNS. *In vitro* studies using pathologically activated rodent microglia or mixed glial cells have demonstrated that various types of antidepressants diminish glial generation of inflammatory molecules. One of the most plausible mechanisms of such anti-neuroinflammatory efficacy of the drugs, as well as their antidepressant actions, seems to involve elevated intracellular cAMP levels. But the exact mechanism has still to be elucidated.

Keywords: Anti-neuroinflammatory effect, astrocytes, cytokine, major depression, microglia.

INTRODUCTION

Inflammatory processes in the central nervous system (CNS), commonly referred to as neuroinflammation, have been implicated in the pathogenesis of a broad spectrum of neurodegenerative diseases [1, 2]. Increasing evidence indicates that neuroinflammation also plays an important role in some cases of major depression (MD) (reviewed in [3-5]. In fact, it has been revealed that concentrations of pro-inflammatory cytokines, such as interleukin (IL)-1β [6] and IL-6 [7], in the cerebrospinal fluid (CSF) of patients with MD are significantly higher than those in healthy control subjects. Furthermore, protein levels of trans-membrane form of tumor necrosis factor (TNF) are reported as increased in frontal cortex of postmortem MD brains [8]. On the other hand, the mRNA expression of the anti-inflammatory cytokine transforming growth factor (TGF)-β1 has been shown to be decreased in frontal cortex of postmortem brains of persons with bipolar disorder [9]. Intriguingly, IL-6 knockout mice show resistance to stress-induced depression-like behaviors while stress increases the hippocampal levels of IL-6 in wild-type mice [10]. If neuroinflammation plays a causative role in the pathophysiology of MD, antidepressants could partially act thorough suppressing such neuroinflammation.

It is not easy to define neuroinflammation exactly, even though it has been used as a "catch-all" term. Neuroinflammation is traditionally defined as the brain's innate immune response [11]. The classical definition of inflammation was based on four cardinal signs, namely heat, redness, swelling and pain. These criteria represent the consequences of a secondary physiological reaction in which inflammatory mediators expand circulation and cause vessels to leak serum into tissues. The brain is exempt from these classic criteria because such leakage is precluded by the blood/brain barrier. In addition, the brain lacks sensory fibers that can detect heat and pain. Accordingly, neuroinflammation is a silent process [12]. Outside the CNS, inflammation typically involves elaborated complement cascades and activated immune cells, including neutrophils, monocytes/macrophages and lymphocytes. Those cells release inflammatory mediators such as prostaglandins, cytokines, chemokines and reactive oxygen species at sites of infection or injury. Although the brain was earlier thought as "immunologically privileged", it is now clear that the brain has its own resident immune system, in which glial cells (microglia and astrocytes) serve as both source and targets of inflammatory mediators, including cytokines responsible for causing glial activation (also referred to as gliosis). Neuroinflammation can therefore be considered as a "glial-cell propagated inflammation" [13]. In MD, the neuroinflammatory processes may be characterized by sustained activation of glial cells in response to external stress or abnormally increased levels of pro-inflammatory cytokines in the diseased brain.

There is accumulating evidence that antidepressants possess anti-inflammatory properties (reviewed in [14, 15]). And anti-inflammatory agents such as the cyclooxygenase (COX)-2 inhibitor celecoxib [16] and the TNF inhibitor etanercept [17] have been reported to have anti-depressant efficacy. These findings suggest that inhibition of neuroinflammation may represent a novel mechanism of action of antidepressant treatment. This mini-review focuses

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on the influence of antidepressants on neuroinflammation, in particular, on inflammatory marker expression in the CNS and on pathological activation of microglia and astrocytes. It also discusses the possible mechanisms by which antidepressants exert anti-inflammatory effects on glial cells.

