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# Immune system to brain signaling: Neuropsychopharmacological implications<sup>☆</sup>

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## ABSTRACT

There has been an explosion in our knowledge of the pathways and mechanisms by which the immune system can influence the brain and behavior. In the context of inflammation, pro-inflammatory cytokines can access the central nervous system and interact with a cytokine network in the brain to influence virtually every aspect of brain function relevant to behavior including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and neurocircuits that regulate mood, motor activity, motivation, anxiety and alarm. Behavioral consequences of these effects of the immune system on the brain include depression, anxiety, fatigue, psychomotor slowing, anorexia, cognitive dysfunction and sleep impairment; symptoms that overlap with those which characterize neuropsychiatric disorders, especially depression. Pathways that appear to be especially important in immune system effects on the brain include the cytokine signaling molecules, p38 mitogen-activated protein kinase and nuclear factor kappa B; indoleamine 2,3 dioxygenase and its downstream metabolites, kynurenine, quinolinic acid and kynurenic acid; the neurotransmitters, serotonin, dopamine and glutamate; and neurocircuits involving the basal ganglia and anterior cingulate cortex. A series of vulnerability factors including aging and obesity as well as chronic stress also appears to interact with immune to brain signaling to exacerbate immunologic contributions to neuropsychiatric disease. The elucidation of the mechanisms by which the immune system influences behavior yields a host of targets for potential therapeutic development as well as informing strategies for the prevention of neuropsychiatric disease in at risk populations.

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**Abbreviations:** ACC, anterior cingulate cortex; ACTH, adrenocorticotropic hormone; BCG, Bacille Calmette-Guerin; BDNF, brain derived neurotrophic factor; BH<sub>4</sub>, tetrahydrobiopterin; BMI, body mass index; CNS, central nervous system; COX, cyclooxygenase; CRH, corticotropin-releasing hormone; CRP, C reactive protein; CSF, cerebrospinal fluid; DA, dopamine; DEX, dexamethasone; DST, dexamethasone suppression test; GR, glucocorticoid receptor; 5-HIAA, 5-hydroxyindoleacetic acid; HPA, hypothalamic–pituitary–adrenal axis; IDO, indoleamine 2,3 dioxygenase; IFN, interferon; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; IRF, interferon regulatory factor; KA, kynurenic acid; KYN, kynurenine; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-κB; PGE, prostaglandin; QUIN, quinolinic acid; NMDA, N-methyl-D-aspartate; NO, nitric oxide; RAR, retinoic acid receptor; RORc, receptor-related orphan receptor C; ROS, reactive oxygen species; STAT, signal transducer activator of transcription; TGF, transforming growth factor; Th17, T helper 17 cells; TNF, tumor necrosis factor; T reg, T regulatory cells; TRP, tryptophan.

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## 1. Introduction

Reciprocal interactions between the immune system and the brain have attracted considerable attention regarding the role of the immune system in neuropsychiatric diseases especially major depression. During the last several decades, research in the field referred to as “Psychoneuroimmunology” has demonstrated an intricate network of bi-directional relationships between the immune system and the brain. Alterations in immune function have been found in depressed patients with major depression and include early reports of immune suppression (e.g., reduced natural killer cell activity and reduced lymphocyte proliferation) followed by evidence of increased inflammatory activity (e.g., increased circulating levels of inflammatory markers) (Kronfol et al., 1983; Irwin & Gillin, 1987; Maes et al., 1993; Anisman et al., 1999; Zorrilla et al., 2001). Much of the recent interest in the role of the immune system in depression has focused on increased inflammation associated with depression. Pro-inflammatory cytokines, including interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-alpha, are released by activated immune cells during the host response to pathogen invasion as well as in the context of tissue injury and psychosocial stress. These soluble factors appear to represent primary mediators of the communication between the immune system and the brain, and not only help orchestrate cellular responses to immune challenge, but also coordinate the behavioral changes that are necessary for recovery. During the course of immune challenge, the release of pro-inflammatory cytokines is usually transient and regulated by anti-inflammatory mechanisms. Consequently, the behavioral effects triggered by the activation of the inflammatory response develop as an adaptive, temporary and *controlled* reaction of the central nervous system (CNS) to immune signals. Nevertheless, when immune challenge becomes chronic and/or unregulated, as is observed in patients receiving chronic cytokine treatments or those exposed to chronic medical illness and/or stress, the behavioral effects of cytokines and the resultant inflammatory response may contribute to the development of clinically relevant behavioral symptoms and neuropsychiatric diseases, including major depression. These immune-based behavioral disorders, as well as the pathophysiological mechanisms involved will be discussed in this review along with relevant treatment implications.

## 2. Behavioral effects of cytokines

### 2.1. Sickness behavior

A rich database has been developed that substantiates the capacity of pro-inflammatory cytokines to induce, in addition to fever and activation of the hypothalamic–pituitary–adrenal (HPA) axis, a constellation of behavioral symptoms referred to as sickness behavior (Dantzer, 2001). Sickness behavior is typically associated with the behavioral changes seen in humans and laboratory animals suffering from microbial infections and includes depressive-like behavior, anhedonia, fatigue, psychomotor slowing, decreased appetite, sleep alterations and increased sensitivity to pain (Hart, 1988; Kent et al., 1992). Relevant to its mediation by pro-inflammatory cytokines, sickness behavior can be reliably reproduced by administration of pro-inflammatory cytokines separately or by treatment with cytokine-inducers, including endotoxin or lipopolysaccharide (LPS) or infectious agents such as *Salmonella typhi* and Bacille Calmette–Guerin (BCG), an attenuated form of *Mycobacterium bovis* (Yirmiya et al., 1999; Brydon et al., 2008; Harrison et al., 2009a, 2009b; O'Connor et al., 2009b). Supporting further the notion that pro-inflammatory cytokines are the key mediators of sickness behavior, administration of cytokine antagonists, such as IL-1 receptor antagonist (IL-1ra), or anti-inflammatory cytokines such as IL-10, can block the behavioral effects of treatment with IL-1 and/or LPS in laboratory rodents (Kent et al., 1992; Bluthé et al., 1995; Avitsur et al., 1997; Dantzer et al., 2008).

In terms of symptom expression, sickness behavior shares many overlapping features with symptoms of depression. In animals, depressive-like behavior, reflected by decreased sucrose consumption and increased immobility (or behavioral despair) in the forced-swimming test or tail-suspension test, can be induced by acute or chronic treatment with inflammatory challenges (Yirmiya, 1996; Anisman et al., 2005; Dantzer et al., 2008; Moreau et al., 2008). Interestingly, chronic (but not acute) treatment with antidepressants, including imipramine and tianeptine, can reduce, or even abolish, the depressive-like effects of LPS treatment in rats (Yirmiya, 1996; Castanon et al., 2001). With respect to the temporal aspects of symptom expression, sickness behavior develops rapidly after administration of LPS in animals and usually peaks 2–6 h post-treatment. Sickness behavior gradually resolves after 6 h and evolves into depressive-like behavior 24 h post-LPS (Frenois et al., 2007; Dantzer et al., 2008).

