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Immune System Contributions to the Pathophysiology of Depression

Abstract: Major depression is a devastating disorder that represents a major public health concern. Of special relevance is the high percentage of patients whose depression does not respond to or who are unable to tolerate conventional antidepressant medications, which primarily target monoamine neurotransmission. Recent data indicate that the immune system may play a role in the pathophysiology of depression, representing a novel pathway for therapeutic development. Patients with major depression have been found to exhibit evidence of an activated innate immune response as reflected by increased biomarkers of inflammation, including innate immune cytokines, acute-phase proteins, chemokines, and adhesion molecules. In addition, administration of innate immune cytokines to laboratory animals and humans has been shown to induce behavioral changes that significantly overlap with the symptom criteria of major depression. Treatment of patients with inflammatory disorders using anticytokine therapies has also been found to reduce depressive symptoms. Interestingly, psychosocial stress, a well-known precipitant of depressive disorders, has been shown to activate the innate immune response. Finally, innate immune cytokines have been shown to influence virtually every pathophysiological domain relevant to depression including monoamine neurotransmission, neuroendocrine function, synaptic plasticity, and regional brain metabolism. Of note, a response to conventional antidepressant medications is associated with a decrease in inflammatory biomarkers, whereas patients with treatment-resistant depression are more likely to exhibit evidence of increased inflammation. Taken together, these data provide the foundation for considering an activated innate immune response as a potential target for further study and therapeutic development in mood disorders, especially in the context of treatment resistance.

Major depression has become a health crisis of epidemic proportions in the modern world. The prevalence of major depression has risen over the last several generations in every country examined (1), and age of symptom onset has decreased (2). One in six individuals in the United States will experience an episode of major depression in his or her lifetime (3), and the risk of subsequent episodes rises dramatically once a person has been depressed (4). Between 10% and 15% of severely depressed people eventually commit suicide (5), and studies indicate that depression significantly increases all-cause mortality (6) and predicts the later development of a number of medical conditions, including cardiac and cerebrovascular disease (7, 8), hypertension (9, 10), diabetes (11, 12), obesity and the metabolic syndrome (13, 14), and cancer (15).

Unfortunately, most patients with depression do not experience a complete resolution of symptoms with conventional antidepressant treatment, and 10%–20% of patients have depression that is refractory to all currently available modalities, including electroconvulsive therapy (16). In addition to efficacy issues, many patients are unable to tolerate the side effects associated with antidepressants or electroconvulsive therapy. The risks of not re-

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Table 1. Divisions of the Immune System: Representative Characteristics of the Innate and Acquired Immune Response

	Innate Immune Response	Acquired Immune Response
Physical and chemical barriers	Skin, mucous membranes	Cutaneous and mucosal immune systems
Cells	Phagocytes (macrophages, neutrophils, natural killer cells)	Lymphocytes (B and T cells)
Soluble mediators	Macrophage-derived cytokines, e.g., IL-1, IL-6, TNF-α, IFN-α	Lymphocyte-derived cytokines, e.g., IL-2, IL-4, IL-5, IL-6, IL-10, IFN-γ
Recognition specificity	Recognition of crude molecular patterns (e.g., Toll-like receptors)	Recognition of specific microbial and nonmicrobial antigens (e.g., T-cell receptor)
Memory	No	Yes
Circulating effector molecules	Complement, acute phase reactants	Antibodies

sponding to (or tolerating) treatment have been highlighted by recent studies documenting the fact that a partial—but incomplete—response is associated with an increased risk of full symptomatic relapse (even when the patient is receiving therapy) and worse long-term disease course, as well as significantly impaired quality of life (17, 18). Treatment resistance also results in a six times increase in direct health care costs (19). These factors highlight the tremendous need to identify novel treatment strategies for depression, especially for depressed patients whose depression is unresponsive to treatment or who are intolerant of conventional therapies.