EFFECTS OF ANTIDEPRESSANTS ON INFLAMMATORY MEDIATORS IN THE CNS

To date there have been a number of studies showing inhibitory effects of antidepressants on elevated levels of inflammatory mediators, especially cytokines, in human blood samples (reviewed in [14, 18]). However, there have been only a few reports which investigated the effect of antidepressants on inflammatory mediators in the human CNS samples, such as CSF or postmortem brain tissues. Pålhagen *et al*. (2010) showed that the selective serotonin reuptake inhibitor (SSRI) citalopram had no effect on increased levels of IL-6 in the CSF of MD patients [19]. Nevertheless, several animal studies have revealed that antidepressants diminish inflammatory mediator expression in inflamed CNS tissues (Table **1**).

Antidepressants have been shown to exert anti-neuroinflammatory actions in the brain of animal models of MD. Intraperitoneal injection of desipramine, a tricyclic antidepressant (TCA), reduced the increase in mRNA expression of TNF-α, IL-1β and inducible nitric oxide synthase (iNOS) in the cortex of rats injected intraperitoneally with lipopolysaccharide (LPS) [20]. Such rats showed depressive-like symptoms [21]. Desipramine administration also inhibited the cortical activity of the transcription factor nuclear factor-κB (NF-κB) [20], whose activation is known to induce gene expression of various pro-inflammatory cytokines and iNOS. Intraperitoneal pretreatment with tianeptine, an atypical TCA, prevented LPS-induced elevation of IL-1β mRNA in the hypothalamus [22]. However, tianeptine had no effect on the increased mRNA levels of TNF-α, IL-6 and IL-10 in the hypothalamus. Also, tianeptine did not inhibit LPS-induced increases in the hippocampal mRNAs of these cytokines.

It was demonstrated that peroral pretreatment with the SSRI paroxetine for 14 days blocked an elevation of IL-1β in the hypothalamus of rats injected subcutaneously with interferon (IFN)-α and showing anxiety behavior [23]. Paroxetine treatment even reduced hypothalamus levels of the anti-inflammatory cytokine IL-10.

Anti-neuroinflammatory efficacy of antidepressants has been also reported in the CNS of animal models of neurological diseases other than MD. Oral treatment with the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine suppressed the elevated mRNA expression of pro-inflammatory cytokines, including IL-12 p40, IFN-γ and TNF-α, and the inflammatory chemokine monocyte chemotactic protein-1 (MCP-1, also known as CCL2) in the spinal cord of experimental autoimmune encephalomyelitis (EAE) mice [24]. However, mRNA expression of brain-derived neurotrophic factor was increased in the EAE spinal cord on treatment with venlafaxine. Intriguingly, venlafaxine treatment ameliorated multiple sclerotic-like EAE symptoms.

Chronic intrathecal infusion of morphine into rats was shown to mimic morphine tolerance accompanied with neuroinflammation. Intrathecal infusion of the TCA amitriptyline reduced the morphine-upregulated protein levels of TNF-α, IL-1β and IL-6 in rat spinal cords [25]. Amitriptyline/morphine coinfusion induced expression of IL-10 that activated its downstream molecules p38 and heme oxygenase-1 (HO-1), a stress-elicited protein with potent anti-inflammatory effects.

Intraperitoneal injection of the SSRI fluoxetine attenuated the increase in hippocampal mRNA amount of TNF-α, IL-1β and COX-2 in a mouse model of epilepsy induced by intracerebroventricular injection of kainic acid (KA) [26]. In addition, fluoxetine administration inhibited NF-κB activity in KA-treated mouse brains. The fluoxetine treatment prevented KA-caused neuronal cell death in hippocampus and remarkably improved KA-induced memory impairment. Intravenous injection of fluoxetine suppressed the raise in mRNA levels of COX-2, IL-1β, and TNF-α in the rat brain of an ischemia model employing middle cerebral artery occlusion (MCAO) [27]. Moreover, these inhibitory effects were accompanied with reductions in NF-κB activity and in infarct volumes in the post ischemic brain.

