

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression

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Recognition that inflammation may represent a common mechanism of disease has been extended to include neuropsychiatric disorders including major depression. Patients with major depression have been found to exhibit increased peripheral blood inflammatory biomarkers, including inflammatory cytokines, which have been shown to access the brain and interact with virtually every pathophysiologic domain known to be involved in depression, including neurotransmitter metabolism, neuroendocrine function, and neural plasticity. Indeed, activation of inflammatory pathways within the brain is believed to contribute to a confluence of decreased neurotrophic support and altered glutamate release/reuptake, as well as oxidative stress, leading to excitotoxicity and loss of glial elements, consistent with neuropathologic findings that characterize depressive disorders. Further instantiating the link between inflammation and depression are data demonstrating that psychosocial stress, a well-known precipitant of mood disorders, is capable of stimulating inflammatory signaling molecules, including nuclear factor kappa B, in part, through activation of sympathetic nervous system outflow pathways. Interestingly, depressed patients with increased inflammatory biomarkers have been found to be more likely to exhibit treatment resistance, and in several studies, antidepressant therapy has been associated with decreased inflammatory responses. Finally, preliminary data from patients with inflammatory disorders, as well as medically healthy depressed patients, suggest that inhibiting proinflammatory cytokines or their signaling pathways may improve depressed mood and increase treatment response to conventional antidepressant medication. Translational implications of these findings include the unique opportunity to identify relevant patient populations, apply immune-targeted therapies, and monitor therapeutic efficacy at the level of the immune system in addition to behavior.

Key Words: Cytokines, depression, excitotoxicity, hypothalamic-pituitary-adrenal axis, inflammation, monoamines, stress

Major depression is a common and sometimes fatal disorder that is a leading cause of disability worldwide (1). Available antidepressant medications, which largely target monoamine pathways, are effective; however, more than 30% of depressed patients fail to achieve remission despite multiple treatment trials (2). Thus, there is a pressing need to identify novel pathophysiologic pathways relevant to depression that 1) reveal neurobiological targets for the development of new medications and 2) elucidate related biomarkers for the identification and monitoring of potentially responsive patients. One promising development in this regard is the emergence of inflammation as a common mechanism of disease. Indeed, numerous studies have demonstrated a clear relationship between inflammation and the development of cardiovascular disease, diabetes, and cancer (3,4). Mounting data indicate that inflammation may also play a role in neuropsychiatric diseases, including major depression. Given the accelerating development of biomarkers and treatments focused on the inflammatory response, there is tremendous promise that these advances, in addition to their relevance to general medicine, may have unique applications in psychiatry.

Evidence for a Cytokine Basis for Major Depression

When compared with nondepressed individuals, both medically ill and medically healthy patients with major depression

have been found to exhibit all of the cardinal features of inflammation, including elevations in relevant inflammatory cytokines and their soluble receptors in peripheral blood and cerebrospinal fluid (CSF), as well as elevations in peripheral blood concentrations of acute phase proteins, chemokines, adhesion molecules, and inflammatory mediators such as prostaglandins (5,6). Associations between inflammatory markers and individual depressive symptoms such as fatigue, cognitive dysfunction, and impaired sleep have also been described (7-9). For example, both dysregulated sleep in depressed patients and sleep deprivation have been associated with increased interleukin (IL)-6, as well as activation of nuclear factor kappa B (NF- κ B), a primary transcription factor in the initiation of the inflammatory response (8,10). Although much of the interest in inflammation and depression has been focused on cytokines, which mediate the innate immune response, including IL-1, tumor necrosis factor (TNF)-alpha, and IL-6, which appears to be one of the most reliable peripheral biomarkers in major depression (6,11), findings of increased markers of T cell activation (e.g., soluble IL-2 receptor) in depressed patients raises the specter that both acquired (e.g., T and B cell) and innate (e.g., macrophage) immune responses may be involved (11). Nevertheless, in contradistinction to the prominence of depression following administration of innate immune cytokines such as interferon (IFN)-alpha to humans (12,13), administration of the T cell cytokine, IL-2, is not uncommonly associated with profound changes in mental status including psychosis, delirium, and agitation (14).

In addition to correlative data linking inflammatory markers with depressive symptoms, several lines of evidence demonstrate that both acute and chronic administration of cytokines (or cytokine inducers such as lipopolysaccharide [LPS] or vaccination) can cause behavioral symptoms that overlap with those found in major depression. For example, normal volunteers injected with LPS exhibited acute increases in symptoms of depression and anxiety (15), and administration of a *Salmonella typhi* vaccine to healthy individuals produced depressed mood, fatigue, mental confusion, and psychomotor slowing (16). In

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Received October 23, 2008; revised November 26, 2008; accepted November 26, 2008.

both cases, symptom severity correlated with increases in peripheral blood cytokine concentrations. These data in humans are consistent with a large literature in laboratory animals demonstrating that cytokines and cytokine inducers can lead to a host of behavioral changes overlapping with those found in depression, including anhedonia, decreased activity, cognitive dysfunction, and altered sleep (17). Long-term exposure to cytokines also has been shown to lead to marked behavioral alterations in humans. For example, 20% to 50% of patients receiving chronic IFN- α therapy for the treatment of infectious diseases or cancer develop clinically significant depression (12,13). Of note, depressive syndromes induced by IFN- α exhibit considerable overlap with idiopathic major depression and like idiopathic major depression, respond to conventional antidepressant medication (12,13).

