

Inflammation, Glutamate, and Glia in Depression: A Literature Review

By Leah McNally, BS, Zubin Bhagwagar, MD, PhD,
and Jonas Hannevad, MD, PhD

ABSTRACT

Multiple lines of evidence suggest that inflammation and glutamate dysfunction contribute to the pathophysiology of depression. In this review we provide an overview of how these two systems may interact. Excess levels of inflammatory mediators occur in a subgroup of depressed patients. Studies of acute experimental activation of the immune system with endotoxin and of chronic activation during interferon- α treatment show that inflammation can cause depression. Peripheral inflammation leads to microglial activation which could interfere with excitatory amino acid metabolism leading to inappropriate glutamate receptor activation. Loss of astroglia, a feature of depression, upsets the balance of anti- and pro-inflammatory mediators and further impairs the removal of excitatory amino acids. Microglia activated by excess inflammation, astroglial loss, and inappropriate glutamate receptor activation

Needs Assessment

Depression is a serious disorder for which available treatments are inadequate and the pathogenesis of which is poorly understood. Recent research has highlighted the potential role of excess inflammation and dysregulated glutamate neurotransmission in depression. The convergence of these two fields may reveal novel treatment targets.

Learning Objectives

At the end of this activity, the participant should be able to:

- List inflammatory mediators commonly elevated in plasma in depression.
- Understand the potential role of the kynurenine pathway in depression.
- Enumerate two ways in which inflammatory mediators and glutamate interact.
- Describe the specific role and interactions between microglia and astroglia and how this may contribute to depression.

Target Audience: Neurologists and psychiatrists

CME Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: April 28, 2008. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

To Receive Credit for This Activity

Read this article and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME posttest and evaluation found on page 528. To obtain credits, you should score 70% or better. Early submission of this posttest is encouraged; please submit this posttest by June 1, 2010, to be eligible for credit. Release date: June 1, 2008. Termination date: June 30, 2010. The estimated time to complete all three articles and the posttest is 3 hours.

Ms. McNally is a fourth-year medical student at Yale University School of Medicine in New Haven, Connecticut. Dr. Bhagwagar is assistant professor and Dr. Hannevad is clinical instructor, both in the Department of Psychiatry at Yale University School of Medicine.

Faculty Disclosures: Ms. McNally and Dr. Hannevad do not have an affiliation with or financial interest in an organization that might pose a conflict of interest. Dr. Bhagwagar receives research/grant support from Bristol-Myers Squibb, and is on the speaker's bureaus of AstraZeneca, Bristol-Myers Squibb, and Janssen.

Submitted for publication: January 17, 2008; Accepted for publication: April 17, 2008.

Please direct all correspondence to: Jonas Hannevad, MD, PhD, Yale University School of Medicine, Department of Psychiatry, Clinical Neuroscience Research Unit, 34 Park St., New Haven, CT 06519; Tel: 203-974-7536, Fax: 203-974-7662; E-mail: jonas.hannevad@yale.edu.

ultimately disrupt the delicate balance of neuroprotective versus neurotoxic effects in the brain, potentially leading to depression.

CNS Spectr. 2008;13(6):501-510

INTRODUCTION

Depression is a common and debilitating disorder for which current treatments are inadequate. The pathogenesis of depression is not well understood. The annual prevalence of depression is 7% and the lifetime prevalence is 16%.^{1,2} In addition to significant disability,³ depression is associated with excess mortality,^{4,5} particularly from cardiovascular disease.⁶ Current antidepressants, which target monoamines, only produce remission in 30% of patients. Part of the problem lies in the fact that the pathophysiology of depression has not been elucidated, and treatments are based on empirical data, not mechanisms of action. It remains unclear how these drugs actually work, since their ability to increase synaptic concentrations of monoamines is immediate, while their clinical effects take 2–4 weeks to become apparent.⁷ The aim of this article is to provide an overview of studies implicating inflammation in depression, and propose a model of how excess inflammation may interact with glutamate and glia to cause depression.

For this review, we searched PubMed with the following combinations of keywords: “depression AND inflammat*”; “depression AND cytokines”; “depression AND glutamate”; “depression AND glia”; “cytokines AND glutamate”; and “inflammat* AND glutamate.” Abstracts were read and articles chosen based on content. Articles addressing the role of inflammatory mediators in depression were selected. In addition, we included all articles addressing interactions between glutamate and inflammation, and between depression and glia.

INFLAMMATION IN DEPRESSION

Immunologic alterations in depression have been described for over 2 decades⁸ and the current hypothesis is that excess inflammation plays a role.^{9,10} The innate immune system can favor a T helper cell type 1 (Th1) or a Th2 response. During a Th1 response activated macrophages secrete so-called pro-inflammatory mediators,

such as interferon- γ (IFN- γ), tumor necrosis factor (TNF), and interleukin-1 (IL-1) and IL-2. A Th2 response is characterized by antibody production and anti-inflammatory mediators, IL-4, IL-5, and IL-10, which inhibit the Th1 response. This balance is essential to prevent excess inflammation which can have deleterious consequences. It has been repeatedly shown that a subgroup of patients with depression has elevated plasma levels of pro-inflammatory mediators, including IL-1, IL-2, IL-6, TNF, and C-reactive protein.^{8,11-14} In patients with depression the ratio of IFN- γ to IL-4 was elevated, and this ratio decreased with antidepressant treatment.¹⁵ Multiple studies^{14,16-18} have shown that there is a decrease in Th1 mediator levels with antidepressant treatment, indicating that one potential mechanism of action of antidepressant treatments is decreased inflammation. Researchers¹⁹ have found that higher levels of TNF at baseline may predict a poor response to escitalopram. In a rare prospective study,²⁰ an increased inflammatory state at baseline (elevated levels of C-reactive protein and increased capacity of leukocytes to produce IL-1) predicted later onset of depression in elderly individuals without a prior history of depression, suggesting that excess inflammation precedes depression. In summary, inflammatory mediator levels are elevated in depression, the Th1:Th2 balance is off, and such excess inflammation may play a role in the development of depression and contribute to poor response to antidepressants.

