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

Rushaniya A. Khairova, Rodrigo Machado-Vieira, Jing Du and Husseini K. Manji
Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

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.

Received 7 August 2008; Reviewed 9 September 2008; Revised 22 December 2008; Accepted 23 December 2008; First published online 19 February 2009

Key words: 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 pro-inflammatory cytokines interleukin-1 (IL-1), IL-18, and tumour necrosis 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; Sluzevska, 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 neurotransmission. 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 pro-inflammatory 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 pro-inflammatory 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 Ca²⁺-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 Ca²⁺ 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 immunomodulation of inflammatory processes, recent evidence suggests that IL-1 may modulate synaptic plasticity

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

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, TNF-R-associated factor 2.
Increased levels of IL-6

Decreased glutamate release (D’Arcangelo et al. 2000); decreased expression of LTP (Tancredi et al. 2000)

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)

AMP A, 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.

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. 2003; Goshen et al. 1999; Gabbay et al. 2008; Raison et al. 2006). Marked cognitive disturbances and depression symptoms in MDD (Capuron et al. 2001a; Raison et al. 2006) and memory in animal models (Aloe et al. 2008; Myint et al. 2007) may result in depression-like symptoms in MDD (Capuron et al. 2001a; Raison et al. 2006). Thus, it has been shown that, in rats, administration of IL-1ra impairs memory and hippocampal-dependent memory in animal models (Dantzer, 2001; Golan et al. 2004) and memory in animal models (Balschun et al. 2004; Bluthe et al. 2004; D’Arcangelo et al. 2000; Heyser et al. 1997).}

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. 2003). 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 antidepressant 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 glutameric 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 pro-inflammatory 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 pro-inflammatory 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. 2007; Madrigal et al. 2002; O’Connor et al. 2003). Further support for the cytokine hypothesis comes from clinical studies in patients with MDD and BP which present with a significant rise in serum levels of pro-inflammatory 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 BP as well as the offspring of BP 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 γ-inducible protein 16 (IFI-16) were found to be differentially regulated in the frontal cortex of patients with BP (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).
2000; Sut cigil 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 (Banasz & 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 administration of the TCA amitriptyline or the SSRI zimelidine transformed TNF-α regulation of norepinephrine release to facilitation, an effect that occurs in association with α2-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 antidepressant-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 celecoxib 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 pro-inflammatory cytokines in patients with mood disorders. As this paper has explored, we propose that

---

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 1 (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 Ca²⁺ 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.

---

Physiological role in regulation of homeostatic plasticity

Pathophysiological role in regulation of synaptic plasticity in depression

- Regulation of homeostatic scaling
- Increased synaptic strength

- Impaired morphological synaptic plasticity
- Impaired functional synaptic plasticity
- Apoptosis

- TNF-α receptor
- AMPA receptor with associated β3 integrin
- IL-1 receptor
- AMPA receptor
- Excitatory amino acid transporter

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 1 (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 Ca²⁺ 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.
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 neuroendocrine 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 pathophysiological 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.

Acknowledgements

This work was supported by the Intramural Research Program of the National Institute of Mental Health (NIMH), National Institutes of Health (NIH), Department of Health and Human Services (DHHS). This work was completed under the auspices of the Intramural Program of the NIMH. Dr Manji is now at Johnson and Johnson PRD. We thank Ioline Henter for outstanding editorial assistance.

Statement of Interest

None.

References


Anisman H, Ravindran AV, Griffiths J, Merazi Z (1999). Interleukin-1 beta production in dysthymia before
and after pharmacotherapy. Biological Psychiatry 46, 1649–1655.


and GABAergic signal transmission with glial involvement in depression. Proceedings of the National Academy of Sciences USA 102, 15653–15658.


Cunningham AJ, Murray CA, O’Neill LA, Lynch MA, O’Connor JJ (1996). Interleukin-1 beta (IL-1 beta) and tumour necrosis factor (TNF) inhibit long-term potentiation in the rat dentate gyrus in vitro. Neuroscience 93, 87–89.


Gadient RA, Otten U (1994). Expression of interleukin-6 (IL-6) and interleukin-6 receptor (IL-6R) mRNAs in rat brain during postnatal development. *Brain Research* 650, 10–14.


Pizzolatto, 263–298. 861


Stewart CA, Reid IC (2000). Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. \textit{Psychopharmacology} 148, 217–223.