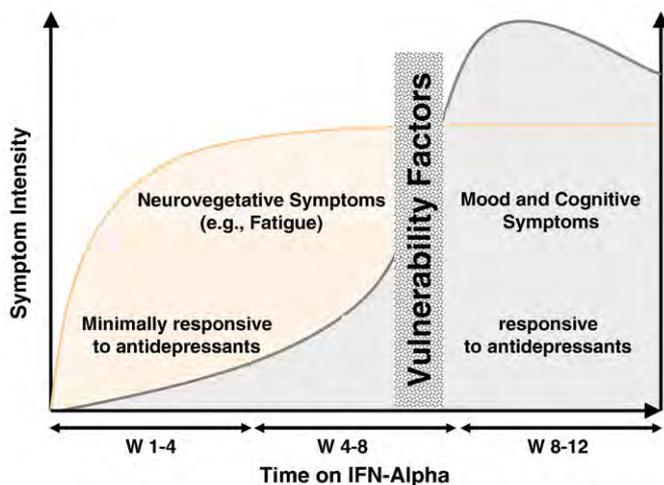
### 2.2. Cytokine-induced neuropsychiatric symptoms in clinical settings

The close resemblance of sickness behavior with symptoms of depression has led to the hypothesis that cytokines and inflammatory factors may be involved in the pathophysiology of neuropsychiatric disorders such as depression (Raison et al., 2006; Dantzer et al., 2008; Miller et al., 2009). Supporting this hypothesis is the high prevalence of psychiatric co-morbidity, including depression, in patients afflicted with chronic medical conditions associated with inflammation such as rheumatoid arthritis, cancer, infectious diseases, autoimmune disorders, and cardiovascular disease (Evans et al., 2005). In addition, there is a rich literature demonstrating elevated concentrations of inflammatory markers including pro-inflammatory cytokines, acute phase reactant, chemokines and adhesion molecules in the blood and cerebrospinal fluid of both medically ill and medically healthy patients with major depression (Zorrilla et al., 2001; Howren et al., 2009; Miller et al., 2009; Dowlati et al., 2010). Significant associations between markers of inflammation and individual neuropsychiatric symptoms including fatigue and cognitive dysfunction have also been described (Musselman et al., 2001; Meyers et al., 2005; Jehn et al., 2006; Lutgendorf et al., 2008; Bower et al., 2009). In depressed patients, TNF-alpha, IL-6, and C reactive protein (CRP) have been found to be the most reliably elevated across studies as demonstrated in three meta-analyses of the literature in this area (Zorrilla et al., 2001; Howren et al., 2009; Dowlati et al., 2010). Of note, increased inflammatory markers in depressed patients have also been associated with non-response to treatment with conventional antidepressant medications as well as early life stress, which is likewise associated with an antidepressant treatment non response (Sluzewska et al., 1997; Lanquillon et al., 2000; Nemeroff et al., 2003; Danese et al., 2007, 2008).

Strong support for the role of inflammatory processes in the pathophysiology of depression also comes from findings obtained in patients undergoing cytokine therapy. Because of their immunomodulatory effects, cytokines such as interferon (IFN)-alpha are currently used for the treatment of cancers and viral infections (e.g., chronic hepatitis C). Despite its clinical efficacy, IFN-alpha is frequently associated with significant psychiatric morbidity, notably in the form of the development of major depression in up to 45 percent of patients (Musselman et al., 2001; Capuron & Miller, 2004; Raison et al., 2005). To further assess the role of cytokines in the pathophysiology of depression, our group and others have used IFN-alpha administration in patients with malignant melanoma or chronic hepatitis C as a way to study cytokine effects on the brain and behavior in humans. IFN-alpha is an innate immune cytokine released early in viral infection that has both antiviral and antiproliferative activities (Roitt et al., 1998). In addition, IFN-alpha is a potent stimulator of pro-inflammatory cytokines, not only at the periphery but also within the CNS (Taylor & Grossberg, 1998; Raison et al., 2009). Relevant to this notion, recent data indicate that IFN-alpha treatment in patients with hepatitis C is associated with activation

of CNS inflammatory pathways as reflected by increased cerebrospinal fluid (CSF) concentrations of IFN- $\alpha$  along with elevated CSF concentrations of IL-6 and monocyte chemoattractant protein (MCP)-1 (Raison et al., 2009).

Dimensional analyses of symptom expression in IFN- $\alpha$  treated patients have shown that administration of the cytokine is responsible for the development of two behavioral syndromes (i.e., a neurovegetative syndrome versus a mood and cognitive syndrome) with distinct phenomenology and responsiveness to antidepressants (Capuron et al., 2002a; Capuron & Miller, 2004). The neurovegetative syndrome, characterized by symptoms of fatigue, psychomotor slowing, anorexia and altered sleep patterns, develops rapidly in almost every individual exposed to cytokines and persists for the duration of cytokine exposure. In contrast, the mood and cognitive syndrome, characterized by symptoms of depressed mood, anxiety, memory and attentional disturbances, usually appears at later stages of cytokine treatment (between the first and third months of IFN- $\alpha$  therapy), especially in patients with intrinsic vulnerability factors (Fig. 1). In addition, whereas IFN- $\alpha$  induced mood and cognitive symptoms appear to be responsive to antidepressant treatment, the neurovegetative symptoms (fatigue in particular) are antidepressant non-responsive (Capuron et al., 2002a; Capuron & Miller, 2004). With respect to the notion of vulnerability factors, the hyper-responsiveness of the stress response system, characterized by HPA axis hyper-reactivity, together with preexisting subclinical depressive traits were found to represent potent risk factors for the development of cytokine-induced depression (Capuron et al., 2003b, 2004; Raison et al., 2005). Recent advances have been made regarding the pathophysiological mechanisms underlying the mood/cognitive versus neurovegetative effects of cytokine therapy. As discussed in more detail below, impaired tryptophan/serotonin metabolism was found to be involved in the development of IFN- $\alpha$ -induced mood and cognitive symptoms (Capuron et al., 2002b, 2003a; Raison et al., 2010b). In contrast, neurovegetative symptoms, including fatigue and anergia, were found to correlate with changes in basal ganglia activity, possibly related to alterations in dopamine (DA) metabolism (Capuron et al., 2007b).



**Fig. 1.** Temporal evolution of the neuropsychiatric symptoms induced by chronic interferon- $\alpha$  therapy. Interferon (IFN)- $\alpha$  therapy induces two types of behavioral symptoms with differential time course and responsiveness to antidepressants. The neurovegetative symptoms (e.g., fatigue, anergia and psychomotor slowing) develop rapidly (as soon as week 1 [W1]) in almost every individuals exposed to cytokines and persist during the duration of IFN- $\alpha$  therapy. These symptoms are minimally responsive to antidepressant treatment. In contrast, the mood and cognitive symptoms (e.g., depressed mood, anxiety, irritability, memory and attentional disturbance) develop in vulnerable patients at later stages of IFN- $\alpha$  therapy (between weeks 8 and 12) and are highly responsive to antidepressant medication (Capuron et al., 2002a).

### 3. Immune to brain signaling

#### 3.1. How do cytokine signals access the brain?

Cytokines are relatively large molecules that do not freely pass through the blood brain barrier. Nevertheless, data indicate that cytokine signals are able to reach the brain through humoral, neural and cellular pathways (Fig. 2). These pathways are comprised of at least five non-exclusive mechanisms, including 1) passage of cytokines through leaky regions of the blood-brain barrier, including the choroid plexus and circumventricular organs, 2) active transport via saturable cytokine-specific transport molecules on brain endothelium, 3) activation of endothelial cells, responsible for the subsequent release of second messengers (e.g., prostaglandins [PGE2] and nitric oxide) within the brain parenchyma, 4) transmission of cytokine signals via afferent nerve fibers, such as the vagus nerve, and 5) entry into the brain parenchyma of peripherally activated monocytes (Watkins et al., 1995; Plotkin et al., 1996; Rivest et al., 2000; Konsman et al., 2002; Quan & Banks, 2007; D'Mello et al., 2009). Data have shown that activation of these specific mechanisms differentially mediates cytokine effects on the CNS. For instance, whereas subdiaphragmatic vagotomy was found to block the LPS-induced sickness behavior in rats, it did not affect the LPS-induced synthesis and release of pro-inflammatory cytokines at the periphery nor the pyrogenic effects of systemic injection of IL-1 $\beta$  (Bluthe et al., 1994; Dantzer et al., 1998; Luheshi et al., 2000).