It is important to keep in mind that the peripheral and central inflammatory systems operate in parallel. In rodents, peripheral inflammatory stimuli induce expression of inflammatory mediators in the brain.⁹ Conversely, over-expression of IL-1 in the rodent brain led to increased peripheral production of inflammatory mediators,²¹ highlighting this bi-directional communication between central and peripheral inflammatory systems. In monkeys, intravenous administration of IL-1 led to increases in IL-6 in cerebrospinal fluid (CSF),²² and in hepatitis C patients receiving IFN- α treatment, CSF levels of IL-6 increased during treatment (A. Miller, MD, et al, written communication, 2007), demonstrating that, as seen in rodents, peripherally activating the immune system activates inflammatory pathways in the primate brain. Consistent with this, in patients with depression levels of IL-1 in CSF are also ele-

vated,²³ suggesting that, in depression, there is excess inflammation both centrally and peripherally. Because an appropriate Th1:Th2 balance is of crucial importance to avoid the deleterious effects of excess inflammation, several redundant mechanisms regulate this balance. For example, a recent study²⁴ demonstrated that repeated endotoxin stimulation of monocytes induced chromatin modifications which silenced the transcription of inflammatory genes, while priming the transcription of antimicrobial genes. It is possible this or other regulatory mechanisms are deficient in depression, leading to excessive inflammation.

In patients with hepatitis C treated with IFN- α up to 45% develop depression.²⁵ IFN- α -induced depression is associated with increases in plasma levels of IL-6 and TNF,²⁶ inflammatory mediators commonly elevated in depression. As previously described, IL-6 levels also increase in CSF. On functional magnetic resonance imaging, IFN- α treatment is associated with hypometabolism in prefrontal and temporal regions, findings similar to those in depression^{27,28} demonstrating that peripherally administered IFN- α affects brain regions implicated in depression. Endotoxin, a cell-wall component of gram-negative bacteria, is a potent stimulus of the innate immune system. In rodents, administration of endotoxin leads to a constellation of behaviors, including decreased sucrose preference (akin to human anhedonia, a core symptom of depression), reduced exploratory and social behaviors, reduced food intake, and increased sleep.⁹ In humans, endotoxin at doses from 2–4 ng/kg causes influenza-like symptoms, such as fever, chills, headache, and myalgias.^{29,30} Lower doses of endotoxin (0.8 ng/kg) are insufficient to cause sickness symptoms, but do cause depressive symptoms.³¹ Another non-sickness-inducing inflammatory stimulus, *Salmonella typhi* vaccine, also induces negative mood.³²

Inflammatory stimuli can induce psychiatric symptoms that are not dependent on the physical discomfort associated with inflammation and do not require a full-blown sickness syndrome.

ANTI-INFLAMMATORY AGENTS HAVE ANTIDEPRESSANT EFFECTS

If depression is associated with excess inflammation, one would expect that inhibiting inflammation would reduce depressive symp-

toms. Eicosanoids are inflammatory mediators that mediate fever, vascular permeability, and neutrophil chemotaxis. The enzyme that converts arachidonic acid to eicosanoids is called cyclooxygenase-2, and inhibition of this enzyme reduces inflammation. In a randomized, placebo-controlled trial of the cyclooxygenase-2 inhibitor celecoxib in depressed patients treated with reboxetine,³³ celecoxib augmentation was more efficacious than placebo. Another anti-inflammatory medication used in various forms of arthritis is etanercept, an antagonist of the inflammatory mediator TNF. In a trial in patients with psoriasis,³⁴ it was demonstrated that etanercept reduced depressive symptoms independent of improvement in psoriatic symptoms, such as skin involvement and joint pain. This study suggests that blocking TNF can treat depressive symptoms, which is consistent with elevations in TNF plasma levels seen in depression, the fact that such levels go down with treatment, and the fact that knocking-out TNF receptors in mice reduces depressive-like behaviors.³⁴

MEDICAL COMORBIDITIES

Disorders associated with excess inflammation or other immune abnormalities, including diabetes, coronary artery disease, Crohn's disease, rheumatoid arthritis, cancers, human immunodeficiency virus, and multiple sclerosis^{36,37} are associated with an increased prevalence of depression. For example, after myocardial infarction (MI), 20% to 30% of patients develop depressive symptoms.⁶ Interestingly, symptoms of post-MI depression differ from classic depression, as post-MI depression is characterized by prominent fatigue, and irritable rather than depressed mood.³⁸ Fatigue and irritability are also common symptoms in IFN- α -induced depression.^{25,39} In cancer survivors, fatigue is associated with inflammatory mediators.⁴⁰ Thus, it is possible that fatigue in post-MI depression and in other medical disorder, and during IFN- α treatment, is caused by excess inflammation. Consistent with this, neurovegetative symptoms of depression, including fatigue and disturbances of sleep and appetite, predict development of atherosclerosis.⁴¹ Because depression is a heterogeneous syndrome, it is necessary to study the associations between inflammation and

specific symptoms, such as fatigue, sleep, and appetite, rather than depression as a categorical construct. Whether fatigue or other neurovegetative symptoms occur more frequently in depressed patients with elevated inflammatory mediator levels is a question that has not been answered. Fatigue, and its neurobiological sibling anhedonia, often do not improve with current treatments, such as selective serotonin reuptake inhibitors,⁴² and this could be because inflammation-related depressive symptoms are more resistant to monoaminocentric treatments. Capuron and colleagues⁴³ showed that increased activity in basal ganglia, specifically the left nucleus accumbens and putamen, correlated with IFN- α -induced fatigue, pointing to a potential neuroanatomical substrate of inflammation-induced fatigue. In the future, such studies may identify brain regions that mediate each specific symptom of depression.

