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A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder

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Abstract

A growing body of data suggests that hyperactivation of the immune system has been implicated in the pathophysiology of major depressive disorder (MDD). Several pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) have been found to be significantly increased in patients with MDD. This review focuses on these two cytokines based on multiple lines of evidence from genetic, animal behaviour, and clinical studies showing that altered levels of serum TNF-α and IL-1 are associated with increased risk of depression, cognitive impairments, and reduced responsiveness to treatment. In addition, recent findings have shown that centrally expressed TNF-α and IL-1 play a dual role in the regulation of synaptic plasticity. In this paper, we review and critically appraise the mechanisms by which cytokines regulate synaptic and neural plasticity, and their implications for the pathophysiology and treatment of MDD. Finally, we discuss the therapeutic potential of anti-inflammatory-based approaches for treating patients with severe mood disorders. This is a promising field for increasing our understanding of the mechanistic interaction between the immune system, synaptic plasticity, and antidepressants, and for the ultimate development of novel and improved therapeutics for severe mood disorders.

Keywords

Bipolar disorder; cytokines; depression; inflammation; synaptic plasticity; treatment

Introduction

Cytokines are small pleiotropic proteins previously discovered in the context of cellular activation and cell-to-cell communication in the immune system. Cytokines can be viewed as either ‘pro-inflammatory’ or ‘anti-inflammatory’, depending on the sum total of their effects on target cells. Although the presence and activity of cytokines in the brain was discovered more than a decade ago, their role in physiological and pathological brain functions remains to be fully elucidated. Early studies of the role of cytokines in the brain suggested that their expression and activity was induced in response to infection, head trauma, ischaemia, stroke, or various neurodegenerative diseases (Lacroix & Rivest, 1998; Licinio, 1997; Pitossi *et al.* 1997; Rivest *et al.* 2000). However, the notion that inflammatory cytokines are only expressed in the brain in response to pathological stimuli has recently been challenged by emerging data indicating that the proinflammatory cytokines interleukin-1 (IL-1), IL-18, and tumour necrosis

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Statement of Interest
None.

factor-alpha (TNF-α) are expressed in normal brain and also play an active role in cellular events that induce structural changes at the synaptic level (reviewed in Pickering *et al.* 2005; Tonelli & Postolache, 2005).

These recently discovered cytokine functions in the brain, and the novel molecular relationship between immunity and neural activity, are of particular relevance to patients suffering from psychiatric or neurological diseases. Notably, patients with depressive disorders have elevated levels of pro-inflammatory cytokines, suggesting a potential link between depressive illness and activation of the inflammatory response (Anisman *et al.* 1999; Kim *et al.* 2007; Maes *et al.* 1999; Muller & Ackenheil, 1998; Nassberger & Traskman-Bendz, 1993; Sluzewska, 1999; Tsao *et al.* 2006; Tuglu *et al.* 2003). In addition, depressive disorders have frequently been observed in association with peripheral inflammatory cytokine activation in several medical conditions, including viral infections, rheumatoid arthritis, cancer, and neurodegenerative diseases (Miller & Raison, 2006; Raison *et al.* 2006; Wichers & Maes, 2002).

Relatedly, increasing pre-clinical and clinical studies have shown that mood disorders such as major depressive disorder (MDD) and bipolar disorder (BPD), which have historically been viewed as neurochemical disorders, are associated with structural and functional impairments of synaptic plasticity in various regions of the central nervous system (CNS) (reviewed in Schloesser *et al.* 2008). Overlap between the molecular actions of synaptic plasticity and those targeted by antidepressants provides further evidence for a mechanistic convergence between the two phenomena. Here, synaptic plasticity refers to the cellular processes that result in lasting changes in the efficacy of neuro-transmission. More specifically, synaptic plasticity refers to both the changes in number of synapses and the variability of the strength of a signal transmitted through a synapse.

Given recent data showing elevated proinflammatory cytokine levels in MDD and animal models of stress, this review evaluates the potential role of cytokine-mediated impairments of synaptic plasticity in mood disorders, with a special emphasis on TNF-α and IL-1. Recent findings from a variety of genetic, animal behaviour, and clinical studies show that increased levels of serum TNF-α and IL-1 correlate with 'sickness behaviour', increased risk of MDD and/ or reduced responsiveness to standard antidepressant treatment. In addition, the finding that centrally expressed TNF-α and IL-1 play a 'double-edged sword' role in regulating synaptic plasticity raises the possibility that it is maintaining the intricate balance between physiological and pathological levels of these cytokines that is key to the pathogenesis of mood disorders. Finally, we discuss potential therapeutic strategies and targets for anti-cytokine therapy in MDD.

Pro-inflammatory cytokines in the normal brain

It has been well-established that peripherally produced cytokines can access the brain and thus affect brain function via several routes, including (1) entry through leaky regions in the blood–brain barrier, such as the circumventricular organs; (2) binding to cytokine-specific carrier molecules expressed on brain endothelium, and (3) activation of vagal afferent fibres that transmit cytokine signals to specific brain nuclei – such as the nucleus of the solitary tract – which then serves as a relay station to other brain nuclei, including the paraventricular nucleus in the hypothalamus (reviewed in Raison *et al.* 2006; Schiepers *et al.* 2005). Interestingly, accumulating evidence suggests that the pro-inflammatory cytokines TNF-α, IL-1, and IL-6, as well as interferons and their receptors, are constitutively expressed in various brain regions (Table 1). However, it is worth mentioning that not all studies have detected the expression or bioactivity of proinflammatory cytokines in the CNS (Cunningham *et al.* 1992; Fontana *et al.* 1984; Gabellec *et al.* 1996; Gayle *et al.* 1998; Holmin *et al.* 1997; Hunt *et al.* 1992; Medana

et al. 1997; Parnet *et al.* 1994; Tchelingerian *et al.* 1993; Turnbull *et al.* 1997; van Dam *et al.* 1998). In the context of this review, it is important to note that TNF-α and IL-1 share similar signal transduction pathways, leading to nuclear factor kappa B (NF-κB) activation. This, in turn, is believed to represent a point of convergence for signalling pathways involved in normal neuronal function and synaptic plasticity (Grilli & Memo, 1999), and may suggest a potential role for constitutive central cytokine production in neuronal development and neuroplasticity.

Regulation of synaptic plasticity by pro-inflammatory cytokines

The relative abundance of pro-inflammatory cytokines in the hippocampus suggests that they may play a role in hippocampal synaptic plasticity, which regulates learning and memory. Indeed, multiple studies have shown that cytokines, notably IL-1 and TNF-α, modulate long-term potentiation (LTP) and glutamatergic-dependent synaptic plasticity (Carlezon & Nestler, 2002; Du *et al.* 2004, 2007, 2008; Kendell *et al.* 2005; Malenka, 2003; Sun *et al.* 2005; Wolf *et al.* 2004).

Regulation of synaptic plasticity by TNF-α

Increased levels of TNF-α have been observed in several neuropathological states associated with learning and memory deficits, such as Alzheimer's disease, leading researchers to explore TNF-α's putative role in regulating neuroplasticity. Indeed, pathophysiological levels of TNF-α have been shown to inhibit LTP in the CA1 region, as well as the dentate gyrus of the rat hippocampus (Butler *et al.* 2004; Cunningham *et al.* 1996; Tancredi *et al.* 1992). LTP is a long-lasting increase in synaptic efficacy, and is thought to be an important underlying mechanism of learning and memory formation (Bliss & Collingridge, 1993). In addition, it has been shown that TNF receptor knockout mice demonstrate impaired long-term depression (LTD) in the CA1 region of the hippocampus (Albensi & Mattson, 2000). The findings relating to the effects of TNF-α on synaptic plasticity appear to have some behavioural correlates *in vivo*. TNF-α knockout mice showed improved performance on spatial memory and learning tasks and, conversely, TNF-α overexpressing mice were significantly impaired on spatial learning and memory tasks (Aloe *et al.* 1999; Golan *et al.* 2004).

Although most studies suggest that TNF-α has deleterious effects on synaptic plasticity, recent evidence shows that physiologically low levels of TNF-α may be important in brain development, as well as the regulation of homeostatic synaptic plasticity, namely 'synaptic scaling' (Golan *et al.* 2004; Stellwagen & Malenka, 2006). TNF-α released from glial cells in response to decreased neuronal activity increases the number of synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and thus synaptic strength, and is therefore critical for homeostatic adjustment of neuronal excitability. Interestingly, removal of TNF-α from brain slices results in weakening synapses (Beattie *et al.* 2002), suggesting that glially released TNF-α is important not only in increasing synaptic strength, but also in maintaining or preserving it. This TNF-α-induced AMPA receptor exocytosis has recently been shown to be mediated by activation of TNF-R1 receptors and is selective for Ca^{2+}-permeable AMPA receptor subunits. Independent of a critical role of TNF-α in homeostatic scaling, it is important to note that this effect of TNF-α on Ca^{2+} homeostasis might also have implications for neuronal toxicity, especially when extracellular levels of TNF-α are high, as seen in a number of neuropathological conditions.

Although recent findings with regard to the role of TNF-α in regulating synaptic plasticity appear initially to be conflicting, it is also possible that it is precisely the delicate balance between pathophysiological and physiological levels of TNF-α that is important. Thus it is conceivable that under pathophysiological conditions, when central levels of TNF-α become elevated, LTP is likely to be inhibited, while under physiological conditions, low levels of TNF-α serve as modulators of homeostatic synaptic plasticity (Table 2).

Regulation of synaptic plasticity by IL-1

In addition to its well-known role in immunoregulation of inflammatory processes, recent evidence suggests that IL-1 may modulate synaptic plasticity and behavioural systems. Indeed, it has been noted that pathophysiological levels of IL-1 can have detrimental effects on hippocampal-dependent memory and learning processes (Barrientos *et al.* 2002; Bellinger *et al.* 1993; Curran & O'Connor, 2001; Gibertini *et al.* 1995; Goshen *et al.* 2008; Oitzl *et al.* 1993; Pugh *et al.* 1999), while stress-induced inhibition of hippocampus-dependent conditioning can be reversed by IL-1ra, an IL-1 receptor antagonist (Maier & Watkins, 1995; Pugh *et al.* 1999, 2000). In accordance with these behavioural effects, IL-1 was found to impair LTP in the hippocampus (Cunningham *et al.* 1996; Murray & Lynch, 1998).