#### 3.2. Cytokine network in the brain

Cytokines function as part of an integrated network, each of them inducing their own synthesis while also inducing the synthesis of other pro-inflammatory cytokines, including TNF- $\alpha$ , IL-1 and IL-6, in a "cascade" fashion (Taylor & Grossberg, 1998). Within the brain, there is a cytokine network consisting of cells, e.g., neurons, microglia and astrocytes, which are able to produce cytokines, express cytokine receptors and amplify cytokine signals (Rothwell et al., 1996; Haas & Schauenstein, 1997). This *neural substrate* of immune signals underlies the potent effects of peripheral pro-inflammatory cytokines on pathways involved in the pathophysiology of neuropsychiatric disorders, including the activation of the HPA axis and corticotropin-releasing hormone (CRH) and the alteration of the metabolism of key monoamines (e.g., serotonin, DA, norepinephrine) (Dantzer et al., 1999; Capuron & Miller, 2004; Raison et al., 2006; Capuron et al., 2007a, 2007b; Miller et al., 2009).

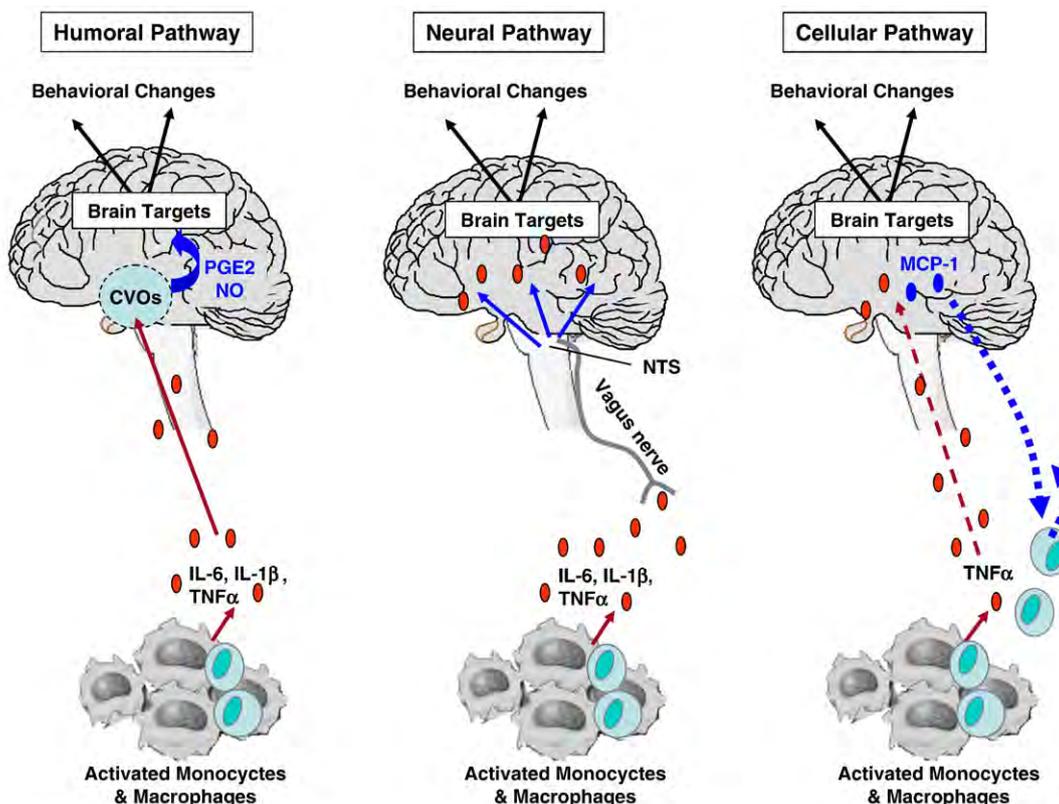
### 4. Pathophysiological mechanisms by which cytokines affect the brain

A number of pathways by which cytokines may influence behavior have been identified. These pathways include effects on neurotransmitter function, neuroendocrine activity, neural plasticity and alterations of brain circuitry (Fig. 3).

#### 4.1. Effects on neurotransmitters

##### 4.1.1. Serotonin

Probably the best studied neurotransmitter system as it relates to the effects of cytokines on the brain and behavior is serotonin. A number of studies in laboratory animals have indicated that acute exposure to a variety of cytokines and cytokine-inducers such as LPS can alter the turnover of serotonin in multiple brain regions (Dunn & Wang, 1995; Dunn et al., 1999; Anisman et al., 2005). Regarding the clinical literature, a compelling case can also be made that in the context of chronic exposure to cytokines, serotonin is involved. Indeed, data have demonstrated that the serotonin reuptake inhibitor, paroxetine, can significantly reduce depressive symptoms in the context of chronic administration of



**Fig. 2.** Communication pathways from the periphery to the brain. Different pathways by which cytokine signals access the brain have been identified. **A) Humoral pathway:** Pro-inflammatory cytokines released by activated monocytes and macrophages access the brain through leaky regions of the blood-brain barrier such as the choroid plexus and circumventricular organs (CVOs). Within the brain parenchyma, the activation of endothelial cells is responsible for the subsequent release of second messengers (e.g., prostaglandins [PGE2] and nitric oxide [NO]) that act on specific brain targets. **B) Neural pathway:** Pro-inflammatory cytokines released by activated monocytes and macrophages stimulate primary afferent nerve fibers in the vagus nerve. Sensory afferents of the vagus nerve relay information to brain areas through activation of the nucleus of the tractus solitarius (NTS) and area postrema. **C) Cellular pathway:** A cellular pathway has been recently described by which pro-inflammatory cytokines, notably TNF- $\alpha$ , are able to stimulate microglia to produce monocyte chemoattractant protein-1 (MCP-1), which in turn is responsible for the recruitment of monocytes into the brain (D'Mello et al., 2009). Abbreviations: interleukin-6: IL-6; interleukin-1 $\beta$ : IL-1 $\beta$ ; tumor-necrosis factor: TNF.

IFN- $\alpha$  (Musselman et al., 2001; Raison et al., 2007), and at least two studies have demonstrated that polymorphisms in the serotonin transporter are associated with the development of depression during IFN- $\alpha$  therapy (Bull et al., 2008; Lotrich et al., 2009). In addition, chronic IFN- $\alpha$  treatment leads to a downregulation of serotonin receptor 1A (Cai et al., 2005). Further relevant to serotonin, special attention has been paid to the role of the enzyme, indoleamine 2,3 dioxygenase (IDO) and the signaling molecule p38 mitogen-activated protein kinase (MAPK).

**4.1.1.1. Indoleamine 2,3 dioxygenase.** IDO can be stimulated by a number of cytokines alone or in combination including IFN- $\alpha$ , IFN- $\gamma$  and TNF- $\alpha$  through activation of a number of inflammatory signaling pathways such as signal transducer and activator of transcription 1a (STAT1a), interferon regulatory factor (IRF)-1, NF- $\kappa$ B and p38 MAPK (Fujigaki et al., 2006). When activated, IDO breaks down tryptophan (TRP), the primary amino acid precursor of serotonin, into kynurenine (KYN) (Schwarcz & Pellicciari, 2002). The breakdown of TRP is believed to contribute to reduced serotonin availability which is not only relevant for the regulation of T cell function but also for CNS serotonin synthesis (Schwarcz & Pellicciari, 2002; Dantzer et al., 2008). Indeed, acute depletion of dietary tryptophan has been shown to precipitate depressive symptoms in vulnerable populations of depressed subjects (Delgado et al., 1994). Consistent with the role of IDO in cytokine-induced depression, decreased TRP and increased KYN in the peripheral blood have been associated with the development of depression in patients administered IFN- $\alpha$  (Bonaccorso et al., 2002; Capuron et al., 2002b,

2003a). Moreover, blockade of IDO has been shown to inhibit the development of depressive-like behavior in mice treated with LPS or BCG (O'Connor et al., 2009a, 2009b).