Finally, several studies in humans suggest that immune-targeted therapies may have clinical benefit. For example, acetylsalicylic acid (which blocks both cyclooxygenase-1 and 2 and the production of prostaglandins) when added to fluoxetine led to increased remission rates in an open-label study of depressed patients previously nonresponsive to fluoxetine alone (18). Similarly, medically healthy depressed patients who received the selective cyclooxygenase-2 inhibitor, celecoxib, in combination with reboxetine showed greater symptomatic improvement versus patients randomized to reboxetine plus placebo (19). Antidepressant activity of anti-inflammatory therapy has also been observed in patients with autoimmune and inflammatory disorders. For example, in a large double-blind, placebo-controlled trial of the TNF- α antagonist, etanercept, for the treatment of psoriasis, participants who received etanercept exhibited significant improvement in depressive symptoms compared with placebo-treated subjects, an effect that was independent of improvement in disease activity (20). These findings are consistent with a vast literature in laboratory animals indicating that cytokine antagonists or anti-inflammatory agents can block the development of behavioral changes following immune activation (17). Moreover, these data are consistent with findings that TNF- α receptor knockout (KO) mice exhibit an antidepressant phenotype (21).

Mechanisms and Mediators of Cytokine-Induced Behavioral Change

Studies have addressed fundamental pathways by which cytokines may contribute to depression. In general, cytokines have been shown to access the brain and interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function, and neural plasticity (5,17). However, it remains unclear whether activation of inflammatory pathways in the central nervous system (CNS) during depression originate primarily in the periphery (e.g., as a function of overt or nascent medical illness or psychological stress—see below) and/or whether stress or other yet to be identified processes (e.g., vascular insults in late life depression) induce inflammatory responses directly within the brain. Such unresolved issues will have a major impact on whether relevant therapeutic targeting will require activity within the brain to be effective. Nevertheless, given that cytokines are relatively large polypeptides (~15–25 kD), experiments have been conducted in laboratory animals to determine how peripheral cytokine signals reach the brain. Pathways that have been elucidated include 1) cytokine passage through leaky regions in the blood-brain-barrier, 2) active transport via saturable transport molecules, 3) activation of endothelial cells and other cell types

(including perivascular macrophages) lining the cerebral vasculature (which then produce cytokines and other inflammatory mediators), and 4) binding to cytokine receptors associated with peripheral afferent nerve fibers (e.g., the vagus nerve) that then relay cytokine signals to relevant brain regions including the nucleus of the solitary tract and hypothalamus (17,22). The inflammatory signaling molecule, NF- κ B, has been found to be an essential mediator at the blood-brain interface that communicates peripheral inflammatory signals to the CNS. Central blockade of NF- κ B in rodents inhibits c-fos activation in multiple brain regions following peripheral administration of IL-1 beta, while also inhibiting IL-1 beta and LPS-induced behavioral changes (23,24).

Data indicate that peripheral cytokine signals can also access the brain in humans and activate relevant cell types that serve to amplify central inflammatory responses. For example, peripheral administration of IFN- α to patients with hepatitis C led to increased CSF IFN- α , which correlated with increased CSF concentrations of IL-6 and the chemokine, monocyte chemoattractant protein (MCP)-1 (25). Monocyte chemoattractant protein-1, which is released by astrocytes and endothelial cells, has been found to prime microglia to produce IL-1 and TNF- α in response to LPS in rodents, an effect that is reduced in MCP-1 KO animals (26). Of note, microglia are a primary source of proinflammatory cytokines in the brain. Indeed, administration of the tetracycline agent, minocycline, which has been shown to inhibit LPS-induced cytokine production by microglia *in vitro*, attenuates both microglial activation and central cytokine induction, as well as behavioral changes following peripheral administration of LPS to mice (27,28). These effects may be mediated, in part, through minocycline's capacity to inhibit NF- κ B (29).

Cytokine Effects on Neurotransmitter Metabolism

Once cytokine signals reach the brain, they have the capacity to influence the synthesis, release, and reuptake of mood-relevant neurotransmitters including the monoamines (30). There is a rich animal literature demonstrating that administration of cytokines or cytokine inducers can profoundly affect the metabolism of serotonin, norepinephrine, and dopamine (DA) (31,32). Moreover, drugs (serotonin and norepinephrine reuptake inhibitors) and gene polymorphisms (serotonin transporter gene) that affect monoamine metabolism have been shown to influence the development of cytokine-induced depressive-like behavior in laboratory animals and humans (12,33,34). Regarding the mechanisms involved, much attention has been focused on the enzyme, indoleamine 2,3 dioxygenase (IDO). Through stimulation of multiple inflammatory signaling pathways, including signal transducer and activator of transcription 1a (STAT1a), interferon regulatory factor (IRF)-1, NF- κ B, and p38 mitogen-activated protein kinase (MAPK), cytokines can activate IDO (35). Indoleamine 2,3 dioxygenase, in turn, breaks down tryptophan (TRP), the primary amino acid precursor of serotonin, into kynurenine (KYN). The breakdown of TRP is believed to contribute to reduced serotonin availability (17,36) (Figure 1). Supportive of 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- α (37). Moreover, blockade of IDO has been shown to inhibit the development of LPS-induced depressive-like behavior in mice (28). Of note, cytokine-induced IDO