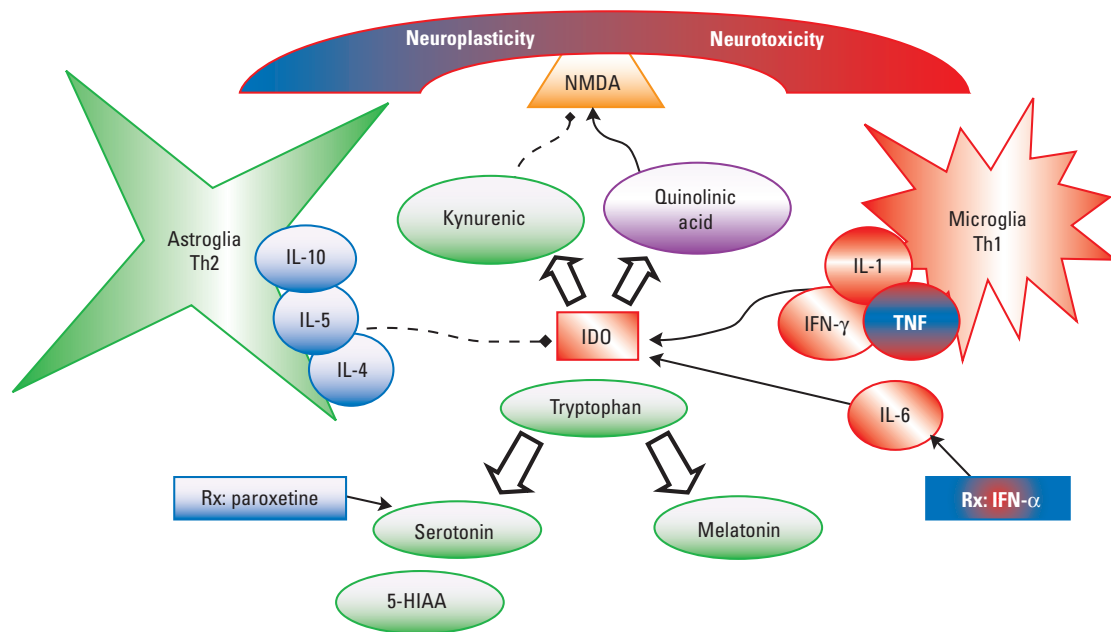
MECHANISMS THROUGH WHICH INFLAMMATION COULD CAUSE DEPRESSION

We have reviewed how depression is associated with increased peripheral inflammation, how inflammatory states can cause depressive symptoms, and how reducing inflammation can alleviate depressive symptoms. We will now review some mechanisms through which inflammation could produce depression, including interference with serotonin (5-HT) synthesis, glutamate metabolism, glial cell function, and neuroplasticity.

Inflammation, Serotonin, and Kynurenine

The amino acid tryptophan is the precursor of 5-HT and melatonin. The enzyme indoleamine 2,3-dioxygenase (IDO) converts tryptophan to kynurenine (Figure 1). When tryptophan is shuttled down the kynurenine pathway there is less tryptophan available to make 5-HT. This is akin to

FIGURE 1.
Tryptophan, kynurenine, and quinolinic acid*



* IDO converts tryptophan to kynurenine acid, an NMDA receptor antagonist. This reduces tryptophan availability for serotonin synthesis. Microglia activated by inflammatory mediators can convert tryptophan to quinolinic acid, an NMDA agonist. Therefore, pro-inflammatory mediators favor the production of quinolinic acid, while anti-inflammatory mediators inhibit synthesis of quinolinic acid. Decreased serotonin availability and excessive glutamate receptor agonism have been implicated in depression. Depression associated with IFN- α treatment may occur because of interference with this pathway, and selective serotonin reuptake inhibitors, such as paroxetine, are, therefore, efficacious in treating depression caused by IFN- α . The word neurotoxicity denote consequences of excess excitatory amino acid levels, however, neurotoxicity has not been unequivocally demonstrated in depression.

NMDA=*N*-methyl-D-aspartate; Th=T helper cell; IL=interleukin; IDO=indoleamine 2,3-dioxygenase; IFN=interferon; TNF=tumor necrosis factor; Rx=prescription; 5-HIAA=5-hydroxyindoleacetic acid.

McNally L, Bhagwagar Z, Hannestad J. *CNS Spectr*. Vol 13, No 6. 2008.

tryptophan depletion, an experimental paradigm used to induce depressive symptoms in susceptible individuals.⁴⁴ In microglia and macrophages, IDO expression is induced by Th1 cytokines, such as IFN- γ , IL-1, and TNF, and inhibited by Th2 cytokines, such as IL-4 and IL-10.⁴⁵ Thus, excess inflammation may reduce 5-HT levels through activation of this pathway in central and peripheral macrophages, contributing to depression.

In IFN- α -induced depression, plasma levels of kynurenine increase, however, paroxetine reduced depressive symptoms without decreasing kynurenine levels,⁴⁶ suggesting that increased synaptic 5-HT caused by paroxetine can compensate for the tryptophan siphoned off to the kynurenine pathway.

Recently, it was shown that IFN treatment in hepatitis patients increased CSF levels of IL-6 and decreased levels of 5-hydroxyindoleacetic acid, a 5-HT metabolite. Depressive symptoms correlated with decreases in 5-hydroxyindoleacetic acid, suggesting that the depressogenic effects of IFN- α may involve the kynurenine pathway (A. Miller, MD, et al, written communication, 2007).

Inflammation and Glutamate

Over the last few years, evidence suggests that glutamate plays a role in depression.^{47,48} Patients with depression, both during an acute episode and during remission, have elevated levels of glutamate in some brain regions.^{49,50} The *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine produces a profound antidepressant effect with almost immediate onset,^{51,52} and recent data^{53,54} on antidepressant properties of the glutamate modulator riluzole are promising. The current hypothesis⁴⁷ holds that excessive glutamate action, especially extrasynaptic glutamate, may be deleterious for neuronal function and contribute to depression.

Inflammatory mediators can, through activation of the kynurenine pathway (Figure 1), increase glutamate receptor agonism. The two main end-products of the kynurenine pathway bind to NMDA receptors: Kynurenic acid is an NMDA receptor antagonist, while quinolinic acid is an NMDA receptor agonist. Although IDO, the rate-limiting enzyme in the kynurenine pathway, is expressed in multiple cell types, microglia are the only cells in the central nervous system that express the complete enzymatic pathway

required for the synthesis of quinolinic acid.⁵⁵ Therefore, inflammatory mediators acting on microglia will increase the quinolinic acid to kynurenic acid ratio, leading to net NMDA agonism.^{15,56} In addition to NMDA agonist action, quinolinic acid directly causes release of glutamate.⁵⁷ Thus, inflammatory mediators can cause an environment of excess glutamate receptor agonism and resultant neurotoxicity. Although glutamate can cause neurotoxicity, it is important to point out that neurotoxicity in depression has not been unequivocally demonstrated.