THE IMMUNE SYSTEM AND DEPRESSION

One consideration that has received increasing attention is the possibility that the immune system may contribute to the pathophysiology of depressive disorders and may thus represent a heretofore unrecognized and novel target for future research and therapeutic exploration. Although early studies focused largely on acquired immune responses in patients with depression (e.g., T- and B-cell functions, which were generally found to be suppressed), more recent research suggests that a significant percentage of depressed patients may experience activation of the innate immune response (20–22).

In contrast to the acquired immune response (Table 1), which develops slowly (i.e., over days) and is highly specific in its recognition of pathogens, the innate immune system provides a rapid, front-line defense against a variety of pathogens and damaged or dead cells, using relatively crude (nonspecific) pattern recognition receptors referred to as Toll-like receptors to initiate and mobilize the response to infection and/or tissue damage and destruction (23). Toll-like receptors in turn are linked to fundamental inflammatory signaling pathways including nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPKs), which when activated stimulate the production of the innate immune cytokines interferon (IFN)-α, interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α); chemokines; adhesion molecules; and other inflammatory mediators including the prostaglandins, histamine, and reactive oxygen and nitrogen species (23, 24). These molecules then orchestrate the local immune response by recruiting and activating relevant immune cells, which leads to the swelling (tumor), redness (rubor), heat (calor), and pain (dolor) that constitute the clinical characteristics of inflammation. Innate immune cytokines also enter the peripheral blood and stimulate local nerve fibers (see below) to mobilize a systemic response to infection and tissue trauma that includes activation of the acute-phase response in the liver, which involves the production of acute-phase proteins such as C-reactive protein (CRP), and a central nervous system (CNS) response, which involves fever, fatigue, reduced environmental exploration, anorexia, and altered sleep. This CNS response, which has been referred to as "sickness behavior," is believed to represent a reorganization of behavioral priorities to conserve and divert essential energy resources to pathogen elimination, tissue repair processes, and protection from future injury or attack (20, 22, 25).

A major breakthrough in terms of the recognition of the potential contribution of the immune system to depression has been the demonstration that all of the cardinal features of inflammation are apparent in patients with major depression (Figure 1). Patients with major depression have been found to exhibit significant elevations of innate immune cytokines and their soluble receptors in both peripheral blood and cerebrospinal fluid (CSF) and have exhibited elevations in acute-phase proteins,

chemokines, and adhesion molecules as well as inflammatory mediators such as the prostaglandins. Given the number and variety of studies done in this area, a meta-analysis has been conducted, and the data indicate that of these markers of inflammation, elevations in IL-6 and CRP are some the most reliable (26). Because of the relationship between body mass index and CRP and IL-6 (adipocytes are capable of producing IL-6 as are macrophages within fatty tissues) (27), elevations of these markers in patients with obesity should be interpreted with caution. In addition to mean increases in inflammatory biomarkers in depressed patients versus control subjects, correlations between depressive symptom severity and increases in measures of peripheral inflammation have been observed in multiple studies (20, 28–31). Although the linkage of inflammatory markers with specific behavioral profiles is still under investigation, it should be noted that fatigue, loss of energy, and psychomotor retardation are some of the most common symptoms after cytokine administration (32, 33).

Another major body of evidence supporting an immune system contribution to the development of depression is the profound behavioral disturbances that occur in patients treated with the innate immune cytokine, IFN-α. IFN-α has both antiviral and antiproliferative activities and is therefore used to treat both infectious diseases and cancer (34). Although an effective therapy, IFN-α is notorious for causing a variety of behavioral alterations including symptoms sufficient to meet criteria for major depression in up to 50% of subjects, depending on the dose (34, 35). Treatment of patients before and during IFN-α therapy with antidepressants has been shown to markedly reduce the incidence of depression (35–37), supporting the notion that cytokine-induced depression not only shares behavioral similarities with major depression in otherwise healthy individuals but also shares pharmacological response characteristics. Of note, rhesus monkeys administered IFN-α also exhibit depressive-like huddling behavior that was initially described in monkeys administered the monoamine-depleting drug, reserpine (38).

