NEUROSCIENCE

Inflammatory Factors Contribute to Depression and Its Comorbid Conditions

Hymie Anisman* and Shawn Hayley

New perspectives have emerged regarding the processes associated with depressive disorders and their many comorbid conditions. Particular attention has been paid to the potential role of inflammatory factors in promoting these illnesses. These inflammatory responses include those elicited by pathogenic stimuli, as well as sterile inflammatory processes, such as those related to severe or chronic stress. These diverse challenges may activate common processes in which cytokines, which are inflammatory signaling molecules, provoke the dysregulation of several growth factors, including brain-derived neurotrophic factor, fibroblast growth factor-2, macrophage migration inhibitory factor, and erythropoietin. The result of such dysregulation favors the development of depressive disorders and their comorbid illnesses, such as heart disease, diabetes, autoimmune conditions, and poststroke depression.

The idea that inflammatory processes contribute to brain-related pathologies, such as depressive disorders, has been gaining traction, particularly because activation of the inflammatory immune response might also account for the frequent comorbidity that occurs between depression and heart disease, metabolic syndrome, diabetes, autoimmune disorders, and stroke recovery (*1*, *2*). This focus has increased further in light of the possibility that inflammatory factors might serve as biomarkers to predict the development of depression and its recurrence, as well as to predict the most efficacious treatments of depressive disorders (*2*). We address current issues linking inflammatory processes to growth factors and hence to depression, and the potential involvement of those processes in the comorbid conditions that have often been associated with depressive disorders (Fig. 1).

The view that inflammatory factors contribute to depression was initially predicated on findings that circulating cytokines (signaling molecules of the immune system) and other inflammatory factors were increased in depressed patients. Furthermore, in rodents, inflammatory agents, such as lipopolysaccharide (LPS), elicited behaviors reminiscent of depression (*1*), and low doses of a bacterial endotoxin provoked low mood or fatigue in humans (*3*). These changes were accompanied by increased amounts of circulating interleukin-6 (IL-6) and tumor necrosis factor–α (TNF-α), increased amygdala neuronal activity in response to socially threatening stimuli, and a feeling of "social disconnection" that could favor the evolution of depression (*4*).

Particularly strong evidence for a cytokine/depression relationship came from studies showing that the administration of interferon-α (IFN-α) for the treatment of some cancers and hepatitis C was accompanied by depression in about 50% of patients, particularly those with a history of depression or with low concentrations of the serotonin (5-HT) precursor tryptophan (*5*). Moreover, in animal models of depression, as well as in humans, antidepressants attenuated the depressive effects of IFN-α, and the positive effects of antidepressant treatments could be enhanced by adjunctive anti-inflammatory agents (*5*, *6*).

Several perspectives have been offered to account for how inflammatory factors might promote brain neurochemical changes that lead to depression. In addition to gaining limited access to the central nervous system (CNS) from the periphery, cytokines are produced in the brain by glial cells, and their production is increased in response to various insults, such as head injury, ischemia, and stroke (*7*), and by physical or psychological stressors (*8*). Once increased, cytokines might have either positive (neuroprotective) or negative (neurodestructive) actions, depending on their abundance. For instance, after ischemic stroke, depressive-like illness is common (*9*), and this condition is probably secondary to increased levels of cytokines. Indeed, a key feature of depression (anhedonia), reflected by reduced consumption of a favored food (sucrose), was elicited in animals models of ischemic stroke, which was attenuated by pretreatment with the IL-1 antagonist IL-1ra (*10*), as were several behavioral changes ordinarily elicited by psychological and physical stressors (*11*).

Typically, considerable psychological distress accompanies events (for example, stroke or traumatic brain injuries) that promote increased cytokine concentrations in the brain. Likewise, IFN-α immunotherapy for cancer and hepatitis C is accompanied by the distress caused by illness, as well as that brought on by the treatment itself. Thus, it has been suggested that the affective effects of treatments or conditions that increase inflammatory factors might be aggravated by stressful consequences that often stem from the treatments or the illness itself. Indeed, in rodents, proinflammatory treatments, including IFN-α, administered on a backdrop of stressors, such as social defeat or social disruption, exaggerated the increases in corticosterone and brain monoamine utilization and mRNA expression of serotonin receptors, as well as diminishing the increase in peripheral and central transcripts for multiple cytokines elicited by the administration of a particular cytokine in the absence of additional stress (*8*, *12*). Likewise, in humans, self-reported signs of depression elicited by a stressor comprising social exclusion were increased after treatment with intravenous endotoxin (*13*).