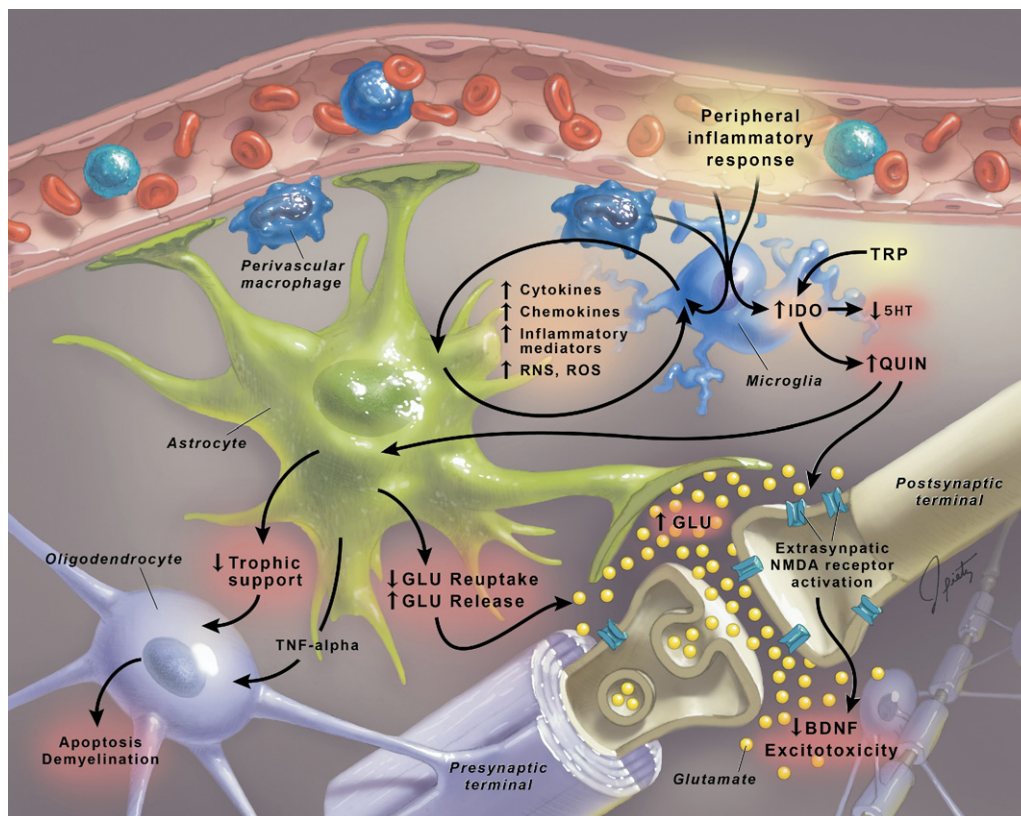


Figure 1. Effects of the CNS inflammatory cascade on neural plasticity. Microglia are primary recipients of peripheral inflammatory signals that reach the brain. Activated microglia, in turn, initiate an inflammatory cascade whereby release of relevant cytokines, chemokines, inflammatory mediators, and reactive nitrogen and oxygen species (RNS and ROS, respectively) induces mutual activation of astroglia, thereby amplifying inflammatory signals within the CNS. Cytokines, including IL-1, IL-6, and TNF- α , as well as IFN- α and IFN- γ (from T cells), induce the enzyme, IDO, which breaks down TRP, the primary precursor of 5-HT, into QUIN, a potent NMDA agonist and stimulator of GLU release. Multiple astrocytic functions are compromised due to excessive exposure to cytokines, QUIN, and RNS/ROS, ultimately leading to downregulation of glutamate transporters, impaired glutamate reuptake, and increased glutamate release, as well as decreased production of neurotrophic factors. Of note, oligodendroglia are especially sensitive to the CNS inflammatory cascade and suffer damage due to overexposure to cytokines such as TNF- α , which has a direct toxic effect on these cells, potentially contributing to apoptosis and demyelination. The confluence of excessive astrocytic glutamate release, its inadequate reuptake by astrocytes and oligodendroglia, activation of NMDA receptors by QUIN, increased glutamate binding and activation of extrasynaptic NMDA receptors (accessible to glutamate released from glial elements and associated with inhibition of BDNF expression), decline in neurotrophic support, and oxidative stress ultimately disrupt neural plasticity through excitotoxicity and apoptosis. 5-HT, serotonin; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; GLU, glutamate; IDO, indoleamine 2,3 dioxygenase; IFN, interferon; IL, interleukin; NMDA, N-methyl-D-aspartate; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNF, tumor necrosis factor; TRP, tryptophan.

activation and the generation of KYN appear to have important effects on neurotransmitters and mood independent of effects on serotonin. For example, administration of KYN alone has been shown to induce depressive-like behavior in mice (28). 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 (Figure 1) (36). Kynurenic acid has been shown to inhibit the release of glutamate, which, by extension, may inhibit the release of dopamine, whose release is regulated in part by glutamatergic activity (38). Indeed, intrastriatal administration of KA has been shown to dramatically reduce extracellular DA in the rat striatum (39). In contrast, QUIN promotes glutamate release through activation of N-methyl-D-aspartate (NMDA) receptors (Figure 1). Quinolinic acid also induces oxidative stress, which in combination with glutamate release may contribute to CNS excitotoxicity (see below) (36,40-42). Thus, the relative induction of KA versus QUIN may determine the effects of

cytokines on the CNS and remains an important area for future investigation, including the therapeutic targeting of IDO and KYN enzymatic pathways.