A final consideration regarding the role of the immune system in depression is the high rate of depression in medically ill patients with disorders that involve the immune system including infectious diseases, cancer, and autoimmune disorders (39). Rates of depression are on average 5–10 times higher in these diseases (40), and studies have shown a relationship between inflammatory markers and depression and other behavioral alterations in these disorders (41–45). These data indicate that there appears to be a specific relationship between inflammation and behavioral symptoms as opposed to a more nonspecific relationship between being ill and emotional distress. Further supporting the specificity of the cytokine-depression link in those who are medically ill is that patients with autoimmune disorders treated with cytokine antagonists have exhibited significant improvement in depressive symptoms (see below) (46, 47). In addition, there is increasing recognition that inflammation may play a prominent role in a number of common disorders including cardiovascular disease, diabetes, and metabolic syndrome and cancer—all disorders with increased rates of depression (48–50). Taken together these data suggest that inflammation may be a shared pathology between these diseases and depression.

IMMUNOLOGICAL MECHANISMS OF BEHAVIORAL CHANGE

Consistent with the notion that innate immune cytokines may be associated with the development of depression are data that these cytokines can influence virtually every pathophysiological domain relevant to depression including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and regional brain activity (Figure 2).

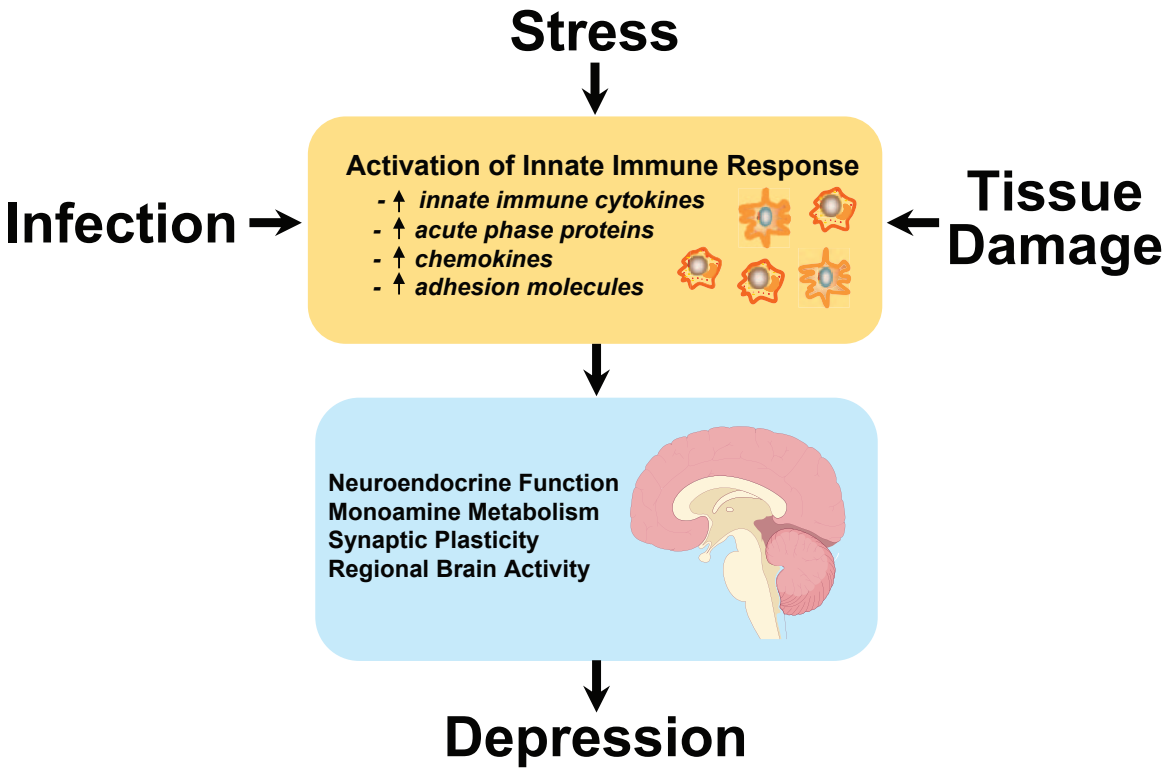
COMMUNICATION WITH THE BRAIN

As part of the consideration of the impact of peripherally elaborated cytokines on the brain and behavior, a great deal of attention has been paid to the pathways by which cytokines signal the brain. In general, four routes have been described including 1) passage through leaky regions of the blood-brain barrier (51), 2) active transport through saturable transport molecules (52), 3) activation of endothelial cells (as well as other cells lining the cerebral vasculature), which then release inflammatory mediators (53, 54), and 4) binding to cytokine receptors in association with afferent nerve fibers (e.g., vagus nerve), which in turn relay cytokine signals to relevant brain nuclei (55). Once cytokine signals access the brain, activation of relevant inflammatory signaling molecules (e.g., NF-κB) in appropriate cells, including astrocytes and microglia, leads to the release of cytokines within the brain parenchyma (22).

NEUROTRANSMITTER METABOLISM