It should be noted that in addition to depletion of TRP, the generation of KYN also appears to have important effects on neurotransmitter function and behavior (Wichers et al., 2005). For example, administration of KYN alone has been shown to induce depressive-like behavior in mice (O'Connor et al., 2009a). In addition, based on the differential expression of relevant metabolic enzymes, KYN is preferentially converted to kynurenic acid (KA) in astrocytes and quinolinic acid (QUIN) in microglia (Schwarcz & Pellicciari, 2002). Kynurenic acid has been shown to inhibit the release of glutamate, which, by extension, may inhibit the release of DA, whose release is regulated in part by glutamatergic activity (Borland & Michael, 2004). Indeed, intrastriatal administration of KA has been shown to dramatically reduce extracellular DA in the rat striatum (Wu et al., 2007). In contrast, QUIN, promotes glutamate release through activation of N-methyl-D-aspartate (NMDA) receptors (Schwarcz & Pellicciari, 2002). QUIN also induces oxidative stress, which in combination with glutamate release may contribute to CNS excitotoxicity (Rios & Santamaria, 1991; Schwarcz & Pellicciari, 2002; Muller & Schwarcz, 2007; McNally et al., 2008).

Data from patients treated with IFN- $\alpha$  indicate that the generation of KYN in the peripheral blood is associated with significant increases in KYN, QUIN and KA in the CSF (Raison et al., 2010b). Increases in CSF KYN and QUIN were in turn correlated with depression. Increased CSF QUIN and KYN were also correlated with CSF MCP-1, consistent with the notion that peripheral blood macrophages, which

are ~20 times more capable of converting KYN to QUIN than microglia, may be attracted to the brain during IFN- $\alpha$  administration and contribute to QUIN production (Guillemin & Brew, 2004; D'Mello et al., 2009; Raison et al., 2010b). Given the capacity of cytokines like IFN- $\alpha$  and cytokine inducers like LPS and BCG to activate IDO pathways, the generation of KYN, QUIN and KA may represent an especially unique aspect of the effects of cytokines and inflammation on behavior.

**4.1.1.2. p38 mitogen-activated protein kinase.** There has been increasing interest in the role of MAPK pathways including p38 in the impact of cytokines on neurotransmitter metabolism. For example, several studies using pharmacologic agonists and cytokines (IL-1 and TNF- $\alpha$ ) to stimulate p38 have shown that activation of p38 signaling pathways in vitro can up-regulate both the expression and activity of the membrane transporters for serotonin as well as norepinephrine in cell lines and rat brain synaptosome preparations (Zhu et al., 2005, 2006). Recently, this work has been extended in vivo with the demonstration that LPS-induced activation of p38 MAPK can upregulate serotonin transporter expression and activity in the hippocampus in association with increased extracellular clearance of serotonin (Zhu et al., 2010). Consistent with these findings is that activated p38 in peripheral blood mononuclear cells has been associated with decreased CSF concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in juvenile rhesus monkeys that were maternally abused as infants (Sanchez et al., 2007). Taken together with the influence of cytokines on serotonin synthesis (via effects on TRP), these data suggest that cytokines may exert a “double hit” on both monoamine synthesis and reuptake, thus contributing to reduced serotonin availability.

#### 4.1.2. Dopamine

Like with serotonin, cytokines have been shown to influence both the synthesis and reuptake of dopamine (as well as its release, as discussed above in relation to KA). For example, administration of species specific IFN- $\alpha$  to rats has been shown to decrease CNS concentrations of tetrahydrobiopterin (BH<sub>4</sub>) and DA in association with the stimulation of nitric oxide (NO) (Kitagami et al., 2003). Tetrahydrobiopterin is an important enzyme co-factor for tyrosine hydroxylase, which converts tyrosine to L-DOPA and is the rate limiting enzyme in DA synthesis. Tetrahydrobiopterin is also required for NO synthesis, and therefore increased NO generation is associated with increased BH<sub>4</sub> utilization (and thus decreased BH<sub>4</sub> to support tyrosine hydroxylase activity). Treatment with an inhibitor of NO synthase was found to reverse IFN- $\alpha$ 's inhibitory effects on brain concentrations of both BH<sub>4</sub> and DA (Kitagami et al., 2003). Activation of microglia is associated with increased NO production (Zielasek & Hartung, 1996), suggesting that cytokine influences on BH<sub>4</sub> via NO may be a common mechanism by which cytokines reduce DA availability in relevant brain regions. Like with the serotonin transporter, cytokine-induced activation of MAPK pathways has also been shown to upregulate the activity of the dopamine transporter (Moron et al., 2003).

#### 4.1.3. Glutamate/excitotoxicity

Another neurotransmitter pathway that is receiving increasing interest in the development and treatment of depression as well as the impact of cytokines on the brain and behavior is glutamate. When activated in the brain, cytokines and associated inflammatory mediators have been shown to stimulate the release of glutamate from glial elements and decrease glutamate reuptake, in part through downregulation of glutamate transporters (Pitt et al., 2003; Volterra & Meldolesi, 2005; Tilleux & Hermans, 2007; Ida et al., 2008). Of particular concern, excessive release of glutamate by astrocytes can access extrasynaptic NMDA receptors, which mediate excitotoxicity and decreased production of trophic factors including brain derived neurotrophic factor (BDNF) (Hardingham et al., 2002; Haydon &

Carmignoto, 2006). In addition to excessive glutamate, cytokines can also stimulate astrocytes and microglia to release reactive oxygen and nitrogen species that in combination with QUIN (see above) can amplify oxidative stress and further endanger relevant cell types including neurons and oligodendrocytes, which are especially vulnerable to oxidative damage (Rios & Santamaria, 1991; Schwarcz & Pellicciari, 2002; Buntinx et al., 2004; Matute et al., 2006; Thornton et al., 2006; Ida et al., 2008; Li et al., 2008; McTigue & Tripathi, 2008). These potential effects of cytokines and central inflammatory processes on glia may in turn contribute to the loss of glial elements including oligodendrocytes and astrocytes in multiple mood-relevant brain regions including the subgenual prefrontal cortex and amygdala. Loss of glial elements in these brain regions has emerged as a fundamental morphologic abnormality in major depression (Ongur et al., 1998; Hamidi et al., 2004; Rajkowska & Miguel-Hidalgo, 2007).

#### 4.2. Effects on neuroendocrine function

Alteration in the function of the HPA axis is a hallmark of neuropsychiatric disorders especially major depression (Pariante & Miller, 2001). Therefore, considerable attention has been paid to the impact of cytokines on HPA axis function. A rich literature has demonstrated that acute administration of cytokines and cytokine inducers can potently activate the HPA axis, consistent with the HPA axis hyperactivity that characterizes many depressed patients. For example, cytokines, especially when administered acutely, have been shown to stimulate the expression and release of CRH, adrenocorticotrophic hormone (ACTH) as well as cortisol, all of which have been found to be elevated in patients with major depression (Besedovsky & del Rey, 1996; Pariante & Miller, 2001; Pace et al., 2007). As noted above, acute activation of the HPA axis by the cytokine, IFN- $\alpha$ , has also been shown to predict the development of depressive symptoms in IFN- $\alpha$ -treated humans, likely related to the role of sensitized CRH pathways in the vulnerability to cytokine-induced depression (Capuron et al., 2003b). Nevertheless, in both laboratory animals and humans, chronic administration of cytokines or inflammatory stimuli is not associated with ongoing activation of the HPA axis response (Capuron et al., 2003b; Harbuz et al., 2003; Wichers et al., 2007). Instead, studies have shown that chronic cytokine exposure or chronic medical illness is associated with flattening of the diurnal cortisol curve and increased evening cortisol concentrations which have been associated with both adverse behavioral effects (depression and fatigue) as well as poor disease outcome in several medical disorders including cardiovascular disease and cancer (Sephton et al., 2000; Matthews et al., 2006; Raison et al., 2010a).