Cytokines also have been shown to influence the synthesis of DA. For example, intramuscular injection of recombinant, species-specific IFN- α to rats has been shown to decrease CNS concentrations of tetrahydrobiopterin (BH_4) and DA in association with the stimulation of nitric oxide (NO) (43). Tetrahydrobiopterin is an important enzyme cofactor for tyrosine hydroxylase, which converts tyrosine to L-3,4-dihydroxyphenylalanine (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_4 utilization (thus decreasing the availability of BH_4 to support tyrosine hydroxylase activity). Treatment with an inhibitor of NO synthase was found to reverse the inhibitory effects of IFN- α on brain concentrations of both BH_4 and DA (43). Activation of microglia is associated with increased NO production (44),

suggesting that cytokine influences on BH₄ via NO may be a common mechanism by which cytokines reduce DA availability in relevant brain regions.

Cytokines and their signaling pathways can also influence the reuptake of monoamines (30). Mitogen-activated protein kinase pathways, including p38 and extracellular signal-regulated kinases (ERK) 1/2, which mediate the effects of cytokines on cell proliferation/differentiation and apoptosis, as well as gene expression of inflammatory mediators, have been found to increase the activity of membrane transporters for serotonin and DA, as well as norepinephrine (45–47). For example, IL-1 and TNF- α have been shown to significantly increase serotonin reuptake in rat brain synaptosomes through activation of p38 MAPK (45). Of note, 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 (48). Extending these findings, recent data in humans administered IFN- α have revealed that decreased CSF 5-HIAA was correlated not only with depressed mood but also increased CSF IL-6, which is capable of activating both MAPK and IDO pathways (25). Taken together with the influence of cytokines on monoamine synthesis, these data suggest that cytokines may exert a “double hit” on both monoamine synthesis and reuptake, thus contributing to reduced monoamine availability.

Cytokine Effects on Neuroendocrine Function

Some of the earliest observed effects of cytokines on mechanisms relevant to major depression involved their impact on the hypothalamic-pituitary-adrenal (HPA) axis (49). Cytokines, especially when administered acutely, have been shown to stimulate the expression and release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), as well as cortisol, all of which have been found to be elevated in patients with depression (49,50). Although acute activation of the HPA axis in humans by IFN- α has been associated with the later development of depression (likely reflecting increased sensitivity of CRH pathways in the vulnerability to depression) (51), chronic administration of cytokines including IFN- α or chronic immune activation has not reliably been associated with persisting elevations in CRH or cortisol in humans or laboratory animals (25,32,52,53). For example, chronic administration of IFN- α to humans led to flattening of the diurnal cortisol slope and increased evening cortisol levels, which, in turn, was correlated with depression and fatigue (53). These findings are consistent with correlations between flattening of the cortisol curve and plasma IL-6 in patients with advanced cancer (54) and flattening of diurnal cortisol secretion and fatigue in breast cancer survivors (55), who have also been found to exhibit increased plasma cytokine soluble receptors (9).

One pathway by which cytokines may influence HPA axis function is through effects on negative feedback regulation. Impaired negative feedback regulation of HPA axis function is a hallmark of major depression and is reflected by 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 dexamethasone/corticotrophin-releasing hormone (DEX-CRH) test and decreased glucocorticoid-mediated inhibition of *in vitro* immune responses (50). Of note, flattening of the cortisol slope has been associated with nonsuppression on the DEX-CRH test in patients with breast cancer (56). Decreased

feedback regulation of HPA axis function by glucocorticoids is believed to be mediated, in part, by alterations in the glucocorticoid receptor (GR) (50). Relevant to inflammation, cytokine activation of relevant inflammatory signaling molecules, including NF- κ B, p38 MAPK, and signal transducer and activator of transcription 5 (STAT5), have been shown to inhibit GR through disruption of GR translocation from cytoplasm to nucleus, as well as through nuclear protein-protein interactions that inhibit GR-DNA binding (57). Cytokines can also influence GR expression, leading to decreased GR α , the active form of the receptor, and increased GR β , a relatively inert GR isoform (57).

Given the potential effects of cytokines on GR signaling and the well-established inhibitory effect of glucocorticoids on inflammation (58), several studies have examined the relationship between inflammatory biomarkers and GR function in patients with major depression. Results from these largely cross-sectional studies have been mixed. One of the earliest studies in this regard showed a significant correlation between post-DEX concentrations of cortisol and the production of IL-1 by peripheral blood mononuclear cells (59). In addition, reduced skin sensitivity to topical glucocorticoid administration in depressed patients was found to significantly correlate with increased blood concentrations of TNF- α (60). Of note, in a study examining neuroendocrine and immune responses to LPS following DEX administration, subjects with evidence of glucocorticoid resistance (as manifested by increased ACTH and cortisol responses) exhibited increased cytokine (IL-6 and TNF- α) responses regardless of whether they were depressed or not, suggesting that the relationship between HPA axis sensitivity to glucocorticoids and responsiveness of the innate immune system may be unrelated to diagnosis (61).