Although most findings to date indicate that IL-1 has deleterious effects on synaptic function and memory, recent evidence suggests that, like TNF-α, it may also be required for the physiological regulation of hippocampal plasticity. Early studies showed that LTP in the hippocampus was accompanied by a long-lasting increase in IL-1 gene expression, and that exposure to IL-1ra impairs the maintenance of LTP (Schneider *et al.* 1998). Furthermore, it has been shown that, in rats, administration of IL-1ra impairs memory in the water-maze and passive-avoidance paradigms, both of which are associated with hippocampal functioning. In contrast, relatively low doses of IL-1β improve avoidance memory (Brennan *et al.* 2003; Song *et al.* 2003; Yirmiya *et al.* 2002). Similarly, mice with a targeted deletion of IL-1R1 (IL-1rKO) display severely impaired hippocampal-dependent memory, diminished short-term plasticity, and exhibit no LTP, both *in vivo* and *in vitro* (Avital *et al.* 2003). Recently, an elegant series of studies by Goshen and colleagues found conclusive evidence that the involvement of IL-1 in hippocampal-dependent memory processes follows an inverted U-shaped pattern, which could explain the observed discrepancy of IL-1 effects on synaptic plasticity (Goshen *et al.* 2007, 2008). They demonstrated that physiological levels of IL-1 are needed for memory formation, and a slight increase in brain IL-1 levels can even improve memory; however, any deviation from the physiological range, either by excess elevation in IL-1 levels (induced by exogenously administered IL-1 or by enhanced endogenous release of IL-1) or by blockade of IL-1 signalling, results in impaired memory (Table 2).

Synaptic plasticity in the pathophysiology and treatment of MDD

Increasing pre-clinical and clinical evidence demonstrates that synaptic plasticity, a fundamental mechanism of neuronal adaptation, is altered in mood disorders, including depression, and in animal models of stress. The impairment of synaptic plasticity includes both structural and functional plasticity.

Neuronal loss and atrophy in mood disorders

Neuroimaging and post-mortem studies suggest that severe mood disorders such as MDD and BPD are associated with structural and functional impairments related to neuroplasticity in various regions of the CNS. Brain imaging and post-mortem studies show prominent neuronal and glial abnormalities in hippocampal and frontal cortex areas in patients with MDD or BPD, especially those who have experienced multiple episodes (Bielau *et al.* 2005; MacQueen *et al.* 2003; Ongur *et al.* 1998; Rajkowska, 2000, 2002; Rajkowska *et al.* 2001; Rajkowska & Miguel-Hidalgo, 2007; Sheline, 2000). In addition, decreased gene expression for astrocytic specific proteins, glutamate transporter, glutamine synthesis, and key oligodendrocyte- and myelin-related genes have also been observed in the frontal cortex tissue of patients with MDD or BPD (Choudary *et al.* 2005; Tkachev *et al.* 2003; Uranova *et al.* 2004). Similarly, multiple studies in rodents and non-human primates demonstrate that exposure to stress can alter processes or number of neurons (reviewed in Duman, 2004; Warner-Schmidt & Duman, 2006). Various behavioural stress paradigms or long-term exposure to high levels of

glucocorticoids induce neuronal atrophy in hippocampus, decrease glial proliferation and alter glial cell glutamate metabolism (Banasr & Duman, 2008; Cook & Wellman, 2004) (reviewed in Banasr & Duman, 2007; Manji & Duman, 2001). Stress can cause a decrease of up to 25% in the number of glial fibrillary acidic protein (GFAP)-positive cells in hippocampus and this number is highly correlated with reduced hippocampal volume (Czeh *et al.* 2006).

Impairments of functional synaptic plasticity in mood disorders

While the precise contribution of such perturbations to the network changes in brain function is difficult to infer, it is conceivable that morphological and/or changes in neuronal and glial function related to stress may contribute to the pathophysiology of mood disorders. Hippocampal synaptic plasticity, as modelled by LTP, is widely believed to represent an important component mechanism of hippocampus-dependent memory formation (Malenka, 2003). It is therefore striking that chronic or severe stress has been shown to disrupt hippocampus-dependent memory in experimental animals (reviewed in Sapolsky, 2003). Furthermore, specific impairments of hippocampus-dependent explicit memory are also seen after treating human subjects with glucocorticoids (de Quervain *et al.* 2000; Newcomer *et al.* 1999) and after stress (reviewed in Shors, 2006). Several independent studies have demonstrated that sufficiently severe stress can impair LTP and facilitate LTD in the rodent hippocampus (reviewed in Connor & Leonard, 1998; Kim & Diamond, 2002). Stress can affect synaptic plasticity via a variety of mechanisms, including glutamatergic and serotonergic-dependent mechanisms, and glucocorticoid receptor-dependent initiation of transcription and translation (Shakesby *et al.* 2002; Xu *et al.* 1998). Consistent with the involvement of these mechanisms in stress modification of plasticity, antagonists of *N*-methyl-D-aspartate (NMDA) receptors, glucocorticoid receptors, or serotonin uptake enhancers prevent LTP blocking by stress.

Interestingly, multiple clinical and experimental studies indicate that stress and depression are also associated with increased circulating concentrations of TNF-α and IL-1 (reviewed in Connor & Leonard, 1998), which can impair synaptic plasticity and cognitive processes and contribute to progression of depressive disorders. Indeed, patients with MDD exhibit prominent deficits in explicit memory (Zakzanis *et al.* 1998), a cognitive capacity that depends on the hippocampus and medial temporal lobe (Cavanagh *et al.* 2002; Clark *et al.* 2002; Eastwood & Harrison, 2001; Squire *et al.* 2004). Notably, several signalling pathways involved in neuronal plasticity have been demonstrated to be impaired in patients with mood disorders or in animal models of stress. Decreased expression of molecular markers of synaptic plasticity, including GAP-43, synapsins and synaptophysins have been demonstrated in the post-mortem brains of patients with BPD (Benowitz & Perrone-Bizzozero, 1991; Vawter *et al.* 2002). Pre-clinical studies have also indicated that the expression of critical molecules involved in the regulation of synaptic plasticity, such as adenosine monophosphate (cAMP) response element-binding protein (CREB), brain-derived neurotrophic factor (BDNF), and Bcl-2 is reduced in response to stress (reviewed in Schloesser *et al.* 2008; Zarate *et al.* 2006).

The effect of antidepressants on synaptic plasticity

If the effects of stress or mood disorders on the mechanisms of synaptic plasticity contribute to the pathophysiology of MDD, then antidepressant treatments might be expected to affect the same mechanisms. Indeed, several studies have demonstrated that antidepressants affect LTP in specific brain regions, such as the dentate gyrus and CA1 area of hippocampus. In the dentate gyrus, both chronic electroconvulsive therapy (ECT) and chemical antidepressant treatment increase LTP (Levkovitz *et al.* 2001; Stewart & Reid, 2000). Recent studies also suggest that chronic administration of a selective serotonin reuptake inhibitor (SSRI) or an atypical antidepressant (tianeptine) increases LTP and blocks the stress-induced impairment of LTP and enhancement of LTD in the CA1 region (Holderbach *et al.* 2007; Vouimba *et al.*

2006). Chronic SSRI administration similarly affects hippocampal–prefrontal cortex circuits, reversing stress-induced impairment of LTP and enhancement of LTD (Rocher *et al.* 2004).

In addition, several studies demonstrate that key signalling components, including glutamatergic receptors, BDNF, and Bcl-2, all of which are important regulators of synaptic plasticity, also serve as major targets for antidepressants and are required for the cellular and behavioural actions of antidepressant treatments. NMDA antagonists, such as MK-801 and AP-7, have antidepressant effects in animal models of depression and in animals exposed to stress (reviewed in Manji *et al.* 2003). There is also evidence that memantine, a high-affinity NMDA receptor antagonist, has a rapid antidepressant effect in patients with severe depression (Zarate *et al.* 2006). Pre-clinical studies have also shown that modulation of AMPA receptors by AMPA receptor potentiators (ampakines) enhances mitogen-activated protein kinase (MAPK) activation and BDNF expression, and exerts an antidepresant effect in animal models of depression and in animals exposed to chronic mild stress (reviewed in Manji *et al.* 2003). Finally, in very preliminary clinical studies, ampakines appear to have beneficial effects on learning and memory (Goff *et al.* 2001). Furthermore, riluzole and lamotrigine, both of which are glutamatergic modulators with anticonvulsant properties, increase the surface expression of the AMPA subunits GluR1 and GluR2 (Du *et al.* 2007). Recent studies have shown that riluzole stimulates the synthesis of growth factors including BDNF (Mizuta *et al.* 2001). Consistent with the evidence that modulating the glutamergic system may be key to the mechanism of antidepressants, one open-label study found that riluzole had significant antidepressant effects in patients with severe depression (Zarate *et al.* 2004a). In addition, several pre-clinical and clinical studies have implicated neurotrophic factors as targets of standard antidepressant treatment (reviewed in Tanis *et al.* 2007). Notably, pramipexole, which up-regulates Bcl-2 levels in several brain areas, had antidepressant effects in one double-blind, placebo-controlled trial of patients with bipolar II depression (Zarate *et al.* 2004b). Together, these studies indicate that chronic antidepressant treatments can regulate intracellular signalling pathways involved in regulating neuroplasticity and reverse impairments of synaptic plasticity and cellular resilience. These changes may be particularly important in understanding the therapeutic effectiveness of these drugs.

Involvement of cytokines in the pathogenesis of depressive disorders

In view of recent data supporting the role of proinflammatory cytokines in the regulation of synaptic plasticity, and emerging data suggesting that synaptic plasticity is impaired in mood disorders, it is conceivable that activation of the immune system network may be related to at least some aspects of the complex pathophysiology of depressive disorders. However, it is beyond the scope of this paper to review in detail the burgeoning literature demonstrating that depressive disorders are pro-inflammatory states. Here we briefly summarize some of the most salient findings; the interested reader is referred to several outstanding papers on the topic (Dantzer *et al.* 2008; Maes, 1994; McNally *et al.* 2008; Miller & Raison, 2006; Raison *et al.* 2006).

Cytokine-induced ‘sickness behaviour’ in animal models

Emerging evidence implicates hyperactivation of the immune system resulting in increased TH1 cytokines in the aetiology of depressive disorders (Maes *et al.* 1995a, b; Sedgwick & Czerkinsky, 1992). For instance, several animal studies have shown that administration of cytokines, such as IL-1 or activation of macrophages and other inflammatory immune cells by systemic lipopolysaccharide (LPS) treatment, provokes behavioural symptoms collectively referred to as ‘sickness behaviour’ (Dantzer, 2001; Goshen *et al.* 2008; Kent *et al.* 1992; Larson & Dunn, 2001; Maier & Watkins, 1998). Motivation and some cognitive functions may also be affected (Dantzer, 2001; Larson & Dunn, 2001). Mice lacking the enzyme required to synthesize IL-1 have reduced ‘sickness behaviour’ and lower expression of neurotoxic and

inflammatory mediator genes in the brain after peripheral endotoxin injection (Mastronardi *et al.* 2007). In addition, deletion of either TNF-α receptor 1 (TNFR1) or TNFR2 genes resulted in antidepressant-like effects (Simen *et al.* 2006).

Interestingly, chronic stress induced depressive-like symptoms concomitantly with an increase in IL-1 expression in hippocampus, but mice with a deletion of the IL-1 receptor or with restricted overexpression of IL-1 antagonist did not display stress-induced behavioural or neuroendocrine changes (Goshen *et al.* 2008). Further support for the role of immune system activation in the pathogenesis of depressive disorders comes from studies noting that the antidepressants desipramine and fluoxetine reduce the inflammatory reaction in ovalbumin-sensitized rats in the LPS murine model of autoimmunity (Roumestan *et al.* 2007).