Administration of cytokines to laboratory animals and humans has been shown to alter the metabolism of the monoamines, serotonin, norepinephrine, and dopamine, in both the peripheral

Figure 1. Activation of Innate Immune Responses and Depression



Note: There are many factors that can lead to activation of the innate immune response, which is characterized by increases in a variety of immune mediators that can be measured in the peripheral blood. These immune mediators can then interact with pathways known to be involved in the pathophysiology of depression.

blood and in brain regions relevant to mood regulation (56–59). Much attention regarding the impact of cytokines on monoamine metabolism has been focused on serotonin. Indeed, data indicate that cytokine activation of the enzyme, indoleamine 2,3-dioxygenase, leads to the breakdown of tryptophan (22, 59), the primary precursor of serotonin, into the metabolites, kynurenine and quinolinic acid, which have neurotoxic properties (60). Studies in patients undergoing treatment with IFN-α have shown correlations between decreases in peripheral blood tryptophan and increases in depression as well as increases in peripheral blood kynurenine in patients who develop symptoms of major depression (59, 61). Activation of the cytokine signaling pathway p38 MAPK may also contribute to alterations in serotonin. For example, activation of p38 MAPK by IL-1β or TNF-α has been shown to upregulate the expression and activity of the serotonin transporter (62). Relevant in this regard, increased phosphorylated (activated) p38 MAPK in peripheral blood mononuclear cells of monkeys subjected to early life abuse and neglect were associated with significant decreases in CSF concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (63). Thus, through activation of both indoleamine 2,3-dioxygenase and p38 MAPK, cytokines may impose a double hit on serotonin availability by influencing both serotonin synthesis and availability in the synapse.

In addition to effects on serotonergic neurotransmission, the effects of cytokines on dopamine metabolism have also received attention. For example, IFN-α-treated rhesus monkeys that displayed depressive-like behavior exhibited significantly greater decreases in CSF concentrations of the dopamine metabolite, homovanillic acid, than monkeys that did not exhibit such behavior (38). Relevant to cytokine-induced activation of indoleamine 2,3-dioxygenase, data indicate that intrastriatal administration of kynurenic acid, a breakdown product of kynurenine, dramatically reduces extracellular dopamine in the rat striatum (64). Of note, cytokine induction of nitric oxide also has been shown to inhibit the activity of tyrosine hydroxylase (the rate-limiting enzyme in the synthesis of dopamine) through effects on the tyrosine hydroxylase coenzyme, tetrahydrobiopterin (65).