Interactions between inflammatory mediators and glutamate are bi-directional. Glutamate causes TNF release from endotoxin-activated microglia.⁵⁸ The NMDA antagonist ketamine inhibits endotoxin-induced TNF production in glia,⁵⁹ and memantine, another NMDA receptor antagonist, decreased endotoxin-induced activation of microglia.⁶⁰ Thus, on one hand, inflammatory mediators can cause an environment of excess glutamate receptor agonism through increased quinolinic acid production and glutamate release. On the other hand, activation of NMDA receptors, by glutamate or quinolinic acid, may activate microglia and cause further release of inflammatory mediators, causing a vicious circle (Figure 2). Astrocytes are responsible for taking up excess glutamate to protect neurons from toxicity. This occurs through excitatory amino acid transporters (EAAT).^{61,62} Knockdown of glial transporters (EAAT1 or EAAT2) leads to glutamate excitotoxicity, while knockdown of the neuronal transporter does not.^{63,64} In cortical lesions in multiple sclerosis, the presence of activated microglia correlated with focal loss of EAAT1/2, while no loss was seen in the absence of activated microglia.⁶⁵ This indicates that inflammatory mediators released by microglia adversely affect astroglial expression of EAAT and, thus, could impair glutamate removal.

Inflammatory mediators can cause excess glutamate receptor agonism through three different mechanisms, including increased production of quinolinic acid, increased release of glutamate, and inhibition of excitatory amino acid removal by astroglia.

Inflammation, Microglia, and Neuroplasticity

Studies in animals and humans indicate that neurotoxicity and loss of neuroplasticity play a

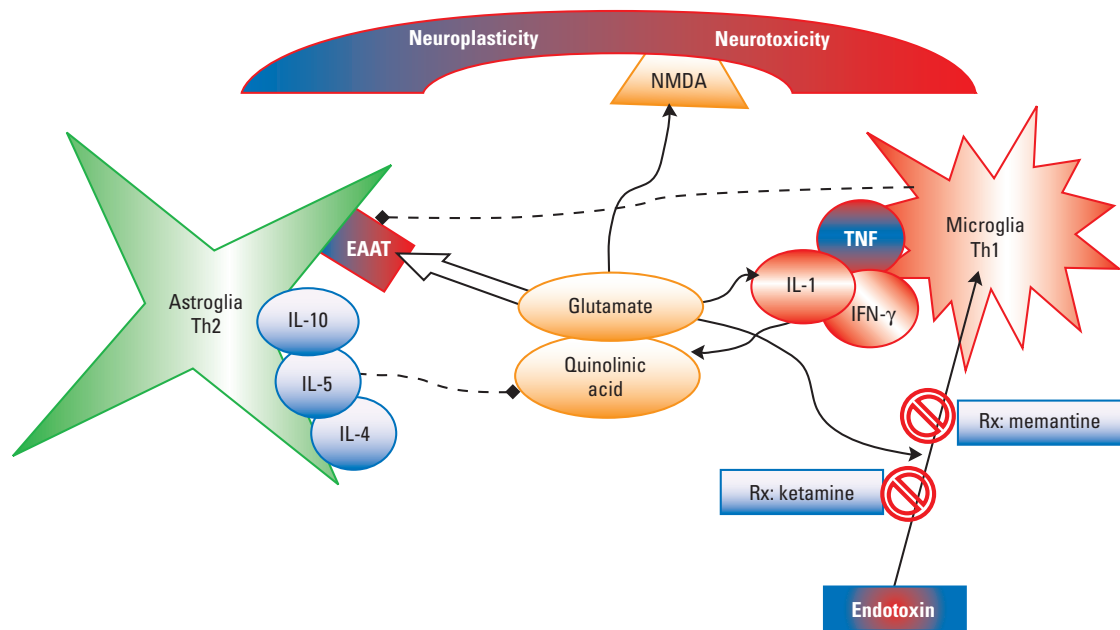
role in depression.⁶⁶⁻⁶⁸ Inflammatory mediators can activate microglia that release neurotoxic substances,⁶⁹ but microglia can also have neurotrophic effects.^{70,71} For example, microglia produce the IL-1 receptor antagonist (IL-1ra) which protects neurons from the harmful effects of IL-1.⁷² In patients who suffered traumatic brain injury, high IL-1ra levels and high IL-1ra:IL-1 ratios in brain microdialysates predicted better outcomes,⁷³ demonstrating the clinical importance of keeping inflammation under control. The Th2 mediator IL-4 induces a neuroprotective microglial phenotype, whereas activation with endotoxin or the Th1 mediator IFN- γ leads to neurotoxic microglia.⁷¹ Thus, an inappropriate Th1:Th2 balance, as found in some patients with depression, could impair neuroplasticity by shifting the microglial phenotype toward a neurotoxic one.

Once stimulated by inflammatory signals, microglia stay activated for several months and continue expressing inflammatory mediators,

including IL-1 and TNF.^{69,74,75} Mice lacking the enzyme required to synthesize IL-1 have reduced sickness behavior and lower expression of neurotoxic and inflammatory mediator genes in the brain after peripheral endotoxin injection.⁷⁶ On the other hand, genetic overexpression of IL-1 in the brain led to reduced spontaneous behavior, axonal injury, and increased peripheral expression of inflammatory mediators.²¹ Of note, blockade of the enzyme required for IL-1 synthesis inhibits glutamate neurotoxicity and activation of microglia,⁷⁷ suggesting that glutamate neurotoxicity requires IL-1 and illustrating the reciprocal and complex interactions among inflammatory mediators, glutamate, and microglia.

A recent study⁷⁸ found that when rats were given IFN- α for 9 weeks degeneration of 5-HT and noradrenergic axons occurred, indicating that neurotoxicity induced by inflammation can specifically target monoaminergic systems involved in depression. This is fascinating given

FIGURE 2.
Excitatory amino acid production and removal*



* Glutamate and quinolinic acid are excitatory amino acids that can have neurotoxic effects through NMDA receptor agonism. Excess glutamate is removed by astroglial EAAT. Microglia, activated by pro-inflammatory mediators, produce quinolinic acid and inhibit EAAT expression, potentially leading to excess NMDA agonism. NMDA antagonists such as ketamine and memantine can inhibit microglial release of pro-inflammatory mediators. How this occurs is not known.