Psychiatric adverse effects associated with cytokine immunotherapy

Interestingly, the findings from animal studies showing that cytokines play a potential role in the development of depression-like behaviours appear to correlate with clinical studies. There is increasing evidence that immunotherapy with IL-2 or IFN-α is often associated with marked cognitive disturbances and neurovegetative symptoms such as fatigue, sleep disturbances, irritability, appetite suppression, and depressed mood that correlate with elevated serum levels of IFN-α, IL-6, IL-8, and IL-10 (Bonaccorso *et al.* 2001, 2002; Capuron *et al.* 2001a, b; Dieperink *et al.* 2000, 2003). In addition, in healthy human volunteers, depression, anxiety, and memory impairment are associated with immune activation by the bacterial endotoxin LPS, and are correlated with serum IL-1 and TNF-α levels induced by that treatment (Yirmiya *et al.* 2000).

The incidence of depressive disorders associated with cytokine therapy is highly variable, ranging from 0% to 45% in different studies. The reasons for these variations are probably related to the disease being treated, the cytokine being used and its dose, as well as assessment measures and psychiatric history (de Beaurepaire, 2002). However, in most cases, the depressive symptoms can be treated effectively with antidepressants.

Clinical evidence for immune activation in MDD

Psychological stress is a common risk factor for the development of MDD, and most initial episodes of MDD are preceded by an identifiable stressor (Kendler *et al.* 2000). Consistent with the notion that stress might provide a link between MDD and inflammation, emerging pre-clinical and clinical evidence indicate that acute and chronic stress elevates levels of proinflammatory cytokines, such as IL-1 and TNF-α and activates their signalling pathways in the periphery and CNS (Deinzer *et al.* 2004; Goebel *et al.* 2000; Madrigal *et al.* 2002; O'Connor *et al.* 2003). Further support for the cytokine hypothesis comes from clinical studies in patients with MDD and BPD who present with a significant rise in serum levels of proinflammatory cytokines, such as TNF-α, IL-1 IL-6, IL-12, soluble IL-6R, IL-2, soluble IL-2R, IL-1ra, and IFN-α (Hestad *et al.* 2003; Kim *et al.* 2007; Kubera *et al.* 2000; Maes, 1994; O'Brien *et al.* 2006; Raison *et al.* 2006; Sluzewska, 1999). Recently, another study demonstrated that, compared to healthy controls, the expression of inflammatory genes – including TNF-α, IL-1, and IL-6 – was increased in the monocytes of a large proportion of individuals with BPD as well as the offspring of BPD patients (Padmos *et al.* 2008). In addition gene expression microarray studies have shown that several receptors for immune genes, such as interferon α/β receptor, IL-8 receptor, and interferon c-inducible protein 16 (IFI-16) were found to be differentially regulated in the frontal cortex of patients with BPD (Bezchlibnyk *et al.* 2001; Iwamoto *et al.* 2004). Interestingly, IFI-16 exerts its immunomodulatory effects through regulation of p53 activity, a key tumour suppressor protein necessary in the signalling cascade activated by TNF-α (Asefa *et al.* 2004; Hofseth *et al.* 2004). It is notable that another severe psychiatric disorder, schizophrenia, has also been associated with increased

inflammatory response and elevated levels of pro-inflammatory cytokines (reviewed in Muller & Schwarz, 2006).

Recently it has been shown that patients with MDD appear to have an imbalance between pro- and anti-inflammatory cytokines, which can be attenuated following treatment with the antidepressants fluoxetine, sertraline, or paroxetine (Kim *et al.* 2007; Kubera *et al.* 2000; Sutcigil *et al.* 2007; Taler *et al.* 2007). Other recent studies found that MDD patients with abnormal allelic variants of the genes for IL-1 and TNF-α and higher levels of TNF-α showed a reduced responsiveness to antidepressant treatment (Eller *et al.* 2008; Fertuzinhos *et al.* 2004; Jun *et al.* 2003; Rosa *et al.* 2004).

A glial–cytokine relationship in MDD

Several pre-clinical and clinical studies also indicate a potential key role for excitotoxicity and microglial activation in the aetiology of MDD. Activation of the immune system has been observed in patients with MDD, resulting in increased levels of circulating pro-inflammatory-cytokines. Specifically, pro-inflammatory cytokines can contribute to glutamate neurotoxicity in multiple ways: (1) directly, via activation of the kynurenine pathway in microglia and increased production of quinolinic acid and glutamate release; (2) indirectly, via decreasing glial glutamate transporter activity leading to reduced glutamate removal from the extracellular space; and (3) by inducing long-term activation of microglia to release TNF-α and IL-1 in a positive feedback manner (reviewed in McNally *et al.* 2008). For instance, riluzole, a glutamatergic modulator with neuroprotective, plasticity-enhancing, and antidepressant properties, enhances glutamate clearance by astrocytes and prevents decrease in glial metabolism (Banasr & Duman, 2008). Furthermore, antidepressants have been shown to inhibit INF-α-induced microglia production of IL-6 and nitric oxide (Hashioka *et al.* 2007), suggesting that inhibiting brain inflammation may represent a novel mechanism of action of antidepressants. Inflammation-mediated imbalance of glutamatergic neurotransmission appears to be similarly implicated in schizophrenia (Muller & Schwarz, 2006), suggesting that immune-mediated glutamatergic disturbance might be a component of the pathophysiology of psychiatric illnesses associated with severe cognitive impairments.

Cytokines as potential therapeutic targets in mood disorders

Therapy with standard antidepressants

More direct support for the role of pro-inflammatory cytokines in regulating synaptic plasticity in the pathogenesis of MDD comes from studies wherein antidepressant drugs from two different pharmacological classes induced changes in TNF-α expression and function in the brain. Both acute and chronic treatment with the tricyclic antidepressant (TCA) desipramine depletes neuron-localized TNF-α mRNA and protein in brain regions implicated in mood expression (Ignatowski *et al.* 1997; Nickola *et al.* 2001). Recently, it was reported that the SSRIs sertraline and paroxetine inhibited TNF-α secretion, leading to the attenuation of pro-inflammatory activity (Taler *et al.* 2007, 2008). In addition, it has been shown that administration of the TCAs desipramine and amitriptyline, as well as the SSRI zimelidine decreased TNF-α levels to facilitate norepinephrine release (Reynolds *et al.* 2005). Furthermore, facilitation of noradrenergic neurotransmission induced by decreased levels of TNF-α in the brain is key to the efficacy of desipramine. This effect appears to be shared by other types of antidepressant drugs; chronic adminstration of the TCA amitriptyline or the SSRI zimelidine transformed TNF-α regulation of norepinephrine release to facilitation, an effect that occurs in association with α_2-adrenergic receptor activation (Nickola *et al.* 2001; Reynolds *et al.* 2004). Collectively, these data demonstrate that dissimilar antidepressants regulate TNF-α levels in the brain, thus ultimately modifying noradrenergic and possibly serotonergic and

dopaminergic neurotransmission, and provide further evidence for the role of TNF-α-induced modulation of synaptic plasticity in the mechanism of antidepressant action.

Anti-cytokine therapy

Both pre-clinical and clinical studies have demonstrated that antidepressants can inhibit the production and/or release of pro-inflammatory cytokines and stimulate the production of anti-inflammatory cytokines, suggesting that reductions in inflammation might contribute to treatment response (Hestad *et al.* 2003; Kenis & Maes, 2002; Lanquillon *et al.* 2000; Tuglu *et al.* 2003). These observations also raise the possibility that inhibiting pro-inflammatory cytokine signalling is a potential strategy for treating depressive disorders, especially in patients with evidence of increased inflammatory activity before therapy, who might be less likely to respond to conventional agents.

Indeed, cytokine antagonists appear to have anti-depressant-like effects, even in the absence of an immune challenge. For example, intracerebroventricular administration of IL-1ra in rodents prevents memory deficits following the psychological stress of social isolation (Pugh *et al.* 1999), and intracerebroventricularly administered antibodies to TNF-α have antidepressant effects in the forced swim test (Reynolds *et al.* 2004). In humans, administration of TNF-α blockers such as etanercept (Enbrel®; Amgen, USA) and infliximab (Remicade®; Johnson and Johnson, USA) has been found to attenuate the depressive symptoms that accompany immune system activation in psoriasis (Dantzer, 1999; Krishnan *et al.* 2007; Tyring *et al.* 2006; Yirmiya, 2000). In addition, inhibition of the production of pro-inflammatory cytokines, such TNF-α and IL-1 by celexocib induced a rapid antidepressant response and prevented cognitive decline in patients with MDD and BPD (Muller *et al.* 2006; Nery *et al.* 2008). Although the putative antidepressant effects of anti-cytokine therapy have not yet been fully illustrated, it is not unreasonable to assume that antagonism of cytokine function may represent a novel target in the treatment of depressive disorders. Alternatively, because it has been shown that imbalance between pro-and anti-inflammatory cytokines might be involved in the pathogenesis of depressive disorders it is possible that anti-inflammatory cytokines with a rather broad spectrum of action (e.g. IL-4 and IL-10) may also be useful anti-cytokine therapies.

Concluding remarks

The present review seeks to bridge the gap between recent findings that implicate both impairments in synaptic plasticity and increased levels of proinflammatory cytokines in patients with mood disorders. As this paper has explored, we propose that cytokine-induced impairments in synaptic plasticity may underlie at least some aspects of the complex pathophysiology of MDD based on the evidence that: (1) elevation of brain cytokine levels is necessary and sufficient to induce depressive symptoms and neuro-endocrine changes in animal models of depression; (2) increased levels of brain cytokines have been shown to impair synaptic plasticity both at morphological and functional levels; and (3) cytokine-induced modulation of neurotransmission and synaptic plasticity plays an important role in the mechanism of antidepressant action and the efficacy of antidepressant treatment.

It is important to note that although the increased levels of cytokines seen in patients with MDD are detrimental to neuroplasticity, physiological levels of pro-inflammatory cytokines are essential for normal brain development and homeostatic regulation of synaptic scaling (Avital *et al.* 2003; Beattie *et al.* 2002; Goshen *et al.* 2007, 2008; Stellwagen & Malenka, 2006). These two conflicting pieces of evidence suggest that it is the disturbance of this intricate equilibrium between physiological and pathophysiolgical levels of cytokines in the brain that affects synaptic plasticity and plays a critical role in the pathophysiology of MDD (Fig. 1).

In the context of this review, it is important to note that despite the accumulating evidence in support of the cytokine hypothesis of MDD, several studies have found only a weak association, or no association, between inflammation and the development of depression when factors such as body mass index, gender, and personality were taken into account (Brambilla & Maggioni, 1998; Carpenter *et al.* 2004; Miller *et al.* 2003; Rothermundt *et al.* 2001). In addition, some otherwise positive studies failed to find a correlation between inflammation and the severity of depressive symptoms (Hestad *et al.* 2003), or found disparate and occasionally opposing correlations for different pro-inflammatory mediators (Miller *et al.* 2002, 2005; Pollmacher *et al.* 2002).