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Innate immune cytokines are potent activators of the hypothalamic-pituitary-adrenal (HPA) axis and

the release of corticotropin-releasing hormone (CRH) (66, 67). Indeed, the HPA axis response to the first injection of IFN-α was found to be significantly greater in patients who developed depression during IFN-α therapy than in those who did not become depressed (67), indicating that sensitivity of CRH pathways may represent a vulnerability factor to cytokine-induced behavioral disturbances. Given the role of CRH in depression (68), cytokine-induced activation of CRH in the brain may be a major pathway by which cytokines influence behavior. Another pathway by which cytokines may influence the HPA axis is through their effects on the glucocorticoid receptor (GR). For example, activation of cytokine signaling pathways such as p38 MAPK has been shown to disrupt translocation of the GR from cytoplasm to nucleus and thereby reduce GR functional capacity (69). Moreover, cytokines have been shown to increase the expression of the inert β-isoform of the GR, which serves to divert glucocorticoids from the active α-isoform (70). Reduced GR function (as manifested typically by an abnormal dexamethasone suppression test and/or a dexamethasone-CRH test) is a hallmark of depression and may contribute to impaired regulation of CRH, which is under negative regulation by glucocorticoids (71, 72). Decreased GR function may also contribute to increased inflammation, given the well-known role of glucocorticoids in suppressing inflammatory responses through inhibition of NF-κB signaling (73).

SYNAPTIC PLASTICITY

Data indicate the importance of growth factors including brain-derived neurotrophic factor (BDNF) and synaptic plasticity in the vulnerability to and development as well as treatment of depression (74). For example, physical and psychological stressors suppress neurogenesis in the hippocampus, promote apoptotic cell death, and reduce density of synaptic connectivity between nerve cells (75). Increasing evidence suggests that inflammatory signaling pathways within the CNS may play a role in these detrimental stress-induced processes. For example, social isolation stress in rodents has been shown to suppress hippocampal neurogenesis and reduce hippocampal BDNF levels, with both effects being reversed by CNS administration of an antagonist to IL-1 (IL-1 receptor antagonist) before exposure to stressors (76). In addition, induction of NF-κB in the brain by cytokines such as IL-1 may contribute to alterations in neuronal growth and survival through the induction of reactive oxygen and nitrogen species such as nitric oxide, which has been shown to decrease the production of BDNF and to reduce neuronal survival of cells in the hippocampus (77, 78).