One mechanism by which chronic cytokine exposure may influence HPA axis function is through inhibitory effects on the receptor for the glucocorticoid, cortisol, the end product of HPA axis activation (Pace & Miller, 2009). By stimulating a number of relevant inflammatory signaling molecules including NF- $\kappa$ B, p38 MAPK and STAT5, cytokines have been shown to reduce the function of glucocorticoid receptors (GR) through disruption of GR translocation from the cytoplasm to nucleus as well as through nuclear protein-protein interactions which inhibit GR-DNA binding (Pace et al., 2007). Cytokines can also influence GR expression, leading to decreased GR alpha, the active form of the receptor, and increased GR beta, a relatively inert GR isoform (Pace et al., 2007). Decreased responsiveness to glucocorticoids (or glucocorticoid resistance) as manifested by increased cortisol concentrations following dexamethasone (DEX) administration in the DEX suppression test (DST) and the DEX-CRH test and decreased glucocorticoid-mediated inhibition of in vitro immune responses are well described in patients with major depression (Pariante & Miller, 2001). Of note, flattening of the cortisol slope has also been associated with nonsuppression on the DEX-CRH test in patients with breast cancer (Spiegel et al., 2006). Thus, cytokines have exhibited the capacity to replicate many of the typical HPA axis features associated with the development of major depression including altered glucocorticoid secretion and impaired GR function.

Given the fundamental role of endogenous glucocorticoids in inhibiting inflammatory responses, cytokine-induced alterations in HPA axis function and decreased GR function might serve to further exacerbate unrestrained inflammation.

#### 4.3. Effects on neural plasticity (neurogenesis)

Although under physiological conditions cytokines provide trophic support to neurons and enhance neuronal integrity, in the context of chronic stress, excessive cytokine production has been shown to lead to depressive-like behavior in part through their disruption of growth factor production and neurogenesis. Neurogenesis is believed to play a fundamental role in the maintenance of neural integrity, and reduced neurogenesis especially in the hippocampus is a hallmark of chronic exposure to stress in laboratory animals (Duman & Monteggia, 2006). Not only does chronic stress activate cytokine expression, in particular IL-1, in the hippocampus, but several studies have shown that blockade of IL-1 through the administration of IL-1ra or transplantation of IL-1ra secreting neural precursor cells or the use of IL-1 knockout mice reverses the reduced growth factor production (i.e. BDNF) and decreased neurogenesis that is associated with chronic stress (while also reversing stress-induced behavioral changes) (Ben Menachem-Zidon et al., 2008; Goshen et al., 2008; Koo & Duman, 2008). In vitro studies have suggested that the effects of IL-1 on neurogenesis appear to occur through activation of NF- $\kappa$ B signaling pathways (Koo & Duman, 2008), while in vivo studies indicate that endogenous glucocorticoids are also involved (Goshen et al., 2008).

#### 4.4. Effects on neurocircuitry

Neuroimaging studies have begun to reveal the neurocircuits that appear to be targeted by cytokines. Neurocircuits in both cortical and subcortical brain regions are involved including most notably the basal ganglia and the subgenual and dorsal aspects of the anterior cingulate cortex (ACC). The basal ganglia play an important role in motor activity and motivation, whereas the subgenual and dorsal ACC are implicated in depression (subgenual ACC) and anxiety, arousal and alarm (dorsal ACC), respectively (Alexander et al., 1990; Eisenberger & Lieberman, 2004; Lozano et al., 2008). Consistent with the notion that cytokines may preferentially target DA neurotransmission and ultimately the basal ganglia are data that IFN- $\alpha$  as well as *S. typhi* vaccination induce motor slowing which in IFN- $\alpha$ -treated patients is correlated with the development of both depression and fatigue (Brydon et al., 2008; Majer et al., 2008). In addition, neuroimaging studies have found that both IFN- $\alpha$  and *S. typhi* vaccination induce altered metabolic activity (as revealed by positron emission tomography) and blood flow (as measured by functional magnetic resonance imaging) in relevant basal ganglia nuclei including the nucleus accumbens, putamen, and substantia nigra (Capuron et al., 2007b; Brydon et al., 2008). In patients administered *S. typhi*, altered activity in the substantia nigra was correlated with peripheral blood IL-6 responses to vaccination (Brydon et al., 2008).

Administration of *S. typhi* has also been associated with increased activation of the subgenual ACC, which correlated with depressed mood (Harrison et al., 2009a). Of note, the subgenual ACC [Brodmann Area (BA) 25] is the target of successful attempts to restore normal mood in highly treatment resistant depressed patients (Lozano et al., 2008). Activation of the dorsal ACC (BA 24) has also been described in patients receiving IFN- $\alpha$  and in patients administered *S. typhi* (Capuron et al., 2005; Harrison et al., 2009a). Increased activity in the dorsal ACC has been associated with high-trait anxiety, neuroticism, obsessive compulsive disorder and bipolar disorder (Eisenberger & Lieberman, 2004), all of which are associated with increased anxiety and arousal. Interestingly, in a recent study, stress-induced inflammatory responses (peripheral blood soluble TNF receptor 2) were

associated with increased activity in the dorsal ACC, consistent with the notion that cytokines may preferentially target dorsal ACC circuits to increase arousal and alarm (Slavich et al., 2010). It has been suggested that by targeting the basal ganglia (which mediate motor activity and motivation) as well as the dorsal ACC, cytokines may be addressing competing survival priorities in a vulnerable, wounded or infected animal, which are to reduce activity to allow fighting of infection and wound healing while fostering hypervigilance to protect against future attack (Miller, 2008).

### 5. Sources of chronic inflammation

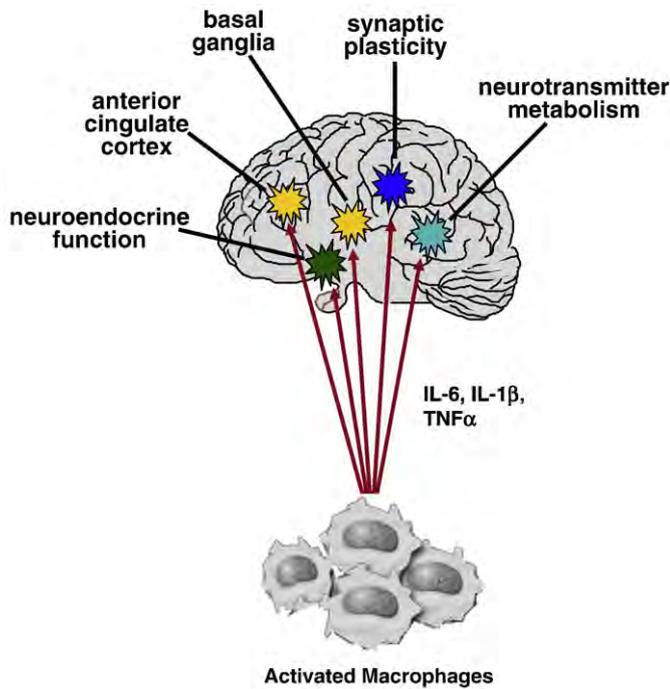
Chronic or non-resolving inflammation may originate from either pathophysiological (e.g., inflammatory diseases, immune-based disorders, T cell dysfunction) or non-pathological conditions including aging and obesity.

#### 5.1. T cell dysfunction

Recent advances in immunology have increasingly recognized the importance of T cell subsets in the regulation of inflammatory responses including the relative role of T regulatory cells (T reg) and T effector cells that produce IL-17 (T helper (Th)17 cells).