Oral administration of mirtazapine, a tetracyclic antidepressant, for 14 days decreased the rise in protein levels of IL-1β and TNF-α in the hippocampus [28] and in the right hemisphere [29] of rats with neuropathic pain caused by L5 spinal nerve transection. The reductions were reversed by both an adrenergic antagonist and a serotonergic antagonist, suggesting that mirtazapine reduced the cytokine production through affecting adrenergic and serotonergic systems [28]. Mirtazapine administration decreased NF-κB activity while it increased IL-10 levels in the right hemisphere [29]. Furthermore, mirtazapine treatment showed significant anti-nociceptive effects in the operated rats [28, 29].

In contrast to these studies, TCAs have been shown to possess augmentative effects on the constitutive expression of inflammatory molecules in normal rat brains. Specifically, intraperitoneal injection of desipramine increased both TNF-α protein levels in the hippocampus [30, 31] and TNF-α mRNA expression in the locus coeruleus [30]. The desipramine-induced increase in TNF-α bioactivity might represent TNF-α production by non-neuronal cells, since desipramine treatment of normal rats specifically decreased the accumulation of TNF-α mRNA in neurons [32]. Desipramine administration also increased MCP-1 production in the frontal cortex of normal rats [33]. Intraperitoneal injection of amitriptyline, another TCA, enhanced both mRNA and protein expression of TNF-α in the hippocampus and in the locus coeruleus of normal rats [34].

Taken together, these studies suggest that antidepressants exert inhibitory effects on the generation of inflammatory molecules, including cytokines, in the inflamed CNS while having the potency to boost constitutive expression of some inflammatory molecules in the normal CNS.

Table 1. Summary of *In Vivo* Studies that Examined the Effect of Antidepressants on Inflammatory Mediator Expression or Glial Activation in the CNS

Study	Antidepressant	Animal model	Region studied	Target studied	Result
O'Sullivan *et al*. (2009) [20]	TCA (Desipramine) i.p.	LPS-injected (i.p.) rats	Cortex	TNF-α mRNA IL-1β mRNA iNOS mRNA NF-κB activity Microgliosis (CD40 mRNA, CD11b mRNA)	Decrease
Castanon *et al*. (2004) [22]	Atypical TCA (Tianeptine) i.p.	LPS-injected (i.p.) rats	Hypothalamus	IL-1β mRNA	Decrease
				TNF-α mRNA IL-6 mRNA IL-10 mRNA	No change
			Hippocampus	TNF-α mRNA IL-1β mRNA IL-6 mRNA IL-10 mRNA	
Myint *et al*. (2007) [23]	SSRI (Paroxetine) p.o., 14 days	IFN-α-injected (s.c.) rats	Hypothalamus	IL-1β IL-10	Decrease
Czeh *et al*. (2006) [44]	SSRI (Fluoxetine) p.o., 28 days	Stressed treeshrews	Hippocampus	Astrogliosis (GFAP i.r.)	Increase
Vollmar *et al*. (2009) [24]	SNRI (Venlafaxine) p.o.	EAE mice	Spinal cord	TNF-α mRNA IFN-γ mRNA IL-12 p40 mRNA MCP-1 mRNA Astrogliosis (GFAP mRNA)	Decrease
				BDNF mRNA	Increase
Tai *et al*. (2009) [25]	TCA (Amitriptyline) i.t.	Morphine-infused (i.t.) rats	Spinal cord	TNF-α IL-1β IL-6	Decrease
				IL-10 p38 phosphorylation, HO-1	Increase
Jin *et al*. (2009) [26]	SSRI (Fluoxetine) i.p.	KA-injected (i.c.v.) mice	Hippocampus	TNF-α mRNA IL-1β mRNA COX-2 mRNA Microgliosis (Iba-1 i.r.) Astrogliosis (GFAP i.r.) Neurotoxicity	Decrease

(Table 1). Contd…..