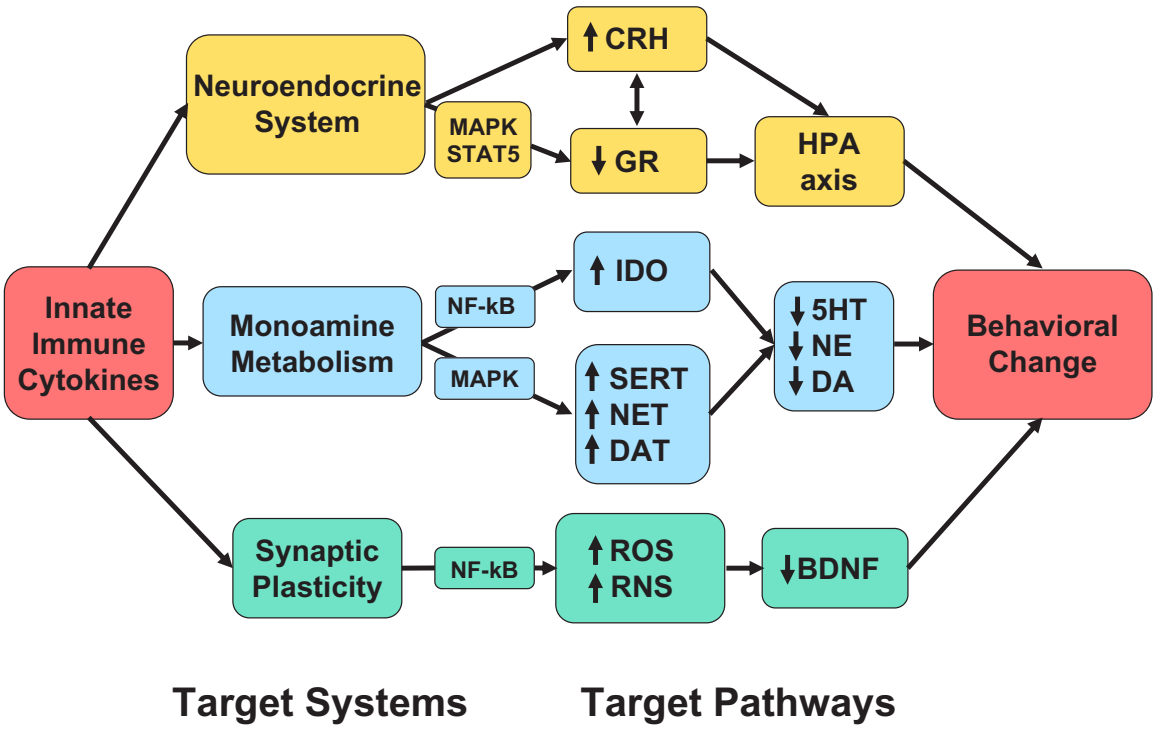
REGIONAL BRAIN ACTIVITY

Results from studies using positron emission tomography and functional magnetic resonance imaging provide further evidence that peripheral cytokine activity can induce centrally mediated behavioral changes. For example, during a functional magnetic resonance imaging task of visuospatial attention, patients given IFN-α exhibited significantly greater activation of the dorsal anterior cingulate cortex compared with control subjects (79). Interestingly, increased dorsal anterior cingulate cortex activity during cognitive tasks has also been demonstrated in patients vulnerable to mood disorders, such as those with high trait anxiety, neuroticism, or obsessive-compulsive disorder (80, 81). IFN-α has also been shown to lead to changes in frontal cortex and basal ganglia metabolic activity (as measured by positron emission tomography) (82, 83). Basal ganglia changes resemble those seen in Parkinson's disease and correlated with fatigue (83).

STRESS, DEPRESSION, AND THE INNATE IMMUNE RESPONSE

One of the most profound discoveries that has linked depression and the immune system is the finding that psychosocial stress, a well-known precipitant of mood disorders, can activate the innate immune response. For example, in a study of normal volunteers subjected to the Trier Social Stress Test (a public speaking task followed by mental arithmetic), examination of peripheral blood inflammatory markers revealed significant increases in NF-κB DNA binding within minutes after stressor cessation (84). These data complement results from a host of studies demonstrating that a variety of both acute and chronic emotional and physical stressors are associated with increases in inflammatory markers including innate immune cytokines and their soluble receptors as well as acute-phase proteins (85–87). Interestingly, the innate immune response to stress appears to be exaggerated in depressed patients exposed to early life stress (ELS). Indeed, depressed male patients with increased ELS exhibited significantly greater peripheral blood IL-6 responses and increased NF-κB DNA binding in response to the Trier Social Stress Test than nondepressed control subjects (88). This relationship between ELS and increased inflamma-

Figure 2. Mechanisms by which Innate Immune Cytokines Can Contribute to Depression



Note: Through influences on the neuroendocrine system, monoamine metabolism, and synaptic plasticity, innate immune cytokines and their signaling pathways (e.g., NF-κB and MAPK) can influence molecules that are believed to play a role in depression including CRH, the GR, serotonin (5HT), norepinephrine (NE), dopamine (DA), and BDNF. Important intermediaries in the effects of cytokines on these target pathways include enzymes that influence monoamine synthesis and release such as indoleamine 2,3-dioxygenase (IDO), monoamine transporters [such as the serotonin transporter (SERT), norepinephrine transporter (NET), and dopamine transporter (DAT)] and reactive oxygen species (ROS) and nitrogen species (RNS).

tion has also been observed in a large population-based study wherein individuals exposed to increasing levels of ELS were found to exhibit increasing levels of CRP in adulthood (87). Given the relationship between stress, depression, and inflammation, these data raise the question as to whether inflammation plays a role in the link between stress, depression, and disease, especially given the recent recognition that inflammation may represent a common mechanism for a number of illnesses including cardiovascular disease, diabetes, and cancer (48–50, 89, 90). As noted above, the effects of stress on relevant growth factors through its effects on the immune system may also play a role in neurodegenerative disorders (in addition to depression) (91).