Interestingly, one of the first observations regarding the immune system in depression was that peripheral blood mononuclear cells from depressed patients exhibited impaired proliferation in response to the T cell mitogens, phytohemagglutinin and concanavalin A (Bartrop et al., 1977; Kronfol et al., 1983; Schleifer et al., 1983, 1984; Stein et al., 1991; Irwin & Miller, 2007; Irwin, 2008). Although the early findings were not always replicated, meta-analytic approaches to the literature in this area have reached the consensus that statistically reliable decreases in lymphocyte responses to T cell mitogens are apparent in depressed individuals (Zorrilla et al., 2001; Irwin & Miller, 2007). In vivo measures of cell-mediated immune function have also indicated decreased T cell activity in depressed patients including reduced skin responses to commonly encountered T cell-relevant antigens (Hickie et al., 1993; Sephton et al., 2009) as well as reduced T cell responses to varicella-zoster virus antigen ex vivo (Irwin et al., 1998).

The mechanisms of impaired T cell proliferation in depression in humans have yet to be established, however, a number of possibilities have been considered. Flow cytometric assessments have revealed that CD4+ T cells from depressed patients exhibit evidence of accelerated spontaneous apoptosis as well as increased expression of the receptor for Fas (CD95), which mediates apoptotic signaling by Fas-ligand (Eilat et al., 1999; Ivanova et al., 2007; Szuster-Ciesielska et al., 2008). T cell proliferation in patients with depression may also be disrupted by inflammatory cytokines, such as TNF- $\alpha$ , which has been shown to be elevated in depressed patients (Miller et al., 2009). Both in vitro and in vivo studies have demonstrated that chronic exposure of T cells to TNF- $\alpha$  decreases T cell proliferation and cytokine production (Cope et al., 1994, 1997; Lee et al., 2008). The effects of TNF- $\alpha$  on T cell function can be reversed by injections of monoclonal antibodies to TNF- $\alpha$  (Cope et al., 1994; Bayry et al., 2007; Lee et al., 2008), and are related in part to disruption of signaling through the T cell receptor (Cope et al., 1994, 1997; Lee et al., 2008). It should be noted that although glucocorticoids are well known to suppress T cell function, no relationship has been found between increased cortisol secretion and decreased in vitro proliferative responses to T cell mitogens in depressed patients (Kronfol et al., 1986; Raison & Miller, 2003). Indeed, if anything, peripheral blood lymphocytes from patients with depression exhibit decreased responsiveness to the in vitro inhibitory effects of glucocorticoids on T cell proliferation and the in vivo effects of glucocorticoids on T cell redistribution (Pariante & Miller, 2001; Bauer et al., 2002, 2003; Raison & Miller, 2003). These findings of glucocorticoid resistance in T cells are consistent with reduced GR function as described above.



**Fig. 3.** Pathways to cytokine-induced pathology. Once cytokine signals reach the brain, they can interact with virtually every pathophysiologic domain relevant to mood regulation. These include effects on neurocircuits that regulate motor activity and motivation (basal ganglia) and mood, anxiety, arousal and alarm (anterior cingulate cortex); effects on growth factors such as brain derived neurotrophic factor, neurogenesis and ultimately synaptic plasticity; effects on the metabolism of monoamine neurotransmitters such as serotonin and dopamine as well as excitatory amino acid neurotransmitters such as glutamate; and effects on neuroendocrine function leading to glucocorticoid resistance and altered glucocorticoid secretion. Abbreviations: interleukin-6: IL-6; interleukin-1β: IL-1β; tumor-necrosis factor: TNF.

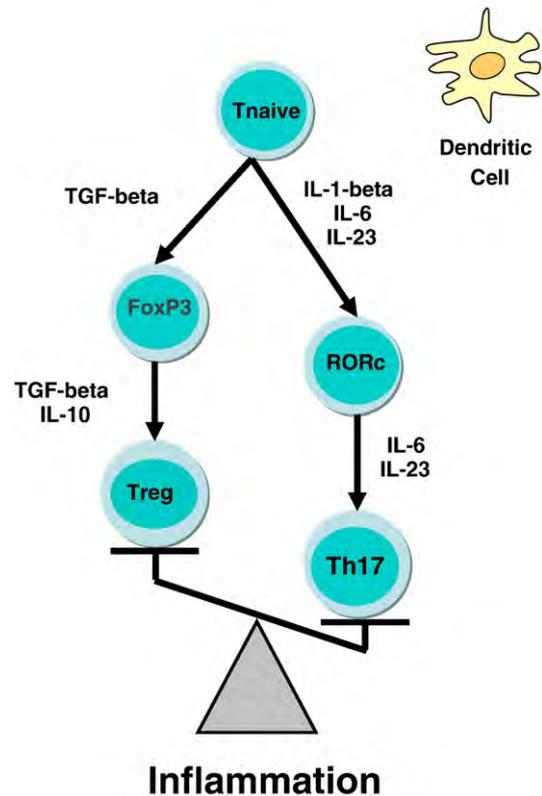
Despite both functional and genetic data indicating that alterations in T cells may be involved in depression (Wong et al., 2008), few studies have directly examined the relative expression and function of relevant T cell subsets beyond the characterization of CD4+ and CD8+ T cell phenotypes and mitogen-induced T cell proliferation (Zorrilla et al., 2001; Irwin & Miller, 2007). Given recent developments in immunology regarding the role of specific T cell subsets in the regulation of inflammation, the relative expression and function of T cell subsets including T reg cells and certain T effector cells including Th17 cells as well as Th1 and Th2 cells are of special relevance.

Most studies to date have imputed the function of relevant T cell subsets through the measurement of peripheral blood concentrations of cytokines that are regulated by these cell subsets (although it is recognized that many of these cytokines can be produced by multiple cell types other than T cells). Based on the available data, the findings in this area have been somewhat contradictory with some studies supporting evidence of increased Th1 cell activity (e.g. increased IFN-gamma) and others supporting increased Th2 cell activity (e.g. increased IL-4) (Schwarz et al., 2001; Myint et al., 2005; Pavon et al., 2006; Kim et al., 2007; Song et al., 2009). Of relevance to T reg, reduced IL-10 and transforming growth factor (TGF)-beta as well as an increased IL-6/IL-10 ratio have been found in depressed patients and are believed to be consistent with reduced T reg expression and/or function (Sutcliffe et al., 2007; Dhabhar et al., 2009). Of note, 2 studies have directly examined CD4+CD25+ T reg expression in depression. One study found decreased T reg percentage in association with reduced IL-10 and TGF-beta in depressed patients versus controls (Li et al., 2010b), and a second study reported that antidepressant treatment led to increased CD4+CD25+ T reg percentage, which was associated with decreased IL-1-beta (Himmerich et al., 2010). These results support the hypothesis that CD4+CD25+ regulatory T cells are

decreased in depressed patients, and given the role of T reg in reducing inflammatory responses, may contribute to increased inflammation in certain depressed individuals. Relevant to increased inflammation in depression, Th1 cells have long been identified as producers of pro-inflammatory mediators, such as TNF-alpha, and other contributors to both autoimmune and inflammatory disorders (Damsker et al., 2010). More recently however, T cells that produce IL-17 (Th17 cells) have been recognized as a distinct, highly pro-inflammatory T cell subset that may play an even more important role in inflammatory disease (Acosta-Rodriguez et al., 2007; Annunziato et al., 2007; Wilson et al., 2007; Tesmer et al., 2008; Damsker et al., 2010). In conjunction with IL-6 and IL-23, IL-1-beta is the most effective inducer of IL-17 expression in naive T cells in humans (Boissier et al., 2008). Based on these developments regarding the regulation of inflammation by T reg and Th17 cell subsets, examination of the hypothesis that high inflammation in patients with major depression is a result of increased Th17 activity in conjunction with reduced T reg function warrants further consideration (Fig. 4).