Cytokine Effects on Neural Plasticity

Cytokines such as IL-1, IL-6, and TNF- α that subserve inflammation in the periphery have complex and Janus-faced functional roles in the CNS. Under physiological conditions, these cytokines are important for providing trophic support to neurons and enhancing neurogenesis, while contributing to normal cognitive functions such as memory in laboratory animals (62,63). However, significant data indicate that in the context of excessive and/or prolonged activation, cytokine networks in the CNS can promote an interconnected suite of abnormalities that are increasingly thought to be relevant to the pathophysiology of depression, including diminished neurotrophic support, decreased neurogenesis, increased glutamatergic activation, oxidative stress, induction of apoptosis in relevant cell types (e.g., astrocytes and oligodendrocytes), and dysregulation of glial/neuronal interactions and cognitive function (Figure 1) (63–77).

A rich animal literature demonstrates that activation of peripheral innate immune cytokine pathways—whether as a result of an immune challenge or acute or chronic stress—leads to increased proinflammatory cytokine production and decreased neurotrophic support and neurogenesis in brain areas important to behavior and cognition (17,64–67). For example, LPS administered peripherally produces cognitive impairment and increased hippocampal concentrations of TNF- α and IL-1, which are associated with decreased hippocampal expression of brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase-B, as well as reduced hippocampal neurogenesis (67). Strongly supporting a causative role for inflammatory mediators in these behavioral and neurobiological changes are studies showing that the effects of acute and chronic stress on behavior,

cognition, neurotrophic factors, and neurogenesis can be prevented by blockade of CNS cytokine activity through administration of IL-1 receptor antagonist (IL-1ra) or transplantation of IL-1ra secreting neural precursor cells into the hippocampus or the use of IL-1 receptor KO mice (64–66,78). Of note, *in vitro* studies have suggested that cytokine effects on neurogenesis are mediated in part by activation of NF- κ B (64), while the release of glucocorticoids may be required for IL-1 effects on the brain during stress *in vivo* (78).

A related pathway to pathology in inflammation-induced effects on behavior includes the capacity of cytokines and inflammatory mediators to increase glutamate release and decrease the expression of glutamate transporters on relevant glial elements, thereby decreasing glutamate reuptake (68,71,75,79,80). Of note, glutamate released by astrocytes has preferential access to extrasynaptic NMDA receptors, which mediate excitotoxicity and decreased production of trophic factors including BDNF (81,82). Cytokines, including TNF- α and IL-1, can also induce both 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 (36,40,69,70,73,75–77,83). Astrocyte and microglial release of cytokines and inflammatory mediators also contributes to mutual amplification of inflammatory pathways within the brain (71,80). Consistent with the effect of cytokines and central inflammatory processes on glia, loss of glial elements, including oligodendrocytes and astrocytes, in multiple mood-relevant brain regions, including the subgenual prefrontal cortex and amygdala, has emerged as a fundamental morphologic abnormality in major depression (74,84,85). Of further relevance to the activation of inflammatory pathways within clinical populations are recent postmortem data suggesting that suicide is associated with increased microglia in the prefrontal cortex (86).

Cytokines, Stress, and Depression

The source of inflammation is clear when depression occurs in the context of medical illnesses in which there is an infectious, autoimmune, or inflammatory component or when there is tissue damage and/or destruction, all of which are associated with activation of peripheral, and in some cases, central inflammatory responses. However, in the case of presumably medically healthy depressed individuals, the source of inflammation is less apparent, albeit nascent inflammatory processes secondary to evolving medical pathologies remain a consideration. Nevertheless, a major breakthrough has been the increasing recognition that psychosocial stress can activate the inflammatory response both peripherally and in the brain (Figure 2). For example, peripheral blood mononuclear cells from healthy human volunteers exposed to a public speaking and mental arithmetic stressor were found to exhibit significant increases in NF- κ B DNA binding (87). Interestingly, NF- κ B and IL-6 responses to psychosocial stress have been shown to be exaggerated in patients with depression, consistent with findings that depressive symptoms are associated with amplified IL-6 responses to antigenic challenge (88,89). A rich database also indicates that chronic stress, including caregiving, marital discord, and perceived stress, is associated with increases in the acute phase protein, C-reactive protein (CRP), as well as IL-6 and other inflammatory mediators (90–92). In addition, increased inflammation appears to be a hallmark of early life stress, in that childhood maltreatment has been

associated with increased peripheral blood CRP (93). Of note, stress-induced activation of cytokine responses in the CNS appears to be largely dependent on activation of microglia (94).