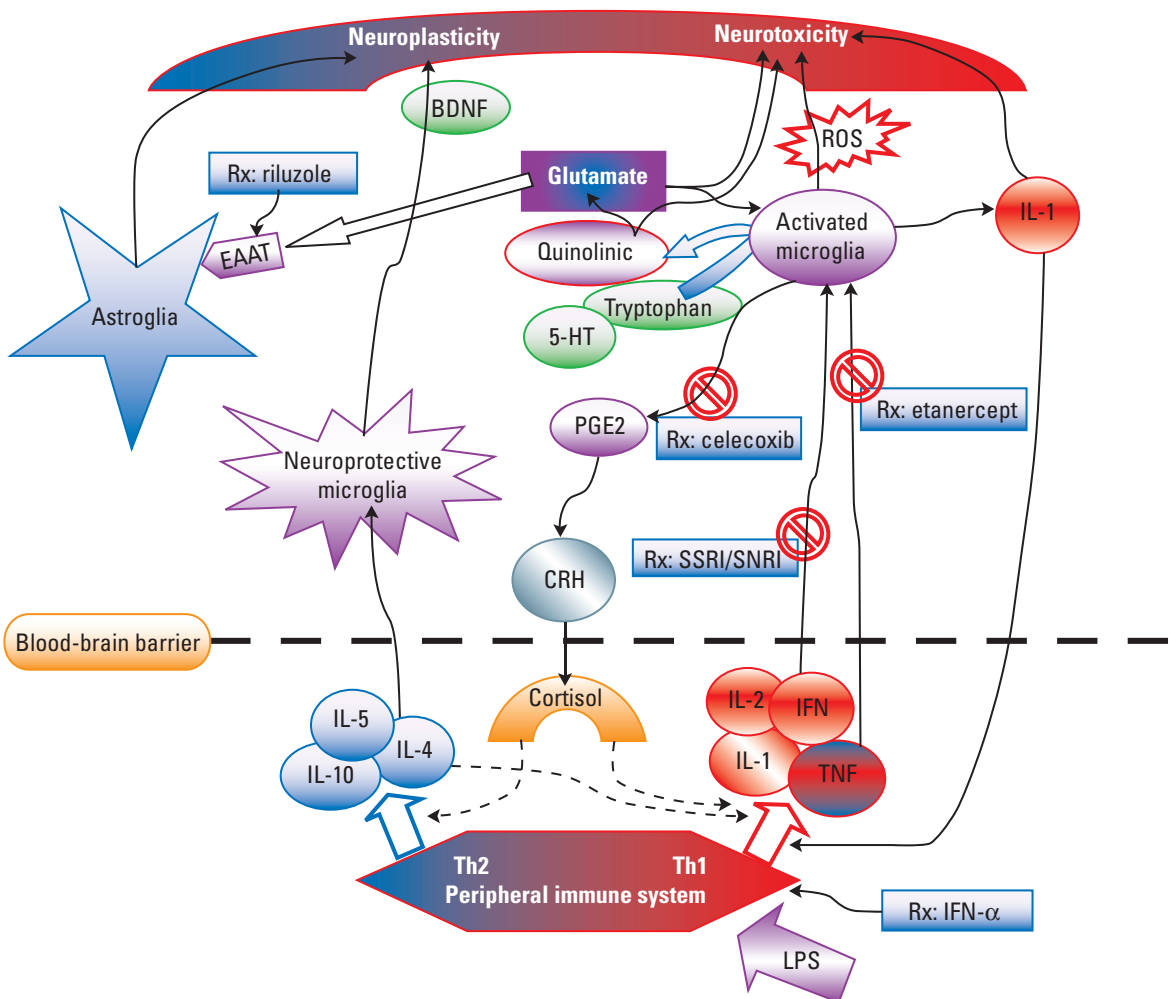
NMDA=*N*-methyl-D-aspartate; Th=T helper cell; IL=interleukin; EAAT=excitatory amino acid transporter; TNF=tumor necrosis factor; IFN=interferon; Rx=prescription.

McNally L, Bhagwagar Z, Hannestad J. *CNS Spectr*. Vol 13, No 6. 2008.

the prevalence of emergent depression during IFN- α treatment. Antidepressants have been shown to inhibit IFN- γ -induced microglial production of IL-6 and nitric oxide,⁷⁹ suggesting that inhibition of brain inflammation may be one mechanism of action of antidepressants. As occurs in peripheral macrophages,^{80,81} microglia express brain-derived neurotrophic factor and its receptor, tyrosine receptor kinase B.⁸²

Brain-derived neurotrophic factor is believed to play an important role in depression,⁸³ and any alteration of microglial production of this or similar growth factors could thus contribute to the occurrence of depression. Figure 3 illustrates the variety of mechanisms through which inappropriate microglial activity could cause depression through deleterious effects on neuroplasticity.

FIGURE 3.
Neurotoxic and neurotrophic actions of microglia and astrocytes*



* Peripheral inflammatory mediators induce microglial activation. This is one pathway through which peripheral immune system activation (eg, endotoxin administration or IFN- α treatment) could produce psychiatric symptoms. This may also explain the antidepressant effects of TNF antagonism. Activated microglia release neurotoxic substances, including ROS, pro-inflammatory cytokines, and eicosanoids, while resting microglia release neurotrophic factors, such as BDNF. An inappropriate Th1:Th2 balance may shift microglia towards a neurotoxic phenotype. Astrocytes release neurotrophic factors and recycle neurotoxic excitatory amino acids, such as glutamate. Pro-inflammatory mediators and activated microglia impair the ability of astrocytes to remove glutamate. The antidepressant properties of riluzole may reside in its ability to enhance astroglial uptake of glutamate, thus countering the deleterious effects of microglial activation and excess inflammation.

BDNF=brain-derived neurotrophic factor; ROS=reactive oxygen species; Rx=prescription; IL=interleukin; EAAT=excitatory amino acid transporters; 5-HT=serotonin; PGE2=prostaglandin E2; CRH=corticotropin-releasing hormone; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor; IFN=interferon; TNF=tumor necrosis factor; Th=T helper cell; LPS=lipopolysaccharide.

McNally L, Bhagwagar Z, Hannestad J. *CNS Spectr*. Vol 13, No 6. 2008.