### 5.2. Non-pathological conditions: Normal aging and obesity

Normal aging is a situation characterized by a chronic low-grade inflammatory state, with an over-expression of circulating inflammatory factors, including pro-inflammatory cytokines, to the detriment of anti-inflammatory factors (Fagiolo et al., 1992, 1993). While the clear origin of chronic inflammation in aging remains to be elucidated, several



**Fig. 4.** An inflammatory imbalance of T cell subsets. Chronic inflammation may be maintained as the result of a preferential differentiation of T cell subsets toward a T helper (Th17) phenotype at the cost of T regulatory cell (T reg) development. Exposure to cytokines derived from dendritic cells and other immune cell types including the proinflammatory cytokines, IL-1β and IL-6, in conjunction with IL-23, increases the expression of the transcription factor, retinoid-related orphan receptor (ROR)c, which ultimately drives differentiation of the naïve T cell to the highly proinflammatory Th17 cell subset. In contrast, the anti-inflammatory cytokines TGF-beta and IL-10 promote the development of the counter-regulatory, anti-inflammatory T regulatory cell subset. Abbreviations: FoxP3: Forkhead box P3; interleukin-6: IL-6; interleukin-1β: IL-1β; interleukin-10: IL-10; transforming growth factor: TGF.

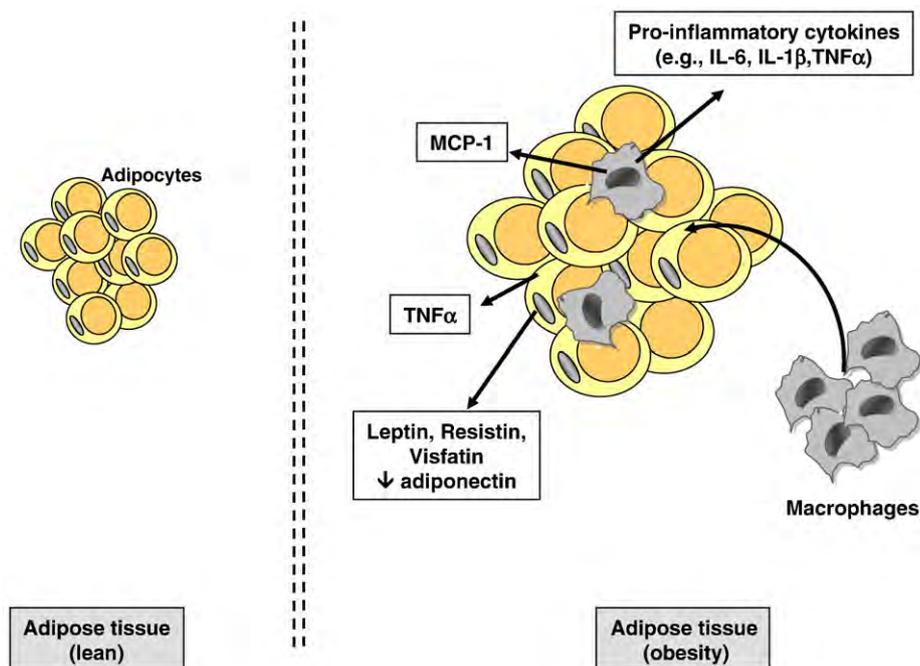
possibilities including immunosenescence-related dysregulation, deficient antioxidant defenses, and impaired pro- versus anti-inflammatory regulatory mechanisms may be involved. Within the brain, this inflammatory characteristic of aging, referred to as *inflammaging* (Franceschi et al., 2000, 2007), manifests primarily by the chronic activation of perivascular and parenchymal macrophages/microglia expressing pro-inflammatory cytokines, while the number of astrocytes increases (Floyd, 1999; Ye & Johnson, 1999; Akiyama et al., 2000). This condition is accompanied by an increase in the brain production of reactive oxygen species (ROS), leading to greater susceptibility to neuronal damage and death (Coyle & Puttfarcken, 1993). Moreover, recent data suggest that aging represents a typical ‘priming’ condition for microglia cells, which become more reactive to noxious stimuli and immune challenge (Dilger & Johnson, 2008). More specifically, it was found in mice that aging was associated with increased markers of activated or primed microglia together with increased inflammation, and that, upon subsequent immune stimulation with LPS administered peripherally, primed microglial cells were responsible for the overproduction of pro-inflammatory cytokines within the CNS (Godbout et al., 2005; Dilger & Johnson, 2008). In terms of behavioral outcomes, this state was associated with an exacerbation of sickness behavior and cognitive alterations following peripheral or central administration of LPS to aged mice (Godbout et al., 2005; Chen et al., 2008; Henry et al., 2009).

Similar to aging, chronic inflammation is a fundamental characteristic of obesity. Obesity is characterized by an excessive accumulation of fat and its diagnosis involves the measurement of the body mass index (BMI), which is calculated by the ratio of the person's weight (kg) divided by the height (in m<sup>2</sup>). The BMI is considered as one of the best clinical indices of adiposity, with differential severity ranging from overweight to severe and morbid obesity. Obesity is a chronic condition which is associated with low-grade inflammatory processes, with increased circulating levels of acute phase proteins (CRP in particular) and pro-inflammatory cytokines being observed in both adult and younger obese subjects (Bastard et al., 1999; Wellen & Hotamisligil, 2003). Part of systemic inflammation in obesity originates from adipose

tissue in which macrophages accumulate and potentially secrete inflammatory factors (Bastard et al., 1999; Wellen & Hotamisligil, 2003; Clement et al., 2004) (Fig. 5). Interestingly, weight loss significantly improves the inflammatory profile of obese subjects (e.g., decreased pro-inflammatory factors and increased anti-inflammatory molecules) and regulate inflammation-related genes in white adipose tissue (Bastard et al., 2000; Clement et al., 2004; Canello et al., 2005; Forsythe et al., 2008). Recent experimental data show evidence of inflammatory processes (ROS generation, elevated PGE2 levels, increased cyclooxygenase (COX)-2 expression, increased pro-inflammatory cytokines) in several brain areas, including the cortex and hippocampus, of animals fed a high-fat diet known to induce obesity (De Souza et al., 2005; Zhang et al., 2005). In addition, recent findings suggest that high-fat diet-related chronic inflammation may participate in the development of obesity through alteration in leptin and insulin signaling in the hypothalamus (Thaler & Schwartz, 2010). Moreover, consistent with the notion of priming, obesity was found to be associated with an increased reactivity of microglial cells under basal conditions and in response to immune challenge (Bilbo & Tsang, 2010). More specifically, it was shown that microglia were activated in the hippocampus of pups born from diet-induced obese female rats at birth, and that, at weaning and in adulthood, these same rats exhibited higher LPS-induced pro-inflammatory cytokine expression in the periphery and hippocampus in comparison to controls (Bilbo & Tsang, 2010). Finally, in nonhuman-primates, increased pro-inflammatory cytokines and markers of activated microglia were measured in the hypothalamus of third-trimester fetuses of high-fat diet fed mothers (Grayson et al., 2010).