The mechanisms of stress-induced activation of immune responses involve both sympathetic nervous system (SNS) and HPA axis pathways (Figure 2). For example, catecholamines acting through alpha- and beta-adrenergic receptors have been shown to increase cytokine expression in the brain and periphery of rats (95), and alpha-adrenergic antagonists have been found to block increased peripheral blood IL-6 associated with altitude stress in humans (96). In addition, *in vitro* studies have demonstrated that stimulation of both alpha- and beta-adrenergic receptors can activate inflammatory signaling pathways, including NF- κ B (87). Nevertheless, it should be noted that catecholamines have complex effects on multiple immune cell subtypes, and anti-inflammatory activities of catecholamines have been described (97). Moreover, the parasympathetic nervous system (PNS) may play a role in the autonomic nervous system regulation of inflammation. For example, studies have shown that stimulation of efferent vagus nerve fibers can inhibit cytokine responses to endotoxin in laboratory animals (98). These effects have been shown to be mediated, in part, by the release of acetylcholine, which, by binding to the α 7 nicotinic acetylcholine receptor, is able to inhibit activation of NF- κ B (98). The observation that increased inflammatory markers (e.g., CRP and IL-6) are associated with decreased parasympathetic activity, as reflected by decreased heart rate variability in young adults, supports the notion that the inhibitory effects of PNS activity on innate immune responses extends to humans (99). Taken together with the proinflammatory effects of catecholamines, these data suggest that there may be a yin-yang influence of the SNS and PNS on inflammation during stress (Figure 2).

Regarding the HPA axis, cortisol is one of the most potent anti-inflammatory hormones in the body (58); yet, in the context of chronic stress or depression, as noted above, the immune system can become glucocorticoid resistant. For example, in a recent study examining gene expression patterns in healthy control subjects versus individuals experiencing the chronic stress of caregiving for cancer patients, caregivers not only exhibited increases in plasma CRP and the expression of genes containing promoter response elements for NF- κ B but also exhibited significant decreases in genes containing promoter elements for the GR, despite similar salivary concentrations of cortisol (92). Taken together, these data suggest that increased activity through SNS pathways coupled with reduced sensitivity to the inhibitory effects of glucocorticoids (e.g., cortisol) may conspire during chronic stress to contribute to chronic activation of inflammatory responses.

Neuroanatomical Substrates of Cytokine Effects on the Brain

An emerging literature is beginning to identify brain regions that may be targets of the effects of cytokines in humans. One important area in this regard is the basal ganglia. Both IFN- α and typhoid vaccination have been associated with psychomotor slowing and/or fatigue in association with changes in neuronal activity in the substantia nigra, putamen, and nucleus accumbens, as measured by functional magnetic resonance imaging (fMRI) and positron emission tomography (16,100). Given the role of basal ganglia in motivational states and locomotor activity (101), cytokine-induced effects on the basal ganglia and DA may represent an important mechanism whereby cytokines inhibit