Regarding the mechanism(s) by which stress influences the innate immune response, emerging data from humans and laboratory animals indicate that the sympathetic and parasympathetic nervous systems may be involved. Antagonism of both α- and β-adrenergic receptors has been shown to abrogate the effects of stress on the induction of innate immune cytokines in both the peripheral blood and brain of laboratory animals (92). Interestingly, increased peripheral blood IL-6 concentrations due to the stress of increased altitude were eliminated by administration of the α-adrenergic agent, prazosin (93). It should be noted, however, that β-agonists are known to have potent anti-inflammatory effects (94, 95), and therefore the role of catecholamines in the regulation of the innate immune response is in need of further study. Indeed, there is some suggestion that stress or inflammation-related induction of α_1-adrenergic receptors (in combination with the effects of stress or inflammation on the β-receptor) may be an important component in determining the net effect of catecholamines on the inflammatory response (96). Finally, there has been recent interest in the role of parasympathetic pathways in inhibiting inflammation. For example, stimulation of the vagus nerve (and parasympathetic outflow pathways) has been shown to inhibit endotoxin induction of TNF-α and the signs of sepsis (97). These effects appear to be mediated by the release of acetylcholine, which through binding to the α7 subunit of the nicotinic acetylcholine receptor can inhibit NF-κB. Nevertheless, given the rich interconnection between sympathetic and parasympathetic nervous systems

including shared mediators, the exact mechanism by which the autonomic nervous system modulates the inflammatory response is an area that warrants further study.

THERAPEUTIC IMPLICATIONS

Given the potential role of the immune system in the development of depression, there has been mounting interest in targeting the innate immune response as a novel therapeutic strategy to treat depression. Of relevance in this regard, successful antidepressant treatment of major depression with selective serotonin reuptake inhibitors or tricyclic antidepressants has been associated with reduced circulating cytokine concentrations, including TNF-α (98, 99) and IL-6 (100) Recent observations suggest that bupropion, a marketed antidepressant, can also reduce circulating concentrations of TNF-α in mice and in subjects with inflammatory disorders including Crohn's disease (101, 102). In vitro studies also indicate that a number of antidepressants can suppress the release of inflammatory cytokines while increasing the release of cytokines that inhibit inflammation such as IL-10 (103). Importantly, patients with increased plasma concentrations of innate immune cytokines are less likely to respond to currently available therapies (100, 104–107) and, conversely, patients with treatment-resistant depression have been shown to be especially likely to demonstrate evidence of an activated innate immune response, including elevated plasma concentrations of innate immune cytokines (100, 104–108). These findings suggest that pharmacological strategies aimed to downregulate inflammatory signaling pathways may have unique antidepressant efficacy and may be especially relevant in patients with treatment-resistant depression with increased inflammation.

Preliminary data suggest that targeting the innate immune response may be a viable antidepressant strategy. For example, increased response rates and improvement of depressive symptoms in patients with major depression was reported in an add-on study using the anti-inflammatory agent, celecoxib, a cyclooxygenase-2 inhibitor, in combination with reboxetine (109). In addition, in patients with psoriasis, the anti-TNF-α agent, etanercept, was found to reduce symptoms of depression (determined by the Hamilton Depression Rating Scale and the Beck Depression Inventory) independently from the clinical improvement of the primary disorder (46). Animal data are also consistent with the notion that immune targeted therapies may have antidepressant potential. Indeed, mice who have had the gene for the TNF-α receptor "knocked out" have been found to exhibit an antidepressant phenotype and are resistant to the anxiety-inducing effects of viral infection (110, 111).

Taken together, the data suggest that interventions that block inflammation may hold therapeutic promise especially in depressed individuals with increased inflammation. Given established cutoff values for increased inflammation as defined by the American Heart Association (i.e., CRP >3 ng/liter) (48), such patients may be readily identified for further study and exploration of novel treatment approaches targeting cytokines or their signaling pathways.

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