Another issue that remains to be elucidated is whether pro-inflammatory cytokines, released peripherally upon immune system activation, play a causal role in the onset of MDD, or whether they represent an immunological side-effect of this disease. Indeed, due to the associative nature of the studies investigating the relationship between immune activation, cytokines, and MDD it is unclear whether the activation of the immune system observed in depressed patients precedes or follows the onset of depressive disorders (reviewed in Dantzer *et al.* 2008; Raison *et al.* 2006). However, the findings that cytokine therapy is often accompanied by adverse psychiatric events, which disappear when cytokine treatment ends or antidepressant treatment begins, suggest a potentially causal role for pro-inflammatory cytokines in the aetiology and pathophysiology of mood disorders; the observation that anti-cytokine treatment produces an antidepressant response in patients with MDD and BPD lends further credence to this notion.

Future research will need to determine the clinical effects of cytokine antagonists on the pathophysiological and psychological features of mood disorders. In order to elucidate the functional role of cytokine-induced alterations of synaptic plasticity in the pathophysiology of MDD, it will also be important to identify the effects of cytokine antagonists and cytokine synthesis inhibitors on neuroplasticity, both at the morphological and functional level. This is a promising field for increasing our understanding of the mechanistic interaction between the immune system, synaptic plasticity, and antidepressants, and for the ultimate development of novel and improved therapeutics for severe mood disorders.

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References

Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. Nature Reviews. Immunology 2003;3:745–756.

Albensi BC, Mattson MP. Evidence for the involvement of TNF and NF-kappaB in hippocampal synaptic plasticity. Synapse 2000;35:151–159. [PubMed: 10611641]

Aloe L, Properzi F, Probert L, Akassoglou K, Kassiotis G, Micera A, Fiore M. Learning abilities, NGF and BDNF brain levels in two lines of TNF-alpha transgenic mice, one characterized by neurological disorders, the other phenotypically normal. Brain Research 1999;840:125–137. [PubMed: 10517960]

Anisman H, Ravindran AV, Griffiths J, Merali Z. Interleukin-1 beta production in dysthymia before and after pharmacotherapy. Biological Psychiatry 1999;46:1649–1655. [PubMed: 10624546]

Asefa B, Klarmann KD, Copeland NG, Gilbert DJ, Jenkins NA, Keller JR. The interferon-inducible p200 family of proteins: a perspective on their roles in cell cycle regulation and differentiation. Blood Cells, Molecules and Diseases 2004;32:155–167.

Avital A, Goshen I, Kamsler A, Segal M, Iverfeldt K, Richter-Levin G, Yirmiya R. Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. Hippocampus 2003;13:826–834. [PubMed: 14620878]

Balschun D, Wetzel W, Del Rey A, Pitossi F, Schneider H, Zuschratter W, Besedovsky HO. Interleukin-6: a cytokine to forget. FASEB Journal 2004;18:1788–1790. [PubMed: 15345694]

Banasr M, Duman RS. Regulation of neurogenesis and gliogenesis by stress and antidepressant treatment. CNS and Neurological Disorders Drug Targets 2007;6:311–320. [PubMed: 18045159]

Banasr M, Duman RS. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. Biological Psychiatry 2008;64:863–870. [PubMed: 18639237]

Barrientos RM, Higgins EA, Sprunger DB, Watkins LR, Rudy JW, Maier SF. Memory for context is impaired by a post context exposure injection of interleukin-1 beta into dorsal hippocampus. Behavioural Brain Research 2002;134:291–298. [PubMed: 12191816]

Bartee E, Mohamed MR, McFadden G. Tumor necrosis factor and interferon: cytokines in harmony. Current Opinion in Microbiology 2008;11:378–383. [PubMed: 18595771]

Beattie EC, Stellwagen D, Morishita W, Bresnahan JC, Ha BK, Von Zastrow M, Beattie MS, Malenka RC. Control of synaptic strength by glial TNFalpha. Science 2002;295:2282–2285. [PubMed: 11910117]

Bellinger FP, Madamba S, Siggins GR. Interleukin 1 beta inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus. Brain Research 1993;628:227–234. [PubMed: 8313151]

Benowitz LI, Perrone-Bizzozero NI. The relationship of GAP-43 to the development and plasticity of synaptic connections. Annals of the New York Academy of Sciences 1991;627:58–74. [PubMed: 1831963]

Benveniste EN. Cytokine actions in the central nervous system. Cytokine & Growth Factor Reviews 1998;9:259–275. [PubMed: 9918124]

Bezchlibnyk YB, Wang JF, McQueen GM, Young LT. Gene expression differences in bipolar disorder revealed by cDNA array analysis of post-mortem frontal cortex. Journal of Neurochemistry 2001;79:826–834. [PubMed: 11723175]

Bielau H, Trubner K, Krell D, Agelink MW, Bernstein HG, Stauch R, Mawrin C, Danos P, Gerhard L, Bogerts B, Baumann B. Volume deficits of subcortical nuclei in mood disorders A postmortem study. European Archives of Psychiatry and Neurological Sciences 2005;255:401–412.

Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 1993;361:31–39. [PubMed: 8421494]

Bluthe RM, Castanon N, Pousset F, Bristow A, Ball C, Lestage J, Michaud B, Kelley KW, Dantzer R. Central injection of IL-10 antagonizes the behavioural effects of lipopolysaccharide in rats. Psychoneuroendocrinology 1999;24:301–311. [PubMed: 10101735]

Boka G, Anglade P, Wallach D, Javoy-Agid F, Agid Y, Hirsch EC. Immunocytochemical analysis of tumor necrosis factor and its receptors in Parkinson's disease. Neuroscience Letters 1994;172:151–154. [PubMed: 8084523]

Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. Journal of Affective Disorders 2002;72:237–241. [PubMed: 12450640]

Bonaccorso S, Puzella A, Marino V, Pasquini M, Biondi M, Artini M, Almerighi C, Levrero M, Egyed B, Bosmans E, Meltzer HY, Maes M. Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. Psychiatry Research 2001;105:45–55. [PubMed: 11740974]

Brambilla F, Maggioni M. Blood levels of cytokines in elderly patients with major depressive disorder. Acta Psychiatrica Scandinavica 1998;97:309–313. [PubMed: 9570493]

Breder CD, Tsujimoto M, Terano Y, Scott DW, Saper CB. Distribution and characterization of tumor necrosis factor-alpha-like immunoreactivity in the murine central nervous system. Journal of Comparative Neurology 1993;337:543–567. [PubMed: 8288770]

Brennan FX, Beck KD, Servatius RJ. Low doses of interleukin-1beta improve the leverpress avoidance performance of Sprague-Dawley rats. Neurobiology of Learning and Memory 2003;80:168–171. [PubMed: 12932432]

Butler MP, O'Connor JJ, Moynagh PN. Dissection of tumor-necrosis factor-alpha inhibition of long-term potentiation (LTP) reveals a p38 mitogen-activated protein kinase-dependent mechanism which maps to early-but not late-phase LTP. Neuroscience 2004;124:319–326. [PubMed: 14980382]

Capuron L, Ravaud A, Dantzer R. Timing and specificity of the cognitive changes induced by interleukin-2 and interferon-alpha treatments in cancer patients. Psychosomatic Medicine 2001a; 63:376–386. [PubMed: 11382265]

Capuron L, Ravaud A, Gualde N, Bosmans E, Dantzer R, Maes M, Neveu PJ. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. Psychoneuroendocrinology 2001b;26:797–808. [PubMed: 11585680]

Carlezon WA Jr, Nestler EJ. Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse? Trends in Neurosciences 2002;25:610–615. [PubMed: 12446127]

Carpenter LL, Heninger GR, Malison RT, Tyrka AR, Price LH. Cerebrospinal fluid interleukin (IL)-6 in unipolar major depression. Journal of Affective Disorders 2004;79:285–289. [PubMed: 15023509]

Cavanagh JT, Van Beck M, Muir W, Blackwood DH. Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. British Journal of Psychiatry 2002;180:320–326. [PubMed: 11925354]

Choudary PV, Molnar M, Evans SJ, Tomita H, Li JZ, Vawter MP, Myers RM, Bunney WE Jr, Akil H, Watson SJ, Jones EG. Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. Proceedings of the National Academy of Sciences USA 2005;102:15653–15658.

Chung IY, Benveniste EN. Tumor necrosis factor-alpha production by astrocytes. Induction by lipopolysaccharide, IFN-gamma, and IL-1 beta. Journal of Immunology 1990;144:2999–3007.

Churchill L, Rector DM, Yasuda K, Fix C, Rojas MJ, Yasuda T, Krueger JM. Tumor necrosis factor alpha: activity dependent expression and promotion of cortical column sleep in rats. Neuroscience 2008;156:71–80. [PubMed: 18694809]

Clark RE, Broadbent NJ, Zola SM, Squire LR. Anterograde amnesia and temporally graded retrograde amnesia for a nonspatial memory task after lesions of hippocampus and subiculum. Journal of Neuroscience 2002;22:4663–4669. [PubMed: 12040072]

Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. Life Sciences 1998;62:583–606. [PubMed: 9472719]

Coogan AN, O'Neill LA, O'Connor JJ. The P38 mitogen-activated protein kinase inhibitor SB203580 antagonizes the inhibitory effects of interleukin-1beta on long-term potentiation in the rat dentate gyrus in vitro. Neuroscience 1999;93:57–69. [PubMed: 10430470]

Cook SC, Wellman CL. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. Journal of Neurobiology 2004;60:236–248. [PubMed: 15266654]

Cunningham AJ, Murray CA, O'Neill LA, Lynch MA, O'Connor JJ. Interleukin-1 beta (IL-1 beta) and tumour necrosis factor (TNF) inhibit long-term potentiation in the rat dentate gyrus in vitro. Neuroscience Letters 1996;203:17–20. [PubMed: 8742036]

Cunningham ET Jr, Wada E, Carter DB, Tracey DE, Battey JF, De Souza EB. In situ histochemical localization of type I interleukin-1 receptor messenger RNA in the central nervous system, pituitary, and adrenal gland of the mouse. Journal of Neuroscience 1992;12:1101–1114. [PubMed: 1532025]

Curran B, O'Connor JJ. The pro-inflammatory cytokine interleukin-18 impairs long-term potentiation and NMDA receptor-mediated transmission in the rat hippocampus in vitro. Neuroscience 2001;108:83–90. [PubMed: 11738133]

Czeh B, Simon M, Schmelting B, Hiemke C, Fuchs E. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. Neuropsychopharmacology 2006;31:1616–1626. [PubMed: 16395301]

D'Arcangelo G, Tancredi V, Onofri F, D'Antuono M, Giovedi S, Benfenati F. Interleukin-6 inhibits neurotransmitter release and the spread of excitation in the rat cerebral cortex. European Journal of Neuroscience 2000;12:1241–1252. [PubMed: 10762353]

Dantzer, R. Cytokines, Stress and Depression. New York: Kluwer Academic/Plenum Publishers; 1999. Mechanisms of the behavioral effects of cytokines.

Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. Annals of the New York Academy of Sciences 2001;933:222–234. [PubMed: 12000023]

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature Reviews Neuroscience 2008;9:46–56.

de Beaurepaire R. Questions raised by the cytokine hypothesis of depression. Brain, Behavior, and Immunity 2002;16:610–617.

de Quervain DJ, Roozendaal B, Nitsch RM, McGaugh JL, Hock C. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nature Neuroscience 2000;3:313–314.

Deinzer R, Granrath N, Stuhl H, Twork L, Idel H, Waschul B, Herforth A. Acute stress effects on local Il-1beta responses to pathogens in a human in vivo model. Brain, Behavior, and Immunity 2004;18:458–467.

Dieperink E, Ho SB, Thuras P, Willenbring ML. A prospective study of neuropsychiatric symptoms associated with interferon-alpha-2b and ribavirin therapy for patients with chronic hepatitis C. Psychosomatics 2003;44:104–112. [PubMed: 12618532]

Dieperink E, Willenbring M, Ho SB. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. American Journal of Psychiatry 2000;157:867–876. [PubMed: 10831463]

Du J, Creson TK, Wu LJ, Ren M, Gray NA, Falke C, Wei Y, Wang Y, Blumenthal R, Machado-Vieira R, et al. The role of hippocampal GluR1 and GluR2 receptors in manic-like behavior. Journal of Neuroscience 2008;28:68–79. [PubMed: 18171924]

Du J, Gray NA, Falke CA, Chen W, Yuan P, Szabo ST, Einat H, Manji HK. Modulation of synaptic plasticity by antimanic agents: the role of AMPA glutamate receptor subunit 1 synaptic expression. Journal of Neuroscience 2004;24:6578–6589. [PubMed: 15269270]

Du J, Suzuki K, Wei Y, Wang Y, Blumenthal R, Chen Z, Falke C, Zarate CA Jr, Manji HK. The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorders. Neuropsychopharmacology 2007;32:793–802. [PubMed: 16936714]

Duman RS. Depression: a case of neuronal life and death? Biological Psychiatry 2004;56:140–145. [PubMed: 15271581]

Eastwood SL, Harrison PJ. Synaptic pathology in the anterior cingulate cortex in schizophrenia and mood disorders. A review and a Western blot study of synaptophysin, GAP-43 and the complexins. Brain Research Bulletin 2001;55:569–578. [PubMed: 11576753]

Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2008;32:445–450. [PubMed: 17976882]

Fahey B, Barlow S, Day JS, O'Mara SM. Interferon-alpha-induced deficits in novel object recognition are rescued by chronic exercise. Physiology & Behavior 2008;95:125–129. [PubMed: 18571208]

Fertuzinhos SM, Oliveira JR, Nishimura AL, Pontual D, Carvalho DR, Sougey EB, Otto PA, Zatz M. Analysis of IL-1alpha, IL-1beta, and IL-1RA [correction of IL-RA] polymorphisms in dysthymia. Journal of Molecular Neuroscience 2004;22:251–256. [PubMed: 14997019]

Fontana A, Weber E, Dayer JM. Synthesis of interleukin 1/endogenous pyrogen in the brain of endotoxin-treated mice: a step in fever induction? Journal of Immunology 1984;133:1696–1698.

Friedman WJ. Cytokines regulate expression of the type 1 interleukin-1 receptor in rat hippocampal neurons and glia. Experimental Neurology 2001;168:23–31. [PubMed: 11170718]

Gabbay V, Klein RG, Alonso CM, Babb JS, Nishawala M, De Jesus G, Hirsch GS, Hottinger-Blanc PM, Gonzalez CJ. Immune system dysregulation in adolescent major depressive disorder. Journal of Affective Disorders. 2008Published online 13 September 2008. doi:10.1016/j.jad.2008.07.022

Gabellec MM, Griffais R, Fillion G, Haour F. Interleukin-1 receptors type I and type II in the mouse brain: kinetics of mRNA expressions after peripheral administration of bacterial lipopolysaccharide. Journal of Neuroimmunology 1996;66:65–70. [PubMed: 8964915]

Gadient RA, Otten U. Expression of interleukin-6 (IL-6) and interleukin-6 receptor (IL-6R) mRNAs in rat brain during postnatal development. Brain Research 1994;637:10–14. [PubMed: 8180786]

Gayle D, Ilyin SE, Flynn MC, Plata-Salaman CR. Lipopolysaccharide (LPS)- and muramyl dipeptide (MDP)-induced anorexia during refeeding following acute fasting: characterization of brain cytokine and neuropeptide systems mRNAs. Brain Research 1998;795:77–86. [PubMed: 9622598]

Gibertini M, Newton C, Friedman H, Klein TW. Spatial learning impairment in mice infected with *Legionella pneumophila* or administered exogenous interleukin-1-beta. Brain, Behavior, and Immunity 1995;9:113–128.

Goebel MU, Mills PJ, Irwin MR, Ziegler MG. Interleukin-6 and tumor necrosis factor-alpha production after acute psychological stress, exercise, and infused isoproterenol: differential effects and pathways. Psychosomatic Medicine 2000;62:591–598. [PubMed: 10949106]

Goff DC, Leahy L, Berman I, Posever T, Herz L, Leon AC, Johnson SA, Lynch G. A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. Journal of Clinical Psychopharmacology 2001;21:484–487. [PubMed: 11593073]

Golan H, Levav T, Mendelsohn A, Huleihel M. Involvement of tumor necrosis factor alpha in hippocampal development and function. Cerebral Cortex 2004;14:97–105. [PubMed: 14654461]

Goshen I, Kreisel T, Ben-Menachem-Zidon O, Licht T, Weidenfeld J, Ben-Hur T, Yirmiya R. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. Molecular Psychiatry 2008;13:717–728. [PubMed: 17700577]

Goshen I, Kreisel T, Ounallah-Saad H, Renbaum P, Zalzstein Y, Ben-Hur T, Levy-Lahad E, Yirmiya R. A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology 2007;32:1106–1115. [PubMed: 17976923]

Grilli M, Memo M. Nuclear factor-kappaB/Rel proteins: a point of convergence of signalling pathways relevant in neuronal function and dysfunction. Biochemical Pharmacology 1999;57:1–7. [PubMed: 9920279]

Hashioka S, Klegeris A, Monji A, Kato T, Sawada M, McGeer PL, Kanba S. Antidepressants inhibit interferon-gamma-induced microglial production of IL-6 and nitric oxide. Experimental Neurology 2007;206:33–42. [PubMed: 17481608]

Heinrich PC, Behrmann I, Muller-Newen G, Schaper F, Graeve L. Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. Biochemical Journal 1998;334:297–314. [PubMed: 9716487]

Hestad KA, Tonseth S, Stoen CD, Ueland T, Aukrust P. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. Journal of ECT 2003;19:183–188. [PubMed: 14657769]

Heyser CJ, Masliah E, Samimi A, Campbell IL, Gold LH. Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin 6 in the brain. Proceedings of the National Academy of Sciences USA 1997;94:1500–1505.

Hofseth LJ, Hussain SP, Harris CC. p53: 25 years after its discovery. Trends in Pharmacological Sciences 2004;25:177–181. [PubMed: 15116721]

Holderbach R, Clark K, Moreau JL, Bischofberger J, Normann C. Enhanced long-term synaptic depression in an animal model of depression. Biological Psychiatry 2007;62:92–100. [PubMed: 17141742]

Holmin S, Schalling M, Hojeberg B, Nordqvist AC, Skeftruna AK, Mathiesen T. Delayed cytokine expression in rat brain following experimental contusion. Journal of Neurosurgery 1997;86:493–504. [PubMed: 9046307]

Hunt JS, Chen HL, Hu XL, Chen TY, Morrison DC. Tumor necrosis factor-alpha gene expression in the tissues of normal mice. Cytokine 1992;4:340–346. [PubMed: 1420994]

Ignatowski TA, Noble BK, Wright JR, Gorfien JL, Heffner RR, Spengler RN. Neuronal-associated tumor necrosis factor (TNF alpha): its role in noradrenergic functioning and modification of its expression following antidepressant drug administration. Journal of Neuroimmunology 1997;79:84–90. [PubMed: 9357451]

Iwamoto K, Kakiuchi C, Bundo M, Ikeda K, Kato T. Molecular characterization of bipolar disorder by comparing gene expression profiles of postmortem brains of major mental disorders. Molecular Psychiatry 2004;9:406–416. [PubMed: 14743183]

Jun TY, Pae CU, Hoon H, Chae JH, Bahk WM, Kim KS, Serretti A. Possible association between-G308A tumour necrosis factor-alpha gene polymorphism and major depressive disorder in the Korean population. Psychiatric Genetics 2003;13:179–181. [PubMed: 12960751]

Kendell SF, Krystal JH, Sanacora G. GABA and glutamate systems as therapeutic targets in depression and mood disorders. Expert Opinion on Therapeutic Targets 2005;9:153–168. [PubMed: 15757488]

Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the 'kindling' hypothesis. American Journal of Psychiatry 2000;157:1243–1251. [PubMed: 10910786]

Kenis G, Maes M. Effects of antidepressants on the production of cytokines. International Journal of Neuropsychopharmacology 2002;5:401–412. [PubMed: 12466038]

Kent S, Bluthe RM, Kelley KW, Dantzer R. Sickness behavior as a new target for drug development. Trends in Pharmacological Sciences 1992;13:24–28. [PubMed: 1542935]

Kim JJ, Diamond DM. The stressed hippocampus, synaptic plasticity and lost memories. Nature Reviews Neuroscience 2002;3:453–462.

Kim YK, Na KS, Shin KH, Jung HY, Choi SH, Kim JB. Cytokine imbalance in the pathophysiology of major depressive disorder. Progress in Neuro-psychopharmacology and Biological Psychiatry 2007;31:1044–1053. [PubMed: 17433516]

Krishnan R, Cella D, Leonardi C, Papp K, Gottlieb AB, Dunn M, Chiou CF, Patel V, Jahreis A. Effects of etanercept therapy on fatigue and symptoms of depression in subjects treated for moderate to severe plaque psoriasis for up to 96 weeks. British Journal of Dermatology 2007;157:1275–1277. [PubMed: 17916204]

Kubera M, Kenis G, Bosmans E, Zieba A, Dudek D, Nowak G, Maes M. Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: comparison between the acute state and after remission. Polish Journal of Pharmacology 2000;52:237–241. [PubMed: 11055582]

Lacroix S, Rivest S. Effect of acute systemic inflammatory response and cytokines on the transcription of the genes encoding cyclooxygenase enzymes (COX-1 and COX-2) in the rat brain. Journal of Neurochemistry 1998;70:452–466. [PubMed: 9453538]

Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology 2000;22:370–379. [PubMed: 10700656]

Larson SJ, Dunn AJ. Behavioral effects of cytokines. Brain, Behavior, and Immunity 2001;15:371–387.