Study	Antidepressant	Animal model	Region studied	Target studied	Result
Lim *et al*. (2009) [27]	SSRI (Fluoxetine) i.v.	Rats with MCAO	Ischemic region	TNF-α mRNA IL-1β mRNA COX-2 mRNA NF-κB activity Microgliosis (Iba-1 i.r., Mac-2 i.r.) Neutrophil infiltration (MPO i.r.) Neurotoxicity	Decrease
Zhu *et al*. (2008) [29]	Tetracyclic antidepressant (Mirtazapine) p.o., 14 days	Rats with L5 transection	Right hemisphere	TNF-α IL-1β NF-κB activity	Decrease
				IL-10	Increase
Zhu *et al*. (2009) [28]	Tetracyclic antidepressant (Mirtazapine) p.o., 14 days	Rats with L5 transection	Hippocampus	TNF-α IL-1β Astrogliosis (GFAP i.r.)	Decrease
Ignatowski & Spengler (1994) [30]; Ignatowski *et al*. (1997) [31]	TCA (Desipramine) i.p.	Normal rats	Hippocampus	TNF-α	Increase
			Locus coeruleus	TNF-α mRNA	
Madrigal *et al*. (2010) [33]	TCA (Desipramine) i.p.	Normal rats	Frontal cortex	MCP-1	Increase
Reynolds *et al*. (2004) [34]	TCA (Amitriptyline) i.p.	Normal rats	Hippocampus	TNF-α mRNA, TNF-α	Increase
			Locus coeruleus	TNF-α mRNA, TNF-α	
Manev and Manev (2001) [45]	SSRI (Fluoxetine) i.p.	Normal rats	Hippocampus	S100B	Increase

i.p., intraperitoneal; p.o., peroral; i.t., intrathecal; i.c.v., intracerebroventricular; s.c., subcutaneous; i.v., intravenous; i.r., immunoreactivity.

EFFECTS OF ANTIDEPRESSANTS ON ACTIVATED MICROGLIA

So far there has been no direct evidence that shows the involvement of activated microglia in the pathogenesis of MD. However, there is some circumstantial evidence. Significant microgliosis was observed in patients with MD who committed suicide, even though such microgliosis was not found in non-suicidal MD patients [35]. In addition, psychological stress was shown to increase microglia proliferation in the murine brain *via* elevation of glucocorticoids [36]. In line with such a theory about MD etiology, several *in vivo* studies have verified the ability of antidepressant to suppress microgliosis (Table **1**). Fluoxetine has been shown to attenuate microgliosis by quantified immunoreactivity of microglial marker such as Iba-1 and Mac-2 in the hippocampus of KA-injected mouse [26] and in the ischemic region of rat brain after MCAO [27]. Desipramine has been reported to suppress mRNA expression of the microglial activation marker CD40 and CD11b in LPS-injected rat cortex, suggesting that LPS-induced microgliosis was attenuated. *In vitro* studies also indicated that various types of antidepressants inhibited microglial activity in terms of inflammatory molecule production following various stimuli (reviewed in [14]). Recent reports have further consolidated this evidence (Table **2**).

Hwang *et al*. (2008) demonstrated that the TCAs clomipramine and imipramine reduced the secretion of nitric oxide (NO) and TNF-α from the mouse microglial BV-2 cells activated by LPS [37]. The TCAs also altered expression of inflammatory molecule genes. Specifically, both clomipramine and imipramine suppressed LPS-induced increases in mRNA expression of iNOS, TNF-α and IL-1β. Furthermore, these drugs inhibited NF-κB activity and phosphorylation of p38, a key upstream regulator of NF-κB. Consequently, both drugs conferred neuroprotection against LPS-caused BV-2 cellular neurotoxicity. The inhibitory effect of the TCAs on NO production was also confirmed in rat microglial HAPI cells and primary murine microglia stimulated with LPS.