Inflammation, Astroglia, and Neuroplasticity

Astroglia also play a role in neuroplasticity through secretion of neurotrophic factors, and the number of astroglia is reduced in depression.⁸⁴ When astroglia were added to neurons in culture, there was an increase in the number of mature synapses,⁸⁵ whereas removal of astroglia caused a decrease in the number of synapses.⁸⁶ As previously mentioned, inflammatory mediators induce microglial production of quinolinic acid, which, like glutamate, can be neurotoxic.⁸⁷⁻⁸⁹ Astrocytes are responsible for removing excess glutamate to protect neurons from toxicity. Down-regulation of astrocytic EAAT in amyotrophic lateral sclerosis may play a role in disease progression.⁹⁰ Interestingly, riluzole, a medication used in amyotrophic lateral sclerosis and that has shown preliminary efficacy in depression,^{53,54} enhances glutamate uptake by astroglia.⁹¹ This may occur through upregulation of astrocytic EAAT expression (G. Sanacora, MD, PhD, unpublished study, 2007). Thus, the antidepressant effects of riluzole may reside in its ability to enhance glutamate uptake in astroglia, possibly compensating for a loss of astroglia and counteracting inhibition of astroglial EAAT expression by activated microglia.

Studies have shown that in patients with depression there is a decrease in glial fibrillary acidic protein staining, indicating a loss of astrocytes.^{92,93} A reduction in the number of astroglia would impair the brain's capacity to recycle neurotoxic excitatory amino acids and decrease the availability of neurotrophic factors. As microglia preferentially synthesize Th1 mediators and astrocytes preferentially secrete Th2 mediators, the balance between microglial and astrocyte activity may be of pivotal importance for optimal brain function. Reduced numbers of astrocytes would impair the Th2 anti-inflammatory effects that inhibit microglial Th1 responses, facilitating a neurotoxic microglial phenotype. This, combined with reduced amounts of astroglia-derived neurotrophic factors and increased excitatory amino acid toxicity, would cause neuronal damage and impaired neuroplasticity (Figure 3). Treatments for depression, such as antidepressants and electroconvulsive therapy, has been shown to increase levels of glial markers and neurotrophic factors produced by glial cells.⁶⁷ Thus, astrocytes and microglia are promising targets in the development of new treatments for depression.

DISCUSSION

Although elevation in plasma levels of inflammatory cytokines in depression has been repeatedly shown, some studies have failed to replicate this finding. One reason is that depression is a heterogeneous disorder and excess inflammation only occurs in a subpopulation of depressed patients. Plasma levels of inflammatory mediators are influenced by genetic polymorphisms.⁹⁴ Although beyond the scope of this review, the genetic background will thus determine what level of inflammation will occur after a specific pathogen exposure and also to what extent this has detrimental effects, such as causing depression.⁹⁵ Although chronic inflammation may be associated with the development of depression and other disorders, chronic inflammation may have provided a survival benefit in terms of fighting off pathogens in an era before antibiotics.¹⁰ Genes that predispose one to chronic inflammation—and perhaps to depression—may thus have been conserved because of their survival benefit. We have seen how abundant evidence supports a link between inflammation and depression. The mechanisms whereby inflammation leads to depression proposed here incorporate current monoaminergic, glutamatergic, and neurotrophic hypotheses rather than demanding an entirely new framework. The interactions between inflammatory systems, on one hand, and 5-HT, glutamate, and neurotrophic systems on the other hand help explain the associations between depression and inflammation. The bidirectional interactions between peripheral and central inflammatory pathways raises the possibility that inflammatory dysfunction in the brain in depression contribute to the peripheral inflammation. This is important for diseases associated with depression, such as cardiovascular disease, in which inflammation may play a pivotal role. Thus, a re-examination of depression and its pathophysiology through the lens of inflammation may lead to a more complete understanding of the disorder and improved ways to treat it.

CONCLUSION

Immunologic abnormalities, especially indices of excess inflammation, are a common finding in patients with depression. Although the causal direction of these associations are unclear, there is increasing evidence suggesting that inflamma-

tion could, in a subgroup of patients and in some medical conditions, contribute to the pathogenesis of depression. This may occur through interference with monoaminergic, glutamatergic, and neurotrophic systems. **CNS**