### 5.3. Relevance for vulnerability to neuropsychiatric symptoms

The prevalence of behavioral symptoms, including depression and cognitive dysfunction, is particularly elevated in the elderly and obese subjects. Given the potential role of inflammation in psychopathology, it is thus highly possible that chronically activated inflammatory signals in aging and/or obesity, although more subtle and expressed at a lower grade, may contribute to an increased vulnerability to neuropsychiatric



**Fig. 5.** Obesity-related chronic inflammation. In obesity, fat accumulation leads to the development of chronic low grade inflammation. This systemic inflammation originates primarily from the adipose tissue in which macrophages accumulate and secrete pro-inflammatory cytokines and monocyte chemoattractant protein-1 (MCP-1), which in turn increases macrophage infiltration. Adipocytes in obesity are also able to secrete inflammatory factors, including tumor necrosis factor (TNF)-alpha and adipokines and related hormones (e.g., increased secretion of leptin, resistin and visfatin and decreased secretion of adiponectin) which also contribute to non-resolving inflammation.

disorders. This hypothesis is supported by recent clinical findings obtained in our group indicating that activated inflammatory processes, in conjunction with poor antioxidant status and altered tryptophan metabolism, were associated with reduced quality of life in the elderly (Capuron et al., 2009). Consistent with these findings, data obtained in patients with the metabolic syndrome indicate that inflammation is one major determinant of the higher prevalence of depressive symptoms in this patient population (Capuron et al., 2008). With respect to obesity, a recent study by our group has shown that adiposity in a sample of obese women is associated with increased concentrations of inflammatory markers (IL-6, CRP and adipokines) that correlate with scores on the depression and anxiety aspects of neuroticism, with higher inflammation predicting higher anxiety and depression (Capuron et al., 2010). Interestingly, and as documented by other groups, surgery-induced weight loss was associated with reduced inflammation (Cancello et al., 2005; Emery et al., 2007), which was associated with significant improvement in emotional status (Capuron et al., 2010). Regarding cognitive dysfunction, similar associations have been documented between inflammatory status and cognitive performance/decline among overweight and obese women (Sweat et al., 2008) and aged individuals with the metabolic syndrome (Yaffe et al., 2004). These findings are consistent with experimental data indicating concomitant increases in brain inflammation and behavioral alterations in aged laboratory animals (Godbout & Johnson, 2009; Laye, 2010) or in animals with diet-induced obesity (Pistell et al., 2010). Interestingly, in this regard, it was found that lifelong caloric restriction in aged rats was associated with reduced secretion of inflammatory markers from adipose tissue together with higher physical performance scores in contrast to lifelong ad-libitum feeding, which was associated with increased inflammation and significant decline in physical performance (You et al., 2007). Altogether, these data suggest that chronic low-grade inflammation may play a role in the increased vulnerability to neuropsychiatric disorders in the elderly or obese subjects. Given the growing elderly population and increasing prevalence of overweight and obesity in modern societies, strategies to regulate chronic inflammatory processes in these conditions and to prevent inflammation-related neuropsychiatric disturbances may appear particularly relevant and urgently required.

## 6. Translational implications

Given the vast knowledge base that has been elaborated regarding the capacity of inflammatory cytokines to influence behavior as well as the data detailing the potential mechanisms involved, there is a wide array of potential pharmacological and behavioral targets that may be relevant for the development of new treatments or prevention strategies for neuropsychiatric disorders including depression.

### 6.1. Pharmacological targets

Probably the most obvious targets for pharmacologic intervention are the cytokines themselves and their signaling pathways. Biologic therapies, which are approved for use in the United States and Europe, that inhibit TNF- $\alpha$  and IL-1 have already been extensively studied in autoimmune and inflammatory disorders, and drugs which target a limited number of inflammatory signaling pathways [e.g., COX 1 and 2] are readily available or are in development. Data from the use of anti-cytokine therapies have already indicated an impact on depressed mood. For example in a large double blind placebo-controlled trial in patients with psoriasis, patients who received the TNF- $\alpha$  antagonist, etanercept, showed significant improvement in depressive symptoms that was independent of changes in symptoms associated with disease activity (e.g. skin lesions and joint pain) (Tyring et al., 2006). In addition, in medically healthy patients with major depression, the COX-2 inhibitor, celecoxib, was shown to significantly enhance antidepressant efficacy of the norepinephrine reuptake inhibitor, reboxetine, in a small

double blind placebo-controlled trial (Muller et al., 2006). Albeit limited, these data suggest that targeting cytokines or their signaling pathways may have antidepressant activity. However, no study has specifically examined depressed patients with increased inflammatory markers and/or patients who may be at special risk for depression with increased inflammation including patients who are treatment resistant, obese and/or have a history of childhood maltreatment. Moreover, there is no data on the potential efficacy of antagonists of other relevant cytokine signaling pathways that appear to be especially germane to the mechanisms by which cytokines influence neurotransmitter metabolism, neuroendocrine function and synaptic plasticity including p38 MAPK and NF- $\kappa$ B. Finally, chemokines such as MCP-1, which can attract monocytes to multiple tissue sites including the brain where they can perpetuate inflammatory responses (D'Mello et al., 2009), are another class of target that may have unique applicability to behavioral disorders associated with increased inflammation.

Studies in both laboratory animals and humans also provide strong evidence for antagonizing IDO and the kynurenine pathway. Indeed, the IDO antagonist, 1-methyl tryptophan, has shown efficacy in animal models of sickness behavior as a consequence of LPS or BCG administration (O'Connor et al., 2009a, 2009b). Given the additional role of IDO and TRP depletion in inhibiting T cell function, there has been interest in IDO inhibitors to improve T cell activity in inflammatory states and cancer, thus indicating broad interest in the development of pharmacologic agents that target IDO (Johnson et al., 2009). Efforts in immunology that also may be relevant to immune-based behavioral disorders are pharmacologic strategies that target IL-17 or Th17 cells through the inhibition of cytokines or transcription factors which promote Th17 differentiation including IL-23 and retinoic acid receptor (RAR)-related orphan receptor C (RORc) (Boissier et al., 2008; Tesmer et al., 2008). Such mutual interests in the development of pharmacologic agents relevant to immunobiology and neurobiology underline the opportunities for cross-fertilization among disciplines that are presented by brain-immune system interactions.

Finally, there is a considerable interest in drugs that antagonize glutamate for the treatment of depression. For example, administration of the glutamate (NMDA) receptor antagonist, ketamine, has led to rapid and dramatic improvements in mood in patients with treatment resistant depression (aan het Rot et al., 2010). Studies in animals suggest that these effects may result from the development of new synapses in the brain as result of activation of the enzyme mTOR (Li et al., 2010a). Interestingly, mTOR has been shown to inhibit NF- $\kappa$ B (Weichhart et al., 2008). Thus glutamate antagonists may not only reduce glutamate-mediated excitotoxicity as a result of cytokine-induced effects on glial glutamate reuptake and release but also may serve to inhibit inflammatory responses through effects on NF- $\kappa$ B.

### 6.2. Non-pharmacological interventions

Given the epidemic of obesity in modern society, it is apparent that the relationship among depression, obesity and inflammation warrants serious attention. Treatments focused on weight loss including dietary modifications and exercise are clearly indicated both as part of the treatment of depression as well as its prevention. In addition, in the context of the immunomodulatory and anti-inflammatory effects of specific nutritional factors, including antioxidants and polyunsaturated fatty acids (omega-3 fatty acids in particular) (Laye, 2010; Su et al., 2010), the possibility to prevent or to modulate neuropsychiatric symptomatology in a context of chronic low-grade inflammation using nutritional interventions is an important consideration. Finally, given data in laboratory animals and humans that stress can activate the inflammatory response through stimulation of sympathetic pathways (in conjunction with parasympathetic withdrawal) (Miller et al., 2009), behavioral interventions focused on stress management and coping as

well as therapies that modulate sympathetic/parasympathetic tone (e.g. meditation and yoga) should also be considered.

## 7. Conclusions

Brain-immune system interactions have opened up new vistas regarding the treatment and prevention of behavioral disorders. Given the interest in inflammation as a common mechanism of multiple diseases including cardiovascular disease, diabetes and cancer, the role of inflammation in neuropsychiatric diseases such as depression puts the neurosciences and psychiatry in lock step with other medical disciplines in identifying and targeting immune relevant molecules and pathways for the treatment of disease. Depression has received the greatest amount of attention to date. Nevertheless, in light of the impact of cytokines on neurotransmitter systems and neurocircuitry relevant to a broader spectrum of neuropsychiatric diseases (e.g., anxiety disorders, personality disorders, and neurodegenerative diseases such as Parkinson's and Alzheimer's disease), it is likely that the importance of brain-immune system interactions may have wide applicability for the development of novel immune-based therapeutics for many neuropsychiatric illnesses.

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