Levkovitz Y, Grisaru N, Segal M. Transcranial magnetic stimulation and antidepressive drugs share similar cellular effects in rat hippocampus. Neuropsychopharmacology 2001;24:608–616. [PubMed: 11331140]

Li H, Gade P, Xiao W, Kalvakolanu DV. The interferon signaling network and transcription factor C/EBP-beta. Cellular & Molecular Immunology 2007;4:407–418. [PubMed: 18163952]

Licinio J. Central nervous system cytokines and their relevance for neurotoxicity and apoptosis. Journal of Neural Transmission (Suppl.) 1997;49:169–175.

Lieberman AP, Pitha PM, Shin HS, Shin ML. Production of tumor necrosis factor and other cytokines by astrocytes stimulated with lipopolysaccharide or a neurotropic virus. Proceedings of the National Academy of Sciences USA 1989;86:6348–6352.

MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, Nahmias C, Young LT. Course of illness, hippocampal function, and hippocampal volume in major depression. Proceedings of the National Academy of Sciences USA 2003;100:1387–1392.

Madrigal JL, Hurtado O, Moro MA, Lizasoain I, Lorenzo P, Castrillo A, Bosca L, Leza JC. The increase in TNF-alpha levels is implicated in NF-kappaB activation and inducible nitric oxide synthase expression in brain cortex after immobilization stress. Neuropsychopharmacology 2002;26:155–163. [PubMed: 11790511]

Maes M. Cytokines in major depression. Biological Psychiatry 1994;36:498–499. [PubMed: 7811853]

Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, Desnyder R. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. Journal of Affective Disorders 1995a;34:301–309. [PubMed: 8550956]

Maes M, Smith R, Scharpe S. The monocyte-T-lymphocyte hypothesis of major depression. Psychoneuroendocrinology 1995b;20:111–116. [PubMed: 7899532]

Maes M, Van Bockstaele DR, Gastel A, Song C, Schotte C, Neels H, DeMeester I, Scharpe S, Janca A. The effects of psychological stress on leukocyte subset distribution in humans: evidence of immune activation. Neuropsychobiology 1999;39:1–9. [PubMed: 9892853]

Maier SF, Watkins LR. Intracerebroventricular interleukin-1 receptor antagonist blocks the enhancement of fear conditioning and interference with escape produced by inescapable shock. Brain Research 1995;695:279–282. [PubMed: 8556346]

Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychological Review 1998;105:83–107. [PubMed: 9450372]

Malenka RC. The long-term potential of LTP. Nature Reviews. Neuroscience 2003;4:923–926.

Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. Psychopharmacology Bulletin 2001;35:5–49. [PubMed: 12397885]

Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff KD, Zarate CA Jr, Charney DS. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. Biological Psychiatry 2003;53:707–742. [PubMed: 12706957]

Mastronardi C, Whelan F, Yildiz OA, Hannestad J, Elashoff D, McCann SM, Licinio J, Wong ML. Caspase 1 deficiency reduces inflammation-induced brain transcription. Proceedings of the National Academy of Sciences USA 2007;104:7205–7210.

McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: a literature review. CNS Spectrums 2008;13:501–510. [PubMed: 18567974]

Medana IM, Hunt NH, Chaudhri G. Tumor necrosis factor-alpha expression in the brain during fatal murine cerebral malaria: evidence for production by microglia and astrocytes. American Journal of Pathology 1997;150:1473–1486. [PubMed: 9095002]

Mendoza-Fernandez V, Andrew RD, Barajas-Lopez C. Interferon-alpha inhibits long-term potentiation and unmasks a long-term depression in the rat hippocampus. Brain Research 2000;885:14–24. [PubMed: 11121525]

Miller AH, Raison CL. Cytokines, p38 MAP kinase and the pathophysiology of depression. Neuropsychopharmacology 2006;31:2089–2090. [PubMed: 16980982]

Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. Brain, Behavior, and Immunity 2003;17:276–285.

Miller GE, Rohleder N, Stetler C, Kirschbaum C. Clinical depression and regulation of the inflammatory response during acute stress. Psychosomatic Medicine 2005;67:679–687. [PubMed: 16204423]

Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. American Journal of Cardiology 2002;90:1279–1283. [PubMed: 12480034]

Mizuta I, Ohta M, Ohta K, Nishimura M, Mizuta E, Kuno S. Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes. Neuroscience Letters 2001;310:117–120. [PubMed: 11585581]

Muller N, Ackenheil M. Psychoneuroimmunology and the cytokine action in the CNS: implications for psychiatric disorders. Progress in Neuropsychopharmacology and Biological Psychiatry 1998;22:1–33.

Muller N, Schwarz M. Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. Neurotoxicity Research 2006;10:131–148. [PubMed: 17062375]

Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Muller B, Spellmann I, Hetzel G, Maino K, Kleindienst N, 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. Molecular Psychiatry 2006;11:680–684. [PubMed: 16491133]

Murray CA, Lynch MA. Evidence that increased hippocampal expression of the cytokine interleukin-1 beta is a common trigger for age- and stress-induced impairments in long-term potentiation. Journal of Neuroscience 1998;18:2974–2981. [PubMed: 9526014]

Myint AM, O'Mahony S, Kubera M, Kim YK, Kenny C, Kaim-Basta A, Steinbusch HW, Leonard BE. Role of paroxetine in interferon-alpha-induced immune and behavioural changes in male Wistar rats. Journal of Psychopharmacology 2007;21:843–850. [PubMed: 17984161]

Nassberger L, Traskman-Bendz L. Increased soluble interleukin-2 receptor concentrations in suicide attempters. Acta Psychiatrica Scandinavica 1993;88:48–52. [PubMed: 8372695]

Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, Bowden CL, Soares JC. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Human Psychopharmacology 2008;23:87–94. [PubMed: 18172906]

Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, Alderson AL. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. Archives of General Psychiatry 1999;56:527–533. [PubMed: 10359467]

Nickola TJ, Ignatowski TA, Reynolds JL, Spengler RN. Antidepressant drug-induced alterations in neuron-localized tumor necrosis factor-alpha mRNA and alpha(2)-adrenergic receptor sensitivity. Journal of Pharmacology and Experimental Therapeutics 2001;297:680–687. [PubMed: 11303058]

O'Brien SM, Scully P, Scott LV, Dinan TG. Cytokine profiles in bipolar affective disorder : focus on acutely ill patients. Journal of Affective Disorders 2006;90:263–267. [PubMed: 16410025]

O'Connor KA, Johnson JD, Hansen MK, Wieseler Frank JL, Maksimova E, Watkins LR, Maier SF. Peripheral and central proinflammatory cytokine response to a severe acute stressor. Brain Research 2003;991:123–132. [PubMed: 14575884]

Oitzl MS, van Oers H, Schobitz B, de Kloet ER. Interleukin-1 beta, but not interleukin-6, impairs spatial navigation learning. Brain Research 1993;613:160–163. [PubMed: 8348300]

Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proceedings of the National Academy of Sciences USA 1998;95:13290–13295.

Padmos RC, Hillegers MH, Knijff EM, Vonk R, Bouvy A, Staal FJ, de Ridder D, Kupka RW, Nolen WA, Drexhage HA. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. Archives of General Psychiatry 2008;65:395–407. [PubMed: 18391128]

Parnet P, Amindari S, Wu C, Brunke-Reese D, Goujon E, Weyhenmeyer JA, Dantzer R, Kelley KW. Expression of type I and type II interleukin-1 receptors in mouse brain. Brain research. Molecular Brain Research 1994;27:63–70. [PubMed: 7877456]

Pickering M, Cumiskey D, O'Connor JJ. Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system. Experimental Physiology 2005;90:663–670. [PubMed: 15944202]

Pitossi F, del Rey A, Kabiersch A, Besedovsky H. Induction of cytokine transcripts in the central nervous system and pituitary following peripheral administration of endotoxin to mice. Journal of Neuroscience Research 1997;48:287–298. [PubMed: 9169855]

Pizzi M, Sarnico I, Boroni F, Benarese M, Dreano M, Garotta G, Valerio A, Spano P. Prevention of neuron and oligodendrocyte degeneration by interleukin-6 (IL-6) and IL-6 receptor/IL-6 fusion protein in organotypic hippocampal slices. Molecular and Cellular Neurosciences 2004;25:301–311. [PubMed: 15019946]

Pollmacher T, Haack M, Schuld A, Reichenberg A, Yirmiya R. Low levels of circulating inflammatory cytokines - do they affect human brain functions? Brain, Behavior, and Immunity 2002;16:525–532.

Pugh CR, Johnson JD, Martin D, Rudy JW, Maier SF, Watkins LR. Human immunodeficiency virus-1 coat protein gp120 impairs contextual fear conditioning: a potential role in AIDS related learning and memory impairments. Brain Research 2000;861:8–15. [PubMed: 10751560]

Pugh CR, Nguyen KT, Gonyea JL, Fleshner M, Wakins LR, Maier SF, Rudy JW. Role of interleukin-1 beta in impairment of contextual fear conditioning caused by social isolation. Behavioural Brain Research 1999;106:109–118. [PubMed: 10595426]

Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends in Immunology 2006;27:24–31. [PubMed: 16316783]

Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biological Psychiatry 2000;48:766–777. [PubMed: 11063973]

Rajkowska G. Cell pathology in mood disorders. Seminars in Clinical Neuropsychiatry 2002;7:281–292. [PubMed: 12382210]

Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biological Psychiatry 2001;49:741–752. [PubMed: 11331082]

Rajkowska G, Miguel-Hidalgo JJ. Gliogenesis and glial pathology in depression. CNS & Neurological Disorders Drug Targets 2007;6:219–233. [PubMed: 17511618]

Rettori V, Belova N, Kamat A, Lyson K, Gimeno M, McCann SM. Blockade by interleukin-1-alpha of nitricoxidergic control of luteinizing hormone-releasing hormone release in vivo and in vitro. Neuroimmunomodulation 1994;1:86–91. [PubMed: 8528890]

Reynolds JL, Ignatowski TA, Sud R, Spengler RN. Brain-derived tumor necrosis factor-alpha and its involvement in noradrenergic neuron functioning involved in the mechanism of action of an antidepressant. Journal of Pharmacology and Experimental Therapeutics 2004;310:1216–1225. [PubMed: 15082752]

Reynolds JL, Ignatowski TA, Sud R, Spengler RN. An antidepressant mechanism of desipramine is to decrease tumor necrosis factor-alpha production culminating in increases in noradrenergic neurotransmission. Neuroscience 2005;133:519–531. [PubMed: 15878644]

Rivest S, Lacroix S, Vallieres L, Nadeau S, Zhang J, Laflamme N. How the blood talks to the brain parenchyma and the paraventricular nucleus of the hypothalamus during systemic inflammatory and infectious stimuli. Proceedings of the Society for Experimental Biology and Medicine 2000;223:22–38. [PubMed: 10632958]

Rocher C, Spedding M, Munoz C, Jay TM. Acute stress-induced changes in hippocampal/prefrontal circuits in rats: effects of antidepressants. Cerebral Cortex 2004;14:224–229. [PubMed: 14704220]

Rosa A, Peralta V, Papiol S, Cuesta MJ, Serrano F, Martinez-Larrea A, Fananas L. Interleukin-1beta (IL-1beta) gene and increased risk for the depressive symptom-dimension in schizophrenia spectrum disorders. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics 2004;124B:10–14.