REFERENCES

- Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:617-627.
- Kessler RC, Berglund P, Delmer O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:590-592.
- Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*. 1997;349:1436-1442.
- Zheng D, Macera CA, Croft JB, Giles WH, Davis D, Scott WK. Major depression and all-cause mortality among white adults in the United States. *Ann Epidemiol*. 1997;7:213-218.
- Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. *J Affect Disord*. 2002;72:227-236.
- Rivelli S, Jiang W. Depression and ischemic heart disease: what have we learned from clinical trials? *Curr Opin Cardiol*. 2007;22:286-291.
- Taylor MJ, Freemantle NJ, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry*. 2006;63:1217-1223.
- Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. *Brain Behav Immun*. 2007;21:374-383.
- Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9:45-46.
- Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006;27:24-31.
- Penninx BW, Kritchovsky SB, Yaffe K, et al. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition Study. *Biol Psychiatry*. 2003;54:566-572.
- Bremner MA, Beekman AT, Deeg DJ, et al. Inflammatory markers in late-life depression: results from a population-based study. *J Affect Disord*. 2008;106:249-255.
- Zorrilla EP, Luborsky L, McKay JR, et al. The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain Behav Immun*. 2001;15:199-226.
- Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl)*. 2003;170:429-433.
- Myint AM, Leonard BE, Steinbusch HW, Kim YK. Th1, Th2, and Th3 cytokine alterations in major depression. *J Affect Disord*. 2005;88:167-173.
- Leonard BE. The immune system, depression and the action of antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001;25:767-780.
- Kenis G, Maes M. Effects of antidepressants on the production of cytokines. *Int J Neuropsychopharmacol*. 2002;5:401-412.
- Hestad KA, Tønseth S, Støen CD, Ueland T, Aukrust P. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. *J Ect*. 2003;19:183-188.
- Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;15:32:445-450.
- van den Beggelaar AH, Gusselklo J, de Craen AJ. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. *Exp Gerontol*. 2007;42:693-701.
- Campbell SJ, Deacon RM, Jiang Y, Ferrari C, Pitossi FJ, Anthony DC. Overexpression of IL-1beta by adenoviral-mediated gene transfer in the rat brain causes a prolonged hepatic chemokine response, axonal injury and the suppression of spontaneous behaviour. *Neurobiol Dis*. 2007;27:151-63.
- Reyes TM, Coe CL. Interleukin-1 beta differentially affects interleukin-6 and soluble interleukin-6 receptor in the blood and central nervous system of the monkey. *J Neuroimmunol*. 1996;66:135-141.
- Levine J, Barak Y, Chengappa KN, Rapoport A, Rebej M, Barak V. Cerebrospinal cytokine levels in patients with acute depression. *Neuropsychobiology*. 1999;40:71-76.
- Foster SL, Hargreaves DC, Medzhitov R. Gene-specific control of inflammation by TLR-induced chromatin modifications. *Nature*. 2007;447:972-978.
- Asnis GM, De La Garza R 2nd. Interferon-induced depression in chronic hepatitis C: a review of its prevalence, risk factors, biology, and treatment approaches. *J Clin Gastroenterol*. 2006;40:322-335.
- Taylor JL, Grossberg SE. The effects of interferon-alpha on the production and action of other cytokines. *Semin Oncol*. 1998;25:23-29.
- Juengling FD, Ebert D, Gut O. Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology (Berl)*. 2000;152:383-389.
- Tanaka H, Maeshima S, Shigekawa Y, et al. Neuropsychological impairment and decreased regional cerebral blood flow by interferon treatment in patients with chronic hepatitis: a preliminary study. *Clin Exp Med*. 2006;6:124-128.
- Michie HR, Manogue KR, Spriggs DR, et al. Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med*. 1988;318:1481-1486.
- Suffredini AF, Hochstein HD, McMahon FG. Dose-related inflammatory effects of intravenous endotoxin in humans: evaluation of a new clinical lot of Escherichia coli O:113 endotoxin. *J Infect Dis*. 1999;179:1278-1282.
- Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001;58:445-452.
- Wright CE, Strike PC, Brydon L, Steptoe A. Acute inflammation and negative mood: mediation by cytokine activation. *Brain Behav Immun*. 2005;19:345-350.
- Müller N, Schwarz MJ, Dehning S, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry*. 2006;11:680-684.
- Tyring S, Gottlieb A, Papp K, et al. Etenarcept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet*. 2006;367:29-35.
- Simen BB, Duman CH, Simen AA, Duman RS. TNF alpha signaling in depression and anxiety: behavioral consequences of individual receptor targeting. *Biol Psychiatry*. 2006;59:775-785.
- Benton T, Staab J, Evans DL. Medical co-morbidity in depressive disorders. *Ann Clin Psychiatry*. 2007;19:289-303.
- Elenkov IJ. Neurohormonal-cytokine interactions: implications for inflammation, common human diseases and well-being. *Neurochem Int*. 2008;52:40-51.
- Huffman JC, Smith FA, Quinn DK, Fricchione GL. Post-MI psychiatric syndromes: six unanswered questions. *Harv Rev Psychiatry*. 2006;14:305-318.
- Constant A, Castera L, Dantzer R, et al. Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry*. 2005;66:1050-1057.
- Bower JE. Cancer-related fatigue: links with inflammation in cancer patients and survivors. *Brain Behav Immun*. 2007;21:863-871.
- Stewart JC, Janicki DL, Muldoon MF, Sutton-Tyrrell K, Kamarck TW. Negative emotions and 3-year progression of subclinical atherosclerosis. *Arch Gen Psychiatry*. 2007;64:225-233.
- Papakostas GI, Nutt DJ, Hallett LA, Tucker VL, Krishen A, Fava M. Resolution of sleepiness and fatigue in major depressive disorder: a comparison of bupropion and the selective serotonin reuptake inhibitors. *Biol Psychiatry*. 2006;60:1350-1355.
- Capuron L, Pagnoni G, Demetrashvili MF, et al. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. *Neuropsychopharmacology*. 2007;32:2384-2392.
- Neumeister A. Tryptophan depletion, serotonin, and depression: where do we stand? *Psychopharmacol Bull*. 2003;37:99-115.
- Müller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol Psychiatry*. 2007;12:988-1000.
- Capuron L, Neurauter G, Musselman DL, et al. Interferon-alpha-induced changes in tryptophan metabolism. Relationship to depression and paroxetine treatment. *Biol Psychiatry*. 2003;54:906-914.
- Pittenger C, Sanacora G, Krystal JH. The NMDA receptor as a therapeutic target in major depressive disorder. *CNS Neurol Disord Drug Targets*. 2007;6:101-115.
- Palucha A, Pilc A. Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. *Pharmacol Ther*. 2007;115:116-147.
- Sanacora G, Gueorguieva R, Epperson CN, et al. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry*. 2004;61:705-713.
- Bhagwagar Z, Wylezinska M, Jezzard P, et al. Reduction in occipital cortex gamma-aminobutyric acid concentrations in medication-free recovered unipolar depressed and bipolar subjects. *Biol Psychiatry*. 2007;61:806-812.
- Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47:351-354.
- Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63:856-864.
- Zarate CA Jr, Payne JL, Quiroz J, et al. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry*. 2004;161:171-174.
- Sanacora G, Kendall SF, Levin Y, et al. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry*. 2007;61:822-825.
- Saito K, Crowley JS, Markey SP, Heyes MP. A mechanism for increased quinolinic acid formation following acute systemic immune stimulation. *J Biol Chem*. 1993;268:15496-15503.
- Myint AM, Kim YK, Verkerk R, Scharpé S, Steinbusch H, Leonard B. Kynurenine pathway in major depression: evidence of impaired neuroprotection. *J Affect Disord*. 2007;98:143-151.
- Fedele E, Foster AC. An evaluation of the role of extracellular amino acids in the delayed neurodegeneration induced by quinolinic acid in the rat striatum. *Neuroscience*. 1993;52:911-917.