To explain how cytokine variations within the brain are translated into depression, it was suggested that increases in cytokines, like that elicited by IFN-α immunotherapy, lead to increased expression of the gene encoding tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO), resulting in diminished 5-HT concentration. Alternatively, depression might result from the conversion of tryptophan to kynurenine by IDO, which in turn produces the metabolites 3-hydroxy kynurenine and quinolinic acid, and the *N*-methyl-D-aspartate (NMDA) antagonist kynurenic acid. The neurotoxic actions of these metabolites might cause the development of depression (*14*, *15*). In this regard, the depression evident after stroke could be due to a cytokine-induced increase in IDO that leads to reduced 5-HT availability (*16*).

The limited improvements that have been witnessed in response to treatments that fo-

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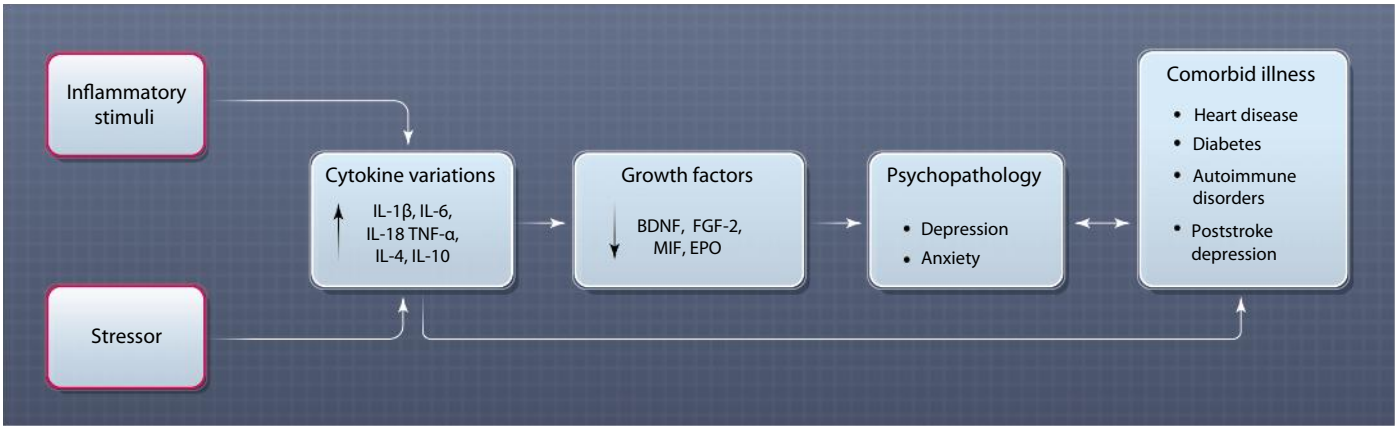

Fig. 1. Inflammatory factors and stressors can additively or synergistically influence cytokine-regulated processes in the periphery and brain. Inflammatory factors include the proinflammatory cytokines interleukin-1β (IL-1β), IL-6, tumor necrosis factor–α (TNF-α), interferon-α (IFN-α), IFN-γ, and those that act in an anti-inflammatory capacity, IL-4 and IL-10. The cytokine variations, in turn, influence several growth factors, such as brain-derived neurotrophic factor (BDNF), fibroblast growth factor–2 (FGF-2), macrophage migration inhibitory factor (MIF), and erythropoietin (EPO), which favor the evolution of depressive disorders and anxiety. The balance between pro- and anti-inflammatory cytokines can also directly influence several illnesses that are comorbid with depression.

cused on serotonergic mechanisms gave rise to the exploration of novel alternatives to 5-HT in mediating depression. The findings that neuroplasticity might be associated with depressive illness and that selective serotonin reuptake inhibitors (SSRIs) might act through effects on neuroplasticity have received considerable support (*17*). The positive effects of several antidepressants (and electroconvulsive shock) were accompanied by enhanced hippocampal neurogenesis. Furthermore, antidepressants and electroconvulsive shock therapy prevented the inhibition of hippocampal cell proliferation induced by stressors (*17*). Conversely, preventing antidepressants from stimulating hippocampal neurogenesis by selective irradiation attenuated the behavioral outcomes induced by antidepressants (*18*). Neuroplasticity associated with depression might be related to the presence of inflammatory factors. For instance, depression in humans was accompanied by reduced hippocampal volume coupled with increased peripheral IL-6 and C-reactive protein, particularly in individuals with lower messenger RNA (mRNA) abundance of the glucocorticoid-inducible genes *GILZ* (encoding the transcriptional regulator glucocorticoid-induced leucine zipper protein) and *SGK1* (encoding serum- and glucocorticoid-regulated kinase 1). Because glucocorticoids normally limit cytokine production, the presumed reductions in glucocorticoids in the depressed patients would favor increased cytokines and hippocampal disturbances (*19*).