Rothermundt M, Arolt V, Fenker J, Gutbrodt H, Peters M, Kirchner H. Different immune patterns in melancholic and non-melancholic major depression. European Archives of Psychiatry and Clinical Neuroscience 2001;251:90–97. [PubMed: 11407444]

Roumestan C, Michel A, Bichon F, Portet K, Detoc M, Henriquet C, Jaffuel D, Mathieu M. Anti-inflammatory properties of desipramine and fluoxetine. Respiratory Research 2007;8:35. [PubMed: 17477857]

Sapolsky RM. Stress and plasticity in the limbic system. Neurochemical Research 2003;28:1735–1742. [PubMed: 14584827]

Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2005;29:201–217. [PubMed: 15694227]

Schloesser RJ, Huang J, Klein PS, Manji HK. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology 2008;33:110–133. [PubMed: 17912251]

Schneider H, Pitossi F, Balschun D, Wagner A, del Rey A, Besedovsky HO. A neuromodulatory role of interleukin-1beta in the hippocampus. Proceedings of the National Academy of Sciences USA 1998;95:7778–7783.

Schobitz B, Van Den Dobbelsteen M, Holsboer F, Sutanto W, De Kloet ER. Regulation of interleukin 6 gene expression in rat. Endocrinology 1993;132:1569–1576. [PubMed: 8462455]

Sedgwick JD, Czerkinsky C. Detection of cell-surface molecules, secreted products of single cells and cellular proliferation by enzyme immunoassay. Journal of Immunological Methods 1992;150:159–175. [PubMed: 1613252]

Shakesby AC, Anwyl R, Rowan MJ. Overcoming the effects of stress on synaptic plasticity in the intact hippocampus: rapid actions of serotonergic and antidepressant agents. Journal of Neuroscience 2002;22:3638–3644. [PubMed: 11978839]

Sheline YI. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. Biological Psychiatry 2000;48:791–800. [PubMed: 11063975]

Shors TJ. Significant life events and the shape of memories to come: a hypothesis. Neurobiology of Learning and Memory 2006;85:103–115. [PubMed: 16289750]

Simen BB, Duman CH, Simen AA, Duman RS. TNFalpha signaling in depression and anxiety: behavioral consequences of individual receptor targeting. Biological Psychiatry 2006;59:775–785. [PubMed: 16458261]

Sluzewska A. Indicators of immune activation in depressed patients. Advances in Experimental Medicine and Biology 1999;461:59–73. [PubMed: 10442167]

Song C, Phillips AG, Leonard B. Interleukin 1 beta enhances conditioned fear memory in rats: possible involvement of glucocorticoids. European Journal of Neuroscience 2003;18:1739–1743. [PubMed: 14622208]

Squire LR, Stark CE, Clark RE. The medial temporal lobe. Annual Review of Neuroscience 2004;27:279–306.

Stellwagen D, Beattie EC, Seo JY, Malenka RC. Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-alpha. Journal of Neuroscience 2005;25:3219–3228. [PubMed: 15788779]

Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. Nature 2006;440:1054–1059. [PubMed: 16547515]

Stewart CA, Reid IC. Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. Psychopharmacology 2000;148:217–223. [PubMed: 10755734]

Sun X, Zhao Y, Wolf ME. Dopamine receptor stimulation modulates AMPA receptor synaptic insertion in prefrontal cortex neurons. Journal of Neuroscience 2005;25:7342–7351. [PubMed: 16093384]

Sutcigil L, Oktenli C, Musabak U, Bozkurt A, Cansever A, Uzun O, Sanisoglu SY, Yesilova Z, Ozmenler N, Ozsahin A, Sengul A. Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. Clinical and Developmental Immunology 2007 2007:26438.

Taler M, Bar M, Korob I, Lomnitski L, Baharav E, Grunbaum-Novak N, Weizman A, Gil-Ad I. Evidence for an inhibitory immunomodulatory effect of selected antidepressants on rat splenocytes: possible relevance to depression and hyperactive-immune disorders. International Immunopharmacology 2008;8:526–533. [PubMed: 18328443]

Taler M, Gil-Ad I, Lomnitski L, Korov I, Baharav E, Bar M, Zolokov A, Weizman A. Immunomodulatory effect of selective serotonin reuptake inhibitors (SSRIs) on human T lymphocyte function and gene expression. European Neuropsychopharmacology 2007;17:774–780. [PubMed: 17499975]

Tancredi V, D'Antuono M, Cafe C, Giovedi S, Bue MC, D'Arcangelo G, Onofri F, Benfenati F. The inhibitory effects of interleukin-6 on synaptic plasticity in the rat hippocampus are associated with an inhibition of mitogen-activated protein kinase ERK. Journal of Neurochemistry 2000;75:634–643. [PubMed: 10899938]

Tancredi V, D'Arcangelo G, Grassi F, Tarroni P, Palmieri G, Santoni A, Eusebi F. Tumor necrosis factor alters synaptic transmission in rat hippocampal slices. Neuroscience Letters 1992;146:176–178. [PubMed: 1337194]

Tanis KQ, Newton SS, Duman RS. Targeting neurotrophic/growth factor expression and signaling for antidepressant drug development. CNS & Neurological Disorders Drug Targets 2007;6:151–160. [PubMed: 17430152]

Tchelingerian JL, Quinonero J, Booss J, Jacque C. Localization of TNF alpha and IL-1 alpha immunoreactivities in striatal neurons after surgical injury to the hippocampus. Neuron 1993;10:213–224. [PubMed: 8439410]

Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, Starkey M, Webster MJ, Yolken RH, Bahn S. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 2003;362:798–805. [PubMed: 13678875]

Tonelli LH, Postolache TT. Tumor necrosis factor alpha, interleukin-1 beta, interleukin-6 and major histocompatibility complex molecules in the normal brain and after peripheral immune challenge. Neurological Research 2005;27:679–684. [PubMed: 16197804]

Tsao CW, Lin YS, Chen CC, Bai CH, Wu SR. Cytokines and serotonin transporter in patients with major depression. Progress in Neuropsychopharmacology and Biological Psychiatry 2006;30:899–905.

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 2003;170:429–433. [PubMed: 12955291]

Turnbull AV, Pitossi FJ, Lebrun JJ, Lee S, Meltzer JC, Nance DM, del Rey A, Besedovsky HO, Rivier C. Inhibition of tumor necrosis factor-alpha action within the CNS markedly reduces the plasma adrenocorticotropin response to peripheral local inflammation in rats. Journal of Neuroscience 1997;17:3262–3273. [PubMed: 9096159]

Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R. Etanercept and clinical outcomes, fatigue, and depression in psoriasis :

double-blind placebo-controlled randomised phase III trial. Lancet 2006;367:29–35. [PubMed: 16399150]

Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophrenia Research 2004;67:269–275. [PubMed: 14984887]

van Dam AM, Poole S, Schultzberg M, Zavala F, Tilders FJ. Effects of peripheral administration of LPS on the expression of immunoreactive interleukin-1 alpha, beta, and receptor antagonist in rat brain. Annals of the New York Academy of Sciences 1998;840:128–138. [PubMed: 9629245]

Van Wagoner NJ, Oh JW, Repovic P, Benveniste EN. Interleukin-6 (IL-6) production by astrocytes: autocrine regulation by IL-6 and the soluble IL-6 receptor. Journal of Neuroscience 1999;19:5236–5244. [PubMed: 10377335]

Vawter MP, Thatcher L, Usen N, Hyde TM, Kleinman JE, Freed WJ. Reduction of synapsin in the hippocampus of patients with bipolar disorder and schizophrenia. Molecular Psychiatry 2002;7:571–578. [PubMed: 12140780]

Vikman KS, Owe-Larsson B, Brask J, Kristensson KS, Hill RH. Interferon-gamma-induced changes in synaptic activity and AMPA receptor clustering in hippocampal cultures. Brain Research 2001;896:18–29. [PubMed: 11277968]

Vitkovic L, Bockaert J, Jacque C. 'Inflammatory' cytokines: neuromodulators in normal brain? Journal of Neurochemistry 2000;74:457–471. [PubMed: 10646496]

Vouimba RM, Munoz C, Diamond DM. Differential effects of predator stress and the antidepressant tianeptine on physiological plasticity in the hippocampus and basolateral amygdala. Stress 2006;9:29–40. [PubMed: 16753931]

Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. Hippocampus 2006;16:239–249. [PubMed: 16425236]

Wichers M, Maes M. The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. International Journal of Neuropsychopharmacology 2002;5:375–388. [PubMed: 12466036]

Wolf ME, Sun X, Mangiavacchi S, Chao SZ. Psychomotor stimulants and neuronal plasticity. Neuropharmacology 2004;47:61–79. [PubMed: 15464126]

Xu L, Holscher C, Anwyl R, Rowan MJ. Glucocorticoid receptor and protein/RNA synthesis-dependent mechanisms underlie the control of synaptic plasticity by stress. Proceedings of the National Academy of Sciences USA 1998;95:3204–3208.

Yasuhara O, Matsuo A, Terai K, Walker DG, Berger AE, Akiguchi I, Kimura J, McGeer PL. Expression of interleukin-1 receptor antagonist protein in post-mortem human brain tissues of Alzheimer's disease and control cases. Acta Neuropathologica 1997;93:414–420. [PubMed: 9113207]

Yirmiya R. Depression in medical illness: the role of the immune system. Western Journal of Medicine 2000;173:333–336. [PubMed: 11069873]

Yirmiya R, Pollak Y, Morag M, Reichenberg A, Barak O, Avitsur R, Shavit Y, Ovadia H, Weidenfeld J, Morag A, Newman ME, Pollmacher T. Illness, cytokines, and depression. Annals of the New York Academy of Sciences 2000;917:478–487. [PubMed: 11268375]

Yirmiya R, Winocur G, Goshen I. Brain interleukin-1 is involved in spatial memory and passive avoidance conditioning. Neurobiology of Learning and Memory 2002;78:379–389. [PubMed: 12431424]

Zakzanis KK, Leach L, Kaplan E. On the nature and pattern of neurocognitive function in major depressive disorder. Neuropsychiatry, Neuropsychology, and Behavioral Neurology 1998;11:111–119.