58. Pocock JM, Kettenmann H. Neurotransmitter receptors on microglia. *Trends Neurosci.* 2007;30:527-535.
59. Shibakawa YS, Sasaki Y, Goshima Y, et al. Effects of ketamine and propofol on inflammatory responses of primary glial cell cultures stimulated with lipopolysaccharide. *Br J Anaesth.* 2005;95:803-810.
60. Rosi S, Vazdarjanova A, Ramirez-Amaya V, Worley PF, Barnes CA, Wenk GL. Memantine protects against LPS-induced neuroinflammation, restores behaviorally-induced gene expression and spatial learning in the rat. *Neuroscience.* 2006;142:1303-1315.
61. Danbolt NC. Glutamate uptake. *Prog Neurobiol.* 2001;65:1-105.
62. Bergles DE, Jahr CE. Glial contribution to glutamate uptake at Schaffer collateral-commissural synapses in the hippocampus. *J Neurosci.* 1998;18:7709-7716.
63. Rothstein JD, Dykes-Hoberg M, Pardo CA, et al. Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. *Neuron.* 1996;16:675-686.
64. Tanaka K, Watase K, Manabe T, et al. Epilepsy and exacerbation of brain injury in mice lacking the glutamate transporter GLT-1. *Science.* 1997;276:1699-1702.
65. Vercellino M, Merola A, Piacentino C, et al. Altered glutamate reuptake in relapsing-remitting and secondary progressive multiple sclerosis cortex: correlation with microglia infiltration, demyelination, and neuronal and synaptic damage. *J Neuropathol Exp Neurol.* 2007;66:732-739.
66. McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism.* 2005;54(5 suppl 1):20-23.
67. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry.* 2006;59:1116-1127.
68. Fuchs E, Czéh B, Kole MH, Michaelis T, Lucassen PJ. Alterations of neuroplasticity in depression: the hippocampus and beyond. *Eur Neuropsychopharmacol.* 2004;14(suppl 5):S481-S490.
69. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci.* 2007;8:57-69.
70. Li L, Lu J, Tay SS, Moochhala SM, He BP. The function of microglia, either neuroprotection or neurotoxicity, is determined by the equilibrium among factors released from activated microglia in vitro. *Brain Res.* 2007;1159:8-17.
71. Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat Neurosci.* 2007;10:1387-1394.
72. Pinteaux E, Rothwell NJ, Boutin H. Neuroprotective actions of endogenous interleukin-1 receptor antagonist (IL-1ra) are mediated by glia. *Glia.* 2006;53:551-556.
73. Hutchinson PJ, O'Connell MT, Rothwell NJ, et al. Inflammation in human brain injury: intracerebral concentrations of IL-1alpha, IL-1beta, and their endogenous inhibitor IL-1ra. *J Neurotrauma.* 2007;24:1545-1557.
74. Qin L, Wu X, Block ML, et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia.* 2007;55:453-462.
75. Maeda J, Higuchi M, Inaji M, et al. Phase-dependent roles of reactive microglia and astrocytes in nervous system injury as delineated by imaging of peripheral benzodiazepine receptor. *Brain Res.* 2007;1157:100-111.
76. Mastronardi C, Whelan F, Yildiz OA, et al. Caspase 1 deficiency reduces inflammation-induced brain transcription. *Proc Natl Acad Sci U S A.* 2007;104:7205-7210.
77. Tikka TM, Koistinaho JE. Minocycline provides neuroprotection against N-methyl-D-aspartate neurotoxicity by inhibiting microglia. *J Immunol.* 2001;166:7527-7533.
78. Ishikawa J, Ishikawa A, Nakamura S. Interferon-alpha reduces the density of monoaminergic axons in the rat brain. *Neuroreport.* 2007;18:137-140.
79. Hashioka S, Klegeris A, Monji A, et al. Antidepressants inhibit interferon-gamma-induced microglial production of IL-6 and nitric oxide. *Exp Neurol.* 2007;206:33-42.
80. Hannestad J, Levanti MB, Vega JA. Distribution of neurotrophin receptors in human palatine tonsils: an immunohistochemical study. *J Neuroimmunol.* 1995;58:131-137.
81. García-Suárez O, Hannestad J, Esteban I, Sainz R, Naves FJ, Vega JA. Expression of the TrkB neurotrophin receptor by thymic macrophages. *Immunology.* 1998;94:235-241.
82. Asami T, Ito T, Fukumitsu H, Nomoto H, Furukawa Y, Furukawa S. Autocrine activation of cultured macrophages by brain-derived neurotrophic factor. *Biochem Biophys Res Commun.* 2006;344:941-947.
83. Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. *Nat Neurosci.* 2007;10:1089-1093.
84. Rajkowska G, Miguel-Hidalgo JJ. Gliogenesis and glial pathology in depression. *CNS Neurol Disord Drug Targets.* 2007;6:219-233.
85. Nägler K, Mauch DH, Pfrieger FW. Glia-derived signals induce synapse formation in neurones of the rat central nervous system. *J Physiol.* 2001;533(pt 3):665-679.
86. Ullian EM, Sapperstein SK, Christopherson KS, Barres BA. Control of synapse number by glia. *Science.* 2001;291:657-661.
87. Kim JP, Choi DW. Quinolinic acid neurotoxicity in cortical cell culture. *Neuroscience.* 1987;23:423-432.
88. Myint AM, Kim YK. Cytokine-serotonin interaction through IDO: a neurodegeneration hypothesis of depression. *Med Hypotheses.* 2003;61:519-525.
89. Tapia R. Release and uptake of glutamate as related to excitotoxicity. *Rev Bras Biol.* 1996;56(suppl 1, pt 1):165-174.
90. Lobsiger CS, Cleveland DW. Glial cells as intrinsic components of non-cell-autonomous neurodegenerative disease. *Nat Neurosci.* 2007;10:1355-1360.
91. Frizzo ME, Dall'Onder LP, Dalcin KB, Souza DO. Riluzole enhances glutamate uptake in rat astrocyte cultures. *Cell Mol Neurobiol.* 2004;24:123-128.
92. Fatemi SH, Laurence JA, Araghi-Niknam M, et al. Glial fibrillary acidic protein is reduced in cerebellum of subjects with major depression, but not schizophrenia. *Schizophr Res.* 2004;69:317-323.
93. Si X, Miguel-Hidalgo JJ, O'Dwyer G, Stockmeier CA, Rajkowska G. Age-dependent reductions in the level of glial fibrillary acidic protein in the prefrontal cortex in major depression. *Neuropsychopharmacology.* 2004;29:2088-2096.
94. Haddy N, Sass C, Maumus S, et al. Biological variations, genetic polymorphisms and familial resemblance of TNF-alpha and IL-6 concentrations: STANISLAS cohort. *Eur J Hum Genet.* 2005;13:109-117.
95. de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci.* 2005;6:463-475.