Table 2. Summary of *In Vitro* Studies that Examined the Effect of Antidepressants on Glial Expression of Inflammatory Mediators*

Study	Antidepressant	Cell used	Target studied	Result
Hwang *et al*. (2008) [37]	TCAs (Clomipramine, Imipramine)	LPS-stimulated mouse microglia (BV-2)	TNF-α mRNA, TNF-α IL-1β mRNA iNOS mRNA, NO p38 phosphorylation NF-κB activity Neurotoxicity	Decrease
		LPS-stimulated rat microglia (HAPI)	NO	
		LPS-stimulated mouse microglia (primary)		
		LPS or LPS/ IFN-γ-stimulated mouse astrocytes (primary)		
Lim *et al*. (2009) [27]	SSRI (Fluoxetine)	LPS-stimulated rat microglia (primary)	iNOS mRNA, NO TNF-α mRNA IL-1β mRNA COX-2 mRNA NF-κB activity	Decrease
Horikawa *et al*. (2010) [38]	SSRIs (Paroxetine, Sertraline)	IFN-γ-stimulated mouse microglia (6-3)	TNF-α NO [Ca++]i	Decrease
		LPS-stimulated rat microglia (primary)	NO	
			TNF-α	No change
	NDRI (Bupropion)	IFN-γ-stimulated mouse microglia (6-3)	NO [Ca++]i	
	NDDI (Agomelatine)			
Bielecka *et al*. (2010) [39]	MAO-A inhibitor (Moclobemide)	LPS-stimulated rat mixed glia (60-65% microglia, 30-35% astrocytes)	TNF-α mRNA, TNF-α IL-1β mRNA, IL-1β IL-10 NF-κB activity	Decrease
			IL-10 mRNA	No change
O'Sullivan *et al*. (2009) [20]	TCA (Desipramine)	LPS-stimulated rat mixed glia (composition not specified)	TNF-α mRNA, TNF-α IL-1β mRNA, IL-1β iNOS mRNA	No change

*Other studies before 2008 are summarized in [14].

Lim *et al*. (2009) determined the fluoxetine's effect on LPS-induced production of inflammatory molecules using rat primary microglia [27]. They demonstrated that fluoxetine treatment repressed both iNOS mRNA expression and NO production. Fluoxetine also blocked the increases of mRNAs for TNF-α, IL-1β and COX-2. Moreover, fluoxetine notably reduced the activity of NF-κB upregulated by LPS.

Horikawa *et al*. (2010) reported the anti-inflammatory effect of the SSRIs paroxetine and sertraline on activated rodent microglial cells [38]. Pretreatment with paroxetine or sertraline for 24 h significantly inhibited the IFN-γ-induced generation of TNF-α and NO by mouse microglial 6-3 cells. The SSRIs also attenuated the amplitude of the IFN-γ-induced increase in the intracellular calcium concentration ($[Ca^{2+}]_i$) in these cells. The inhibitory effect of the SSRIs on NO production was also verified in rat primary microglial cells stimulated with LPS, while these drugs did not inhibit TNF-α release from such cells. On the other hand, neither the noradrenaline-dopamine reuptake inhibitor (NDRI) bupropion nor the noradrenaline-dopamine disinhibitor (NDDI) agomelatine reduced the IFN-γ-induced secretion of NO or the $[Ca^{2+}]_i$ elevation in 6-3 cells.

Bielecka *et al*. (2010) tested moclobemide, the first reversible selective inhibitor of monoamine oxidase-A (MAO-A) [39]. They employed an LPS-stimulated rat mixed glial culture, which consisted of 60-65% microglia and 30-35% astrocytes. Moclobemide treatment led to a significant decrease in glial production of TNF-α and IL-1β at both mRNA and protein levels. The drug had no influence on IL-10 mRNA but slightly reduced IL-10 secretion. Consistent with studies mentioned above, moclobemide also inhibited LPS-increased NF-κB activation.

Although majority of studies showed that antidepressants of various classes diminished microglial expression of inflammatory mediators, O'Sullivan *et al*. (2009) found that desipramine treatment did not influence LPS-elicited release of TNF-α and IL-1β from rat mixed glial cells on either mRNA or protein levels [20]. Similarly, glial expression of iNOS mRNA was unaffected by desipramine after LPS stimulation.