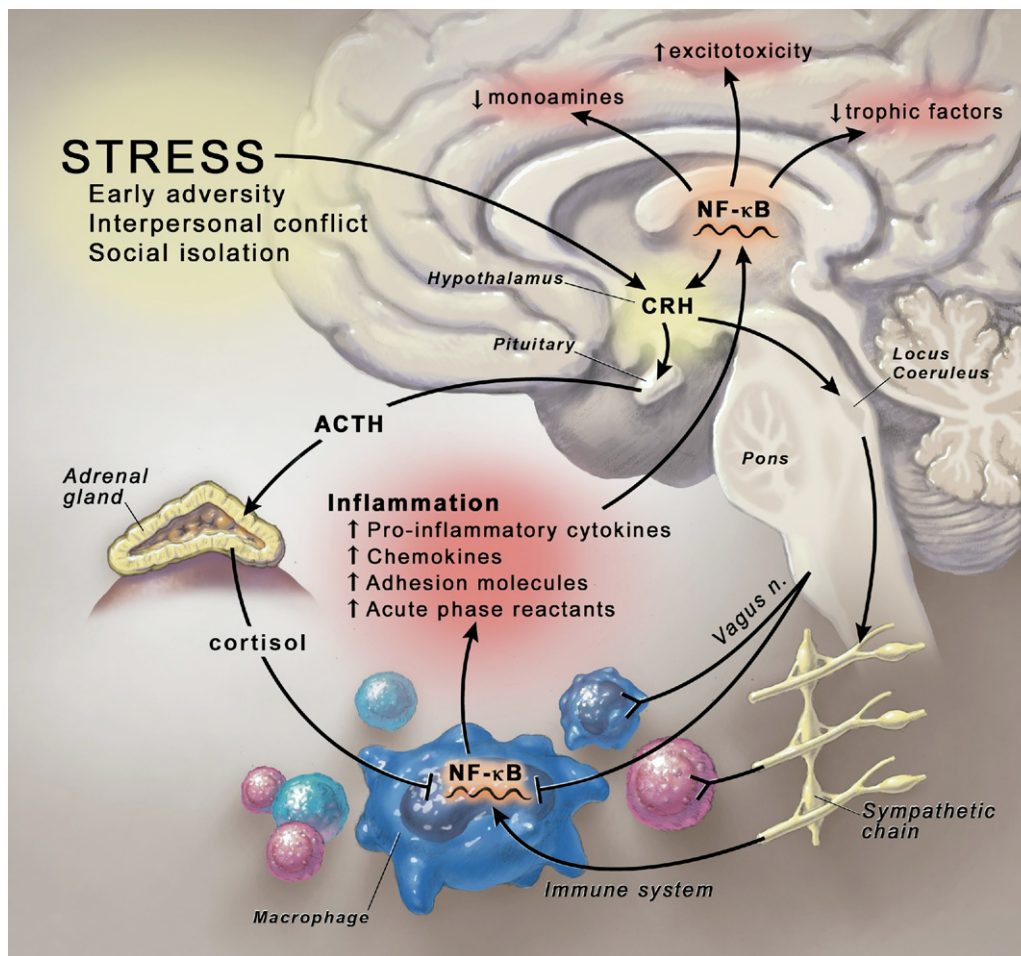


Figure 2. Stress-induced activation of the inflammatory response. Psychosocial stressors activate central nervous system stress circuitry, including CRH and ultimately sympathetic nervous system outflow pathways via the locus coeruleus. Acting through alpha and beta adrenergic receptors, catecholamines released from sympathetic nerve endings can increase NF- κ B DNA binding in relevant immune cell types, including macrophages, resulting in the release of inflammatory mediators that promote inflammation. Proinflammatory cytokines, in turn, can access the brain, induce inflammatory signaling pathways including NF- κ B, and ultimately contribute to altered monoamine metabolism, increased excitotoxicity, and decreased production of relevant trophic factors. Cytokine-induced activation of CRH and the hypothalamic-pituitary-adrenal axis, in turn, leads to the release of cortisol, which along with efferent parasympathetic nervous system pathways (e.g., the vagus nerve) serve to inhibit NF- κ B activation and decrease the inflammatory response. In the context of chronic stress and the influence of cytokines on glucocorticoid receptor function, activation of inflammatory pathways may become less sensitive to the inhibitory effects of cortisol, and the relative balance between the proinflammatory and anti-inflammatory actions of the sympathetic and parasympathetic nervous systems, respectively, may play an increasingly important role in the neural regulation of inflammation. CRH, corticotropin-releasing hormone; NF- κ B, nuclear factor kappa B.

behavioral activation, thereby supporting evolutionarily derived pressures to reallocate energy resources from environmental exploration to fighting infection and wound healing (see below) (30).

Symptoms of anxiety, irritability, and hyperarousal are also apparent following cytokine administration to humans. Such symptoms have been observed after acute administration of endotoxin as well as chronic treatment with IFN- α (13,15, 30,102). Indeed, a significant percentage of patients receiving IFN- α therapy have been shown to exhibit hypomanic and, in some cases, manic features, including marked irritability, inability to sleep, and hyperactivity (102). Similar findings have been reported in rhesus monkeys administered recombinant human IFN- α (32). Of potential relevance to these symptoms is that patients receiving IFN- α for hepatitis C exhibit significantly greater activation in the dorsal anterior cingulate cortex (dACC) (Brodmann's area [BA] 24), compared with non-IFN-

α -treated control subjects (103). The dACC has been shown to play an important role in error detection and conflict monitoring (104), and increased activity in this brain region has been associated with high trait anxiety, neuroticism, obsessive-compulsive disorder, and bipolar disorder (105), all of which are associated with increased anxiety and arousal. Interestingly, activation of the dACC also has been found during an fMRI task of social rejection and consistent with the role of this brain region in the processing of social pain, was correlated with task-related emotional distress (105). Combined with its role in error detection and conflict monitoring, the processing of social pain by the dACC has been suggested to comprise a neural "alarm system," which can both detect and respond to threatening environmental stimuli (105). Based on the neuroimaging data from IFN- α -treated patients, it appears that one mechanism by which cytokines may lead to increased arousal, anxiety, and alarm is through increased activation of neural circuits involving the

dACC (103). Of note regarding the potential evolutionary significance of these data, an animal that has been infected or wounded is vulnerable to attack and therefore must maintain increased vigilance to respond to intrusions from a predator (30). Thus, taken together with the effects of cytokines on the basal ganglia, which serve to reduce exploratory behavior, the effects of cytokines on neurocircuits within the brain appear to subserve competing evolutionary survival priorities that promote reduced activity to allow healing, while fostering hypervigilance to protect against future attack (30).

Translational Implications

Relevant to the potential clinical applications of the association between inflammation and depression, data indicate that inflammatory biomarkers may identify depressed patients who are less likely to respond to conventional antidepressant treatment and may provide an indicator of treatment response. For example, patients with evidence of increased inflammatory activity prior to treatment have been reported to be less responsive to antidepressants, lithium, or sleep deprivation (a potent short-term mood elevator) (106–108). Moreover, patients with a history of nonresponse to antidepressants have been found to demonstrate increased plasma concentrations of IL-6 and acute phase reactants when compared with treatment-responsive patients (108,109). In addition, a nascent literature suggests that functional allelic variants of the genes for IL-1 beta and TNF-alpha, as well as genes critical for T cell function, may increase the risk for depression and may be associated with reduced responsiveness to antidepressant therapy (110–112). Of note, antidepressant treatment has been associated with decreases in inflammatory markers in 11 of 20 studies that examined immune responses as a function of antidepressant therapy (Supplement 1). Such data are consistent with *in vitro* findings that antidepressants can inhibit LPS-induced production of proinflammatory cytokines while promoting anti-inflammatory cytokines such as IL-10 (113). It should be mentioned that of studies that found increased markers of inflammation following antidepressant administration, two reported that the increases occurred in association with antidepressant-induced increases in body mass index (BMI) (Supplement 1). Of relevance in this regard is that BMI has been shown to correlate with increased peripheral markers of inflammation, in part related to the capacity of adipose tissue to produce IL-6 and other cytokines (114,115). Thus, the association between increased BMI and inflammation represents a complicating factor in the relationship among inflammation, depression, and antidepressant treatment.