Brain-derived neurotrophic factor (BDNF) may drive neuroplastic changes—in particular, neurogenesis—and thus reductions in BDNF, which may be stimulated by inflammatory factors, may promote depression (*17*). This view was supported by the observation that in humans, chronic or strong life stressors and the accompanying depression were associated with reduced *BDNF* expression, which may be due to epigenetic silencing, and hippocampal neurogenesis (*20*). Moreover, in mice, the administration of LPS or the individual cytokines IL-1β, IL-6, or TNF-α reduces hippocampal neurogenesis and BDNF abundance (*21*).

The proinflammatory cytokines IL-1β and TNF-α have also been reported to disrupt hippocampal long-term potentiation (*21*, *22*), a form of neuroplasticity associated with memory and involving several types of glutamate receptors, including the NMDA-type and AMPA-type receptors. Administration of the NMDA receptor antagonist ketamine even to treatment-resistant and suicidal patients has produced an immediate antidepressant response (*23*). The antidepressant and memory effects of ketamine appear to be related to altering the balance of signaling between the types of glutamate receptors and promoting the production of BDNF (*24*). These signaling effects in turn are linked to enhanced protein synthesis and increased synaptogenesis (*24*), which may underlie the protracted changes in mood and emotional memories that occur after a single ketamine injection. Thus, combining anti-inflammatory or possibly even anti-cytokine agents with NMDA receptor antagonists, such as ketamine, could potentially produce synergistic antidepressant effects.

Impaired fibroblast growth factor–2 (FGF-2) signaling, resulting from proinflammatory signals, may also contribute to this disorder. In rodents, brain *FGF-2* expression was reduced by physical stressors, such as tailshock (*25*), and in depressed humans that died by suicide, *FGF-2* expression was reduced in the prefrontal cortex (*26*). Moreover, FGF-2 administered directly into the brain of rodents reduced stressor-provoked depressive-like behaviors, whereas the positive behavioral effects of antidepressant treatment in attenuating the effects of stressors were abolished by the administration of an FGF-2 antagonist (*27*). It is uncertain how FGF-2 comes to produce its antidepressant effects, although it could involve changes in glutamatergic signaling or in excitatory synapses.

Yet another cytokine that might influence depression is macrophage migration inhibitory factor (MIF). This cytokine was increased in the circulation of individuals with high depression scores (*28*), and depressive symptoms were correlated with enhanced MIF production in response to a challenge consisting of influenza virus vaccination (*29*). Studies in rodents have also indicated that *MIF* expression in proliferating cells in the hippocampus was reduced by repeated exposure to stressful stimuli and that genetic deletion of *MIF* disturbed hippocampal-dependent memory, along with promoting signs of anxiety and depression (*30*). Electroconvulsive shock and exercise, treatments that are effec-

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tive in reducing depressive-like behavior in animal models, increased hippocampal *BDNF* and *MIF* (*31*). Similarly, recombinant MIF treatment increased the expression of *BDNF* and *FGF-2* in the hippocampus. Although long-term exercise induced mRNA expression of hippocampal *BDNF* in wild-type mice, this did not occur among the $MIF^{-/-}$ mice, which also exhibited reduced basal abundance of BDNF. In addition to these effects, treatment with MIF also increased the amount of 5-HT, as did prolonged exercise or electroconvulsive shock (*31*).

Paralleling these effects, aerobic exercise induced the production of the hematopoietic cytokine erythropoietin (EPO), which has potent trophic effects, including the induction of BDNF and hippcoampal neurogenesis and other pro-neuroplastic factors (*32*). EPO may also have an antidepressive effect, which might be mediated by action on EPO receptors located in the CNS (*33*). Thus, the antidepressant-like effects of nonpharmacological strategies, such as exercise, could be related to the promotion of endogenous protective mechanisms involving MIF and EPO.

MIF and EPO could be viewed as important general factors involved in regulating a constellation of neuroplastic and neuroimmune processes that collectively are important not only in depression but also in a range of comorbid conditions. Indeed, increased MIF might be fundamental for cardiovascular events (*34*), and deficits in EPO could give rise to anemia and immunosuppressive disorders, as well as cognitive disturbances. Findings such as these are consistent with the view that developing novel means of regulating endogenous MIF and EPO within the brain and periphery could yield substantial therapeutic benefits, and routinely measuring these factors might provide biomarkers that predict illness comorbidity (*35*). Whatever the case, future personalized medical treatments should consider multipronged strategies for dealing with complex disorders, such as depression and the range of comorbid symptom clusters. Such approaches ought to consider targeting the neuroimmune and neuroplastic factors that are likely to contribute to and sustain the spectrum of depressive symptoms.

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