EFFECTS OF ANTIDEPRESSANTS ON ACTIVATED ASTROCYTES

Histological analyses using Nissl staining revealed a decreased number of glial cells in the prefrontal cortex of postmortem brains from MD patients [40, 41], but it is uncertain whether such a glial reduction is a cause or a result of MD. Recent postmortem studies using immunohistochemistry and immunoblotting have shown that in young subjects the cell density of glial fibrillary acidic protein (GFAP)-immunoreactive astrocytes [42] and protein levels of GFAP [43] in the dorsolateral prefrontal cortex of MD are significantly decreased compared to those of normal controls. In accord with these findings in postmortem MD brains, in an animal model of MD using treeshrews long-term psychosocial stress reduced the cell number of GFAP-positive astrocytes in the hippocampus [44]. Interestingly, oral administration of fluoxetine for 28 days prevented the stress-induced numerical decrease of astrocytes [44]. In the rat hippocampus, fluoxetine is also reported to increase protein levels of S100B, an astrocyte-derived neurotrophic factor [45].

In the inflamed CNS there is evidence that antidepressants have the opposite effect on astrocytes, namely attenuating proliferation or activity of astrocytes (Table **1**). Venlafaxine administration suppressed GFAP mRNA expression, an indicator of reactive astrogliosis, in the spinal cord of EAE mice [24]. Fluoxetine treatment prevented KA-induced astrogliosis, as shown by GFAP immunoreactivity, in the mouse hippocampus [26]. Mirtazapine also reduced GFAP immunoreactivity in the hippocampus of rats with L5 spinal nerve transection [28].

To the best of the author's knowledge, there has been no *in vitro* study that examined the effects of antidepressants on inflammatory mediators produced by purified astrocytes. Nevertheless, amitriptyline has been shown to increase the mRNA expression of glial cell line-derived neurotrophic factor (GDNF) in human astrocytes and in rat astrocytoma C6 cells [46]. Since neither the antipsychotic haloperidol nor the benzodiazepine anxiolytic diazepam can elicit GDNF release from C6 cells [47], the GDNF production may be attributed to an antidepressant-specific action on astrocytic cells. Intriguingly, GDNF has been demonstrated to reduce the amount of TNF-α and IL-1β at both mRNA and protein levels and inhibit NF-κB activity in experimental colitis [48].

POSSIBLE MECHANISMS OF ANTI-INFLAMMATORY EFFECTS OF ANTIDEPRESSANTS ON GLIAL CELLS

There has thus far been no all-encompassing hypothesis concerning the mechanisms of antidepressant action. In fact, treatments for MD are still based on empirical data. In addition, it is uncertain whether or not the mechanism by which antidepressants exert anti-inflammatory properties on glial cells is relevant to the molecular basis of antidepressant action. Nevertheless, several mechanisms for their anti-neuroinflammatory properties are possible and schematized in Fig. (**1**).

Various mechanisms proposed for antidepressant action are consistent with an increase in cyclic adenosine monophosphate (cAMP) production. In fact, a number of *in vivo* studies (reviewed in [49, 50]) and *in vitro* studies [51, 52] have shown such upregulation by various antidepressants. Anti-neuroinflammatory actions may also be attributed to elevated levels of intracellular cAMP, since activation of cAMP-dependent protein kinase A (PKA) pathway has been shown to inhibit activity of the inflammatory transcription factor NF-κB [53]. In addition, an upregulated cAMP/PKA signaling pathway is documented to suppress IFN-γ-activated signal transducer and activator of transcription (STAT) 1 [54]. Activated STAT1 is reported to transactivate IFN-γ-responsive genes, including iNOS. A previous *in vitro* study with 6-3 mouse microglia cells demonstrated that different classes of antidepressants inhibited IFN-γ-induced microglial production of IL-6 and NO. These inhibitions were reversed by the cAMP inhibitor SQ 22536 and by the PKA inhibitor Rp-adenosine3', 5'-cyclic monophosphorothioate triethylammonium salt, indicating that the anti-inflammatory effects of antidepressants on microglial cells are at least partially mediated by the cAMP/PKA pathway [55]. Similar findings with fluoxetine were observed in a study using human whole blood stimulated with LPS and phytohemagglutinin [56]. Taken together, these data support the view that an antidepressant-induced upregulation of cAMP/PKA pathway mediates the inhibitory effects of antidepressants on LPS or IFN-γ-evoked inflammatory transactivations in glial cells.