Zarate CA Jr, Payne JL, Quiroz J, Sporn J, Denicoff KK, Luckenbaugh D, Charney DS, Manji HK. An open-label trial of riluzole in patients with treatment-resistant major depression. American Journal of Psychiatry 2004a;161:171–174. [PubMed: 14702270]

Zarate CA Jr, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, Charney DS, Manji HK. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. Biological Psychiatry 2004b;56:54–60. [PubMed: 15219473]

Zarate CA Jr, Singh J, Manji HK. Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. Biological Psychiatry 2006;59:1006–1020. [PubMed: 16487491]

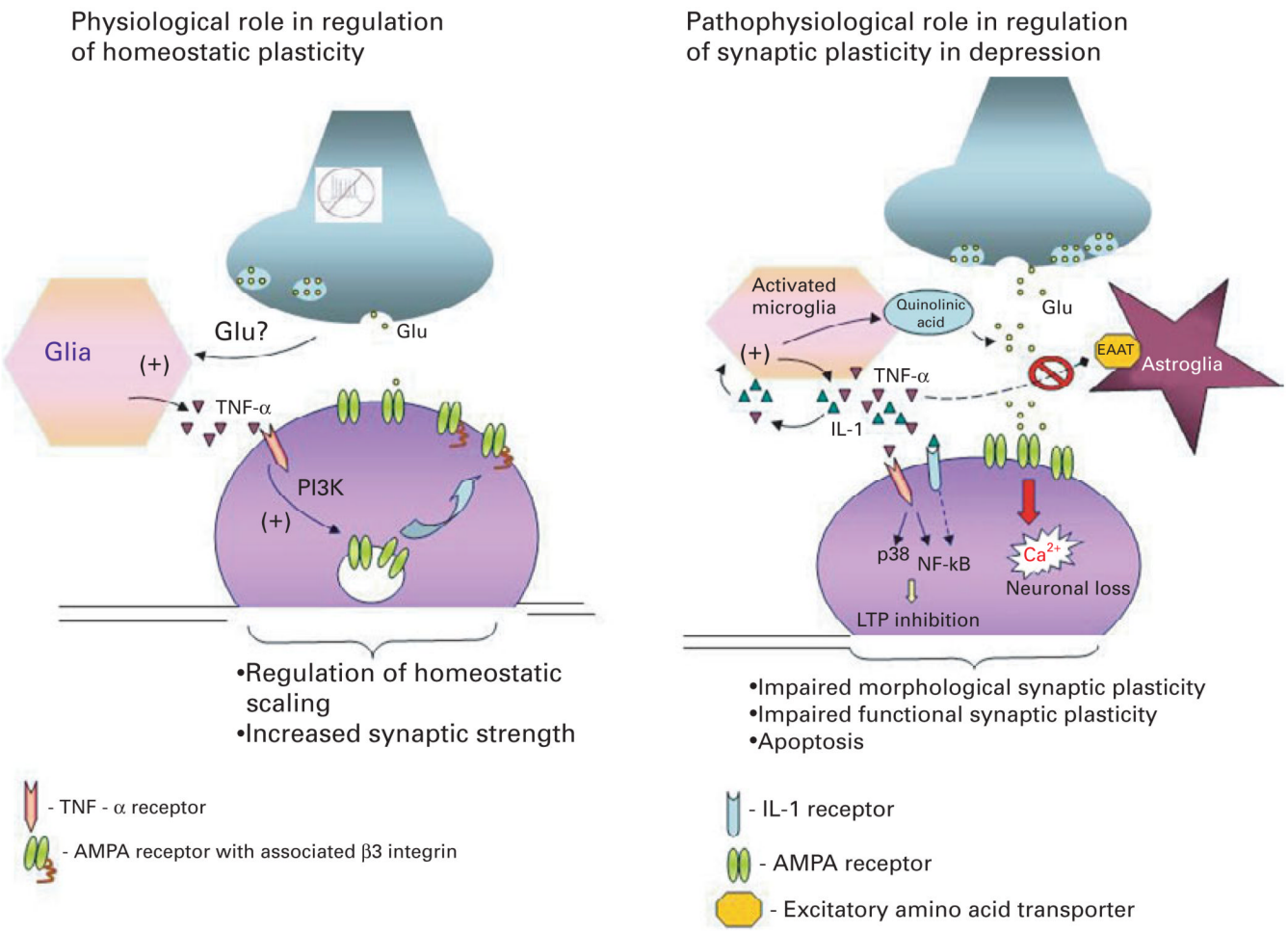

Fig. 1.

Dual role of pro-inflammatory cytokines in regulating synaptic plasticity. The diagram on the left depicts the critical role of constitutively expressed TNF-α in regulation of homeostatic synaptic plasticity in the normal brain. Decreased neuronal activity and consequently reduced glutamate release from axons is sensed by glia, which triggers release of TNF-α. TNF-α activates neuronal TNF-α receptors type I (TNFR1) leading to activation of the phosphoinositide-3 kinase (PI3K) pathway and up-regulation of specific adhesion molecule-β3 integrin, which in turn triggers α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor insertion to the membrane and increases synaptic strength. The diagram on the right depicts the various signalling cascades initiated by high pathophysiological levels of pro-inflammatory cytokines in the brain by activated microglia, which might underlie at least some aspects of the pathophysiology of depression. (1) TNF-α and IL-1 trigger production of quinolinic acid and release of glutamate by microglia; (2) TNF-α and IL-1 inhibit glutamate removal by astrocytes, leading to excess extracellular glutamate and neurotoxicity; (3) TNF-α acts via TNFR1 to up-regulate membrane expression of Ca-permeable AMPA receptor subunits, thus leading to increased Ca^{2+} influx and neuronal death; (4) TNFR1 activation coupled to activation of p38 and NF-κB pathways inhibits the early and late phases of LTP. These effects of pathophysiological levels of pro-inflammatory cytokines on synaptic plasticity at both morphological and functional levels might underlie the cognitive disturbances and impairments of memory seen in patients with depression.

Table 1

Expression profile and signalling pathways of selected pro-inflammatory cytokines in the normal brain

Cytokine	Primary localization of cytokine	Primary localization of cytokine receptor	Associated signalling cascades
TNF-α	Neurons in hypothalamus, caudal raphe nuclei (Breder *et al.* 1993; Churchill *et al.* 2008); astrocytes (Chung & Benveniste, 1990; Lieberman *et al.* 1989)	TNFR1 and TNFR2 in neurons and glia in the cortex, hippocampus, thalamus (Boka *et al.* 1994; Tchelingerian *et al.* 1993)	TNFR1 (via FADD) caspase 8 and caspase 3 pathwayTNFR1 and TNFR2 (via TRAF2) – JNK, p38MAPK and NF-κB pathways (Aggarwal, 2003)
IL-1 family (IL-1α, IL-1β, IL-18)	Glial cells in cerebal cortex and hypothalamus (Breder *et al.* 1993; Vitkovic *et al.* 2000); Neurons in hypothalamus (Friedman, 2001; Rettori *et al.* 1994; Yasuhara *et al.* 1997)	IL-1RI and IL-1RII in neurons in hippocampus, hypothalamus and dentate gyrus (Cunningham *et al.* 1992; Parnet *et al.* 1994)	IL-1RI (via IRAK) – NF-κB pathwaysIL-1Rs – JNK, p42/44 MAPK, p38MAPK pathways (Vitkovic *et al.* 2000)
IL-6	Neurons in hippocampus and cortex (Gadient & Otten, 1994; Schobitz *et al.* 1993) astrocytes (Van Wagoner *et al.* 1999)	Neurons in hippocampus and cortex (Gadient & Otten, 1994; Schobitz *et al.* 1993)	Jak/STAT and Ras/MEK/MAPK pathways (Heinrich *et al.* 1998; Pizzi *et al.* 2004)
INFs (INF-α/β, INF-γ)	Neurons, astrocytes and microglia (Benveniste, 1998)	Neurons in hippocampus and cortex (Gadient & Otten, 1994; Schobitz *et al.* 1993)	Jak/STAT and PI3K pathways (Bartee *et al.* 2008; Li *et al.* 2007)

FADD, Fas-associated death domain; IL-6, interleukin 6; IL-1RI, IL-1 receptor type I; IL-1RII, IL-1 receptor type II; INF, interferon; IRAK, interleukin 1 receptor-associated kinase; Jak/STAT, Janus kinases/signal transducers and activators of transcription; JNK, c-Jun N-terminal kinases/stress-activated protein kinase; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal-related kinase (ERK) kinase; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide-3 kinase; TNFR1, TNF-α type I receptor; TNFR2, TNF-α type 2 receptor; TRAF2, TNFR-associated factor 2.

Table 2

Regulation of synaptic plasticity and behavioural correlates by pro-inflammatory cytokines

Cytokine	Effect on synaptic plasticity	Behavioural correlates
Physiological levels of TNF-α	Up-regulation of AMPA receptor trafficking; increased synaptic strength (Beattie *et al.* 2002; Stellwagen *et al.* 2005)	?
High pathological levels of TNF-α	Inhibition of LTP (Butler *et al.* 2004; Coogan *et al.* 1999; Cunningham *et al.* 1996; Tancredi *et al.* 1992)	'Depressive-like ' behaviour, impaired learning and memory in animal models (Aloe *et al.* 1999; Dantzer, 2001; Golan *et al.* 2004) Depressive symptoms, anxiety and memory impairments in mood disorders (Dantzer *et al.* 2008; Raison *et al.* 2006)
Physiological levels of IL-1	Maintenance of short-term plasticity and LTP (Avital *et al.* 2003; Goshen *et al.* 2007, 2008; Yirmiya *et al.* 2002)	Improved hippocampal-dependent memory (Avital *et al.* 2003; Brennan *et al.* 2003; Song *et al.* 2003)
High pathological levels of IL-1 or IL-18	Impaired LTP (Coogan *et al.* 1999; Curran & O'Connor, 2001; Goshen *et al.* 2007)	'Depressive-like ' behaviour and impaired hippocampal-dependent memory in animal models (Dantzer, 2001; Dantzer *et al.* 2008; Gibertini *et al.* 1995)
Increased levels of IL-6	Decreased glutamate release (D'Arcangelo *et al.* 2000); decreased expression of LTP (Tancredi *et al.* 2000)	'Depressive-like ' behaviour, impaired learning and memory in animal models (Balschun *et al.* 2004; Bluthe *et al.* 1999; Heyser *et al.* 1997) Marked cognitive disturbances and depression symptoms in MDD (Capuron *et al.* 2001a; Raison *et al.* 2006)
Increased levels of INF-α and INF-γ	Decreased dendritic AMPA receptor clustering (Vikman *et al.* 2001); inhibition of glutamate-mediated excitatory post-synaptic potentials and LTP (Mendoza-Fernandez *et al.* 2000)	Anxiety and learning deficits in animal models (Fahey *et al.* 2008; Myint *et al.* 2007) Depressive symptoms and cognitive deficits in MDD (Gabbay *et al.* 2008; Raison *et al.* 2006)

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; IL-1, interleukin 1; IL-6, interleukin 6; INF-α, interferon-alpha; INF-γ, interferon-gamma; LTP, long-term potentiation; MDD, major depressive disorder.