More direct treatment implications of the inflammation-depression hypothesis are the development of treatments that target pathways by which the immune system impacts the brain. Obvious targets include the cytokines themselves, their signaling pathways, and downstream inflammatory mediators, as well as the activation of relevant CNS immune cell types (e.g., microglia) (Table 1). Anti-inflammatory cytokines such as IL-10, as well as insulin-like growth factor, which has been shown to block both LPS- and TNF-alpha-induced behavioral changes, also warrant consideration (116). In addition, treatments addressing immunologic effects on monoamine metabolism, CNS excitotoxicity (NMDA antagonists), and decreased trophic support are also indicated. Finally, given the influence of stress and stress-induced activation of the SNS, behavioral interventions that address psychological and autonomic reactivity to stress, including psychotherapy, exercise, and meditation, may have efficacy

Table 1. Potential Translational Targets for Inflammation-Induced Depression

Immune System
Cytokines (e.g., TNF-alpha, IL-1, IL-6)
Cytokine signaling pathways (e.g., NF-κB and MAPK)
Inflammatory mediators (e.g., COX-2, PG)
RNS/ROS (e.g., NO, H ₂ O ₂)
Immune cells in the brain (e.g., microglia)
Central Nervous System
Monoamines (e.g., 5-HT, NE, DA)
IDO and its metabolites (e.g., KYN, QUIN, KA)
Extrasynaptic NMDA receptors
Excitotoxic neurotransmitters (e.g., glutamate)
Neurotrophic factors (e.g., BDNF)
Neuroendocrine System
HPA axis hormones (e.g., CRH, cortisol) and receptors (e.g., GR)
Autonomic Nervous System and Stress
Catecholamines and receptors (e.g., alpha and beta adrenergic receptors)
Parasympathetic outflow pathways (e.g., vagal nerve, alpha 7 nAChR)
Stress (e.g., interpersonal conflict, early adversity)

5-HT, serotonin; BDNF, brain-derived neurotrophic factor; COX-2, cyclooxygenase-2; CRH, corticotropin-releasing hormone; DA, dopamine; GR, glucocorticoid receptor; H₂O₂, hydrogen peroxide; HPA, hypothalamic-pituitary-adrenal; IDO, indoleamine 2,3 dioxygenase; IL, interleukin; KA, kynurenic acid; KYN, kynurenine; MAPK, mitogen activated protein kinase; nAChR, nicotinic acetylcholine receptor; NE, norepinephrine; NF-κB, nuclear factor kappa B; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; PG, prostaglandin; RNS, reactive nitrogen species; ROS, reactive oxygen species; QUIN, quinolinic acid; TNF, tumor necrosis factor.

both regarding treatment and prevention. Indeed, in a recent study on compassion meditation, compared with an educational control group, individuals who engaged in meditation practice exhibited significantly reduced IL-6 responses to a laboratory psychosocial stressor (117).

It should also be noted that an exciting opportunity regarding clinical trial design in studies targeting the immune system is the availability of pathophysiology-specific biomarkers that can be monitored early in treatment to determine whether a given therapy is effective in reducing immune activation. Such biomarkers can be used not only to monitor response but also, as noted above, can be used to identify patient populations that may be most likely to benefit from inflammation-targeted therapies. Of relevance in this regard is that published guidelines have already established categories of inflammation based on peripheral blood concentrations of CRP, with values >3 mg/L reflecting high inflammation (4). The availability of peripheral biomarkers that can both identify patients with specific pathophysiologic processes and serve to objectively monitor therapeutic responses within relevant pathways is truly unique and may represent a major advance in the personalization of the treatment of depression. Coupled with concerted efforts across medical disciplines to develop medications and biomarkers that target inflammatory responses, the notion that depression, like other medical disorders, may share an inflammatory component represents an exciting venue for transdisciplinary collaboration and the integration of resources from immunology, the neurosciences, and a variety of medical specialties to address a pressing need to develop novel approaches to treat patients with major depression.

This study was supported in part by grants from the National Institutes of Health (NIH) (K05 MH069124, K23 MH064619, R01

MH070553, R01 HL073921, T32 MH020018), an NIH/National Center for Research Resources (NCRR) General Clinical Research Center Grant (M01 RR00039), and the Centers for Disease Control and Prevention.

Artwork was kindly provided by Jordan Pietz and Kim Hoggatt Krumwiede, Biomedical Communications Graduate Program, University of Texas, Southwestern Medical Center, Dallas, Texas.

Charles L. Raison is on the speakers' bureau for Lilly, Wyeth, and Schering-Plough and has served as a consultant or an advisory board member for Schering-Plough, Wyeth, Lilly, and Centocor; Vladimir Maletic is on the speakers' bureau for Lilly, Takeda, and Novartis and has served as a consultant for Lilly, Takeda, and Pfizer; Andrew H. Miller has served as a consultant for AstraZeneca, Schering-Plough, and Centocor and has received research support from Schering-Plough, Centocor, and GlaxoSmithKline.

Supplementary material cited in this article is available online.

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