It remains unclear as to how antidepressants increase intracellular cAMP levels, especially *in vitro* where extracellular monoamine levels do not change. One possibility is that antidepressants directly suppress cellular activity of phosphodiesterases (PDEs), which degrade cAMP, since PDE genes are reported to be associated with a susceptibility to MD and antidepressant treatment response [57]. Another possibility is that antidepressants facilitate G protein activation of adenylate cyclase (AC). Rasenick's group has published seminal studies along this line. *In vivo* studies using membrane of rat cerebral cortex [58] and *in vitro* studies with C6 glioma cells [59] have shown that chronic treatment of various antidepressants upregulates AC

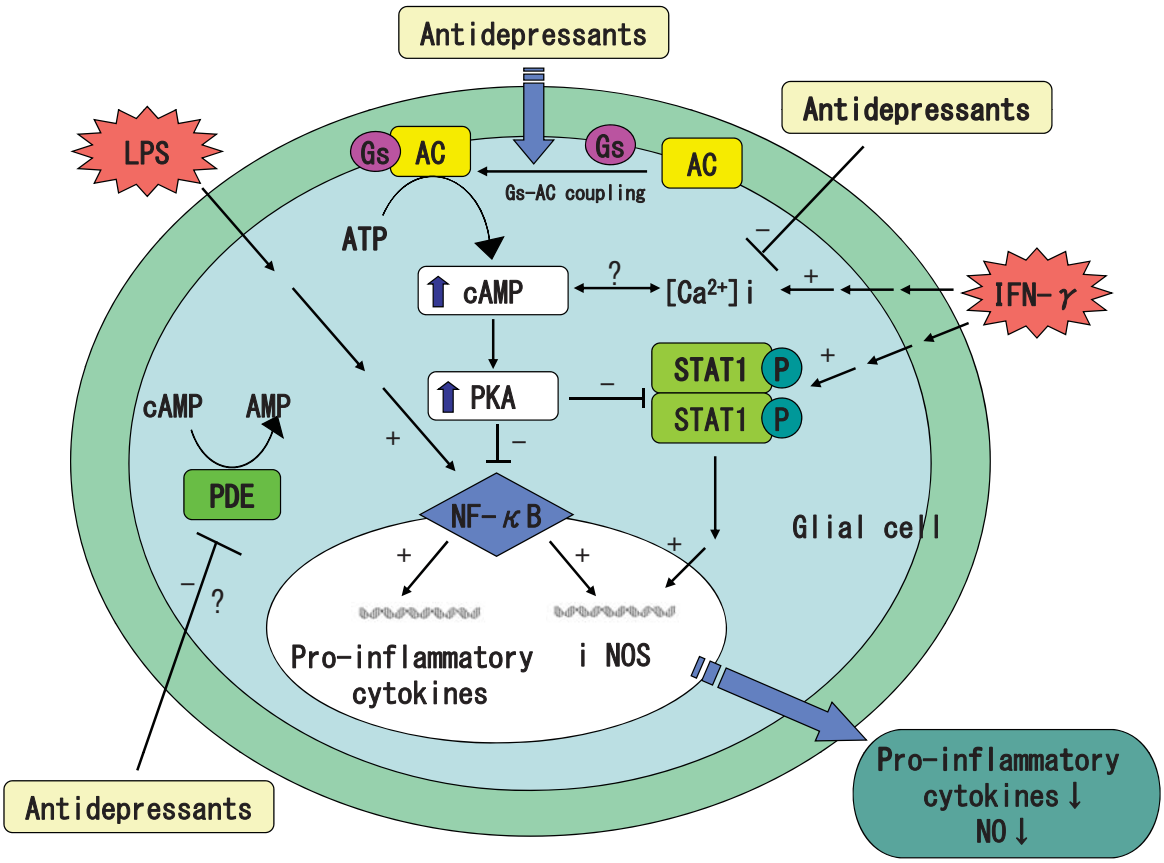

Fig. (1). Scheme for possible mechanisms by which antidepressants exert anti-inflammatory effects on glial cells. Antidepressants may inhibit LPS or IFN-γ-evoked inflammatory transactivations by upregulation of the cAMP/PKA pathway *via* facilitating coupling between the stimulatory α-subunit of the G protein Gs and AC in glial cells. Antidepressant modulation of $[Ca^{2+}]_i$ may also contribute to anti-neuroinflammatory efficacy. See text for details.

activity through facilitating coupling between the stimulatory α-subunit of the G protein Gs and AC, resulting in an increase in cellular cAMP. Since membranes prepared from liver and kidney of antidepressant-treated rats did not show enhanced Gs-stimulated AC activity, some property unique to neurons or glia may be involved in the antidepressant efficacy [58]. Furthermore, both *in vivo* [60] and *in vitro* [61] studies have shown that, in response to chronic antidepressant, Gs migrates from a lipid raft containing domain to a non-lipid raft membrane domain where it is more feasible for Gs to interact with AC. Intriguingly, in line with these findings, postmortem studies of brains from suicide victims with MD have shown a decreased activity of AC [62, 63] and an increased localization of Gs in lipid raft domains [64] compared to non-psychiatric control subjects.

SSRIs have been recently demonstrated to suppress IFN-γ-caused elevation of $[Ca^{2+}]_i$ accompanied with decreases in TNF-α and NO release from mouse microglial cells [38]. Such antidepressant inhibition of $[Ca^{2+}]_i$ may be attributed to antidepressant-induced activation of the cAMP/PKA pathway and *vice versa*, since calcium and cAMP pathways are known to be closely interrelated [65]. However, antidepressant inhibition of $[Ca^{2+}]_i$ may be sufficient to exert anti-neuroinflammatory effects, since chelating intracellular calcium has been demonstrated to reduce NF-κB activity and generation of IL-6 and MCP-1 in murine astrocytes exposed to the human immunodeficiency virus protein Tat [66]. Further studies on the correlation between antidepressant inhibition of $[Ca^{2+}]_i$ and the antidepressant-activated cAMP/PKA pathway are warranted.

CONCLUSION

Both *in vivo* and *in vitro* studies indicate that antidepressants possess anti-neuroinflammatory properties, inhibiting inflammatory mediator expression and pathological activation of glial cells. One of the most plausible mechanisms of the anti-neuroinflammatory efficacy of the drugs, as well as their antidepressant actions, seems to involve elevated intracellular cAMP levels. But the exact mechanism is still to be elucidated.

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ABBREVIATIONS

AC = adenylate cyclase

cAMP = cyclic adenosine monophosphate

CNS = central nervous system

COX = cyclooxygenase

CSF = cerebrospinal fluid

EAE = experimental autoimmune encephalomyelitis

GDNF = glial cell line-derived neurotrophic factor

GFAP = glial fibrillary acidic protein

Gs = stimulatory α-subunit of the G protein

HO-1 = heme oxygenase-1

IFN = interferon

IL = interleukin

iNOS = inducible nitric oxide synthase

KA = kainic acid

LPS = lipopolysaccharide

MAO-A = monoamine oxidase-A

MD = major depression

MCAO = middle cerebral artery occlusion

MCP-1 = monocyte chemotactic protein-1

NDDI = noradrenaline-dopamine disinhibitor

NDRI = noradrenaline-dopamine reuptake inhibitor

NF-κB = nuclear factor-κB

NO = nitric oxide

PDE = phosphodiesterase

PKA = protein kinase A

SNRI = serotonin-noradrenaline reuptake inhibitor

SSRI = selective serotonin reuptake inhibitor

STAT = signal transducer and activator of transcription

TCA = tricyclic antidepressant

TGF-β1 = transforming growth factor-β1

TNF = tumor necrosis factor

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