The Inflammatory Hypothesis of Depression

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CLINICAL SYNTHESIS

Abstract: This article will review the evidence for the "inflammatory hypothesis of depression." The authors summarize the literature suggesting that immune-mediated changes contribute to the pathophysiology of MDD; describe potential underlying mechanisms; and discuss translational targets, including proinflammatory cytokines and cytokine-signaling pathways, for the development of novel antidepressants.

Introduction

For centuries, the view that the mind can shape our susceptibility to illness has captured the artistic imagination. Robert Dantzer, a pioneer in the field of psychoneuroimmunology, points to the following illustrative quote from the author, Franz Kafka, who suffered from tuberculosis (1): "It is all my mind that is ill; the affection of my lungs is nothing else than the spillover of my ill mind" (2). The reverse view, however, that the immune system may modulate the brain—and its emotional and cognitive functioning—has only recently been explored. In the 1990s, a research group in the Department of Psychiatry at the Stuivenberg in Antwerp, Belgium, found evidence of immune activation in major

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depressive disorder (MDD), including elevated levels of proinflammatory cytokines and increased numbers of peripheral leukocytes, monocytes, and T cells (3). Their findings have since been replicated and expanded by multiple independent investigators (4), giving rise to the hypothesis that "inflammation has a role in at least some significant sub-population of depressed patients" (5).

EVIDENCE LINKING MOOD AND IMMUNE SYSTEMS

A BRIEF REVIEW OF THE INFLAMMATORY RESPONSE

When pathogens invade the body, our first line of defense consists of phagocytic cells (monocytes, tissue macrophages, and liver Kupffer cells). Phagocytes possess Toll-like receptors, an ancient family of receptors, which recognize molecules that are shared by pathogens but are distinguishable from host cells (referred to as pathogen-associated molecular patterns [PAMPs]). Activated phagocytes will ingest pathogens for internal degradation; Toll-like receptors will also initiate cellular activation through increased DNA binding to the transcription factor nuclear factor-κB (NF-κB), which upregulates the expression of proinflammatory cytokines such as interferon 1 (IF-1) and tumor necrosis factor alpha (TNF-alpha).

Cytokines then mediate diverse components of the inflammatory response: cytokines, known as chemokines, attract lymphocytes to the area of infection and facilitate the flow of antigen-presenting cells to nearby lymph nodes; other cytokines trigger fever, increase blood vessel permeability, and enhance nociception. This response underlies the cardinal features of infection: dolor (pain), calor (heat), rubor (redness), and tumor (swelling) (6).

SICKNESS BEHAVIOR

In addition to recruiting local and systemic inflammatory responses, proinflammatory cytokines can also act on the brain to produce dramatic changes in behavior, termed "sickness behavior." Symptoms of sickness behavior—malaise, anhedonia, anorexia, impaired concentration, and sleep disturbance—are easy to recognize from our own experience of sickness, and closely resemble the neurovegetative features of depression. In rodent models, administration of proinflammatory cytokines or cytokine inducers have been associated with depression-like behavioral changes, including increased immobility time on the forced swim test, anhedonia, sleep disruption, and anorexia (4). These symptoms can be reversed through acute treatment with an anti-inflammatory cytokine (IL-10) or cytokine antagonist (IL-1RA) or chronic treatment with a serotonergic antidepressant (7). Additionally, mice lacking the enzyme, caspase 1, required to synthesize IL-1, exhibit reduced sickness behavior (8), and deletion of genes for the TNF-alpha receptors has been associated with antidepressant effects (9).

In humans, both biological inducers, such as microbial pathogens, and psychosocial stressors can activate the inflammatory response (7). For example, in healthy volunteers, public speaking and mental arithmetic tasks have been found to increase DNA binding to the inflammatory transcription factor NF-κB (10). In a study by Brydon and colleagues (11), healthy participants were injected with either typhoid vaccine (previously shown to induce negative mood states in healthy subjects and to increase circulating levels of inflammatory cytokines) or placebo and then exposed to rest or stress conditions. IL-6 levels were highest in the vaccine/stress group; these levels also correlated with higher levels of negative mood, suggesting a potential synergy between psychosocial and immune stressors. It is not uncommon to see in clinical practice patients who experience transient worsenings of mood in the context of upper respiratory infections and an otherwise stable response to continued antidepressant therapy. Such worsenings are typically transient and end once the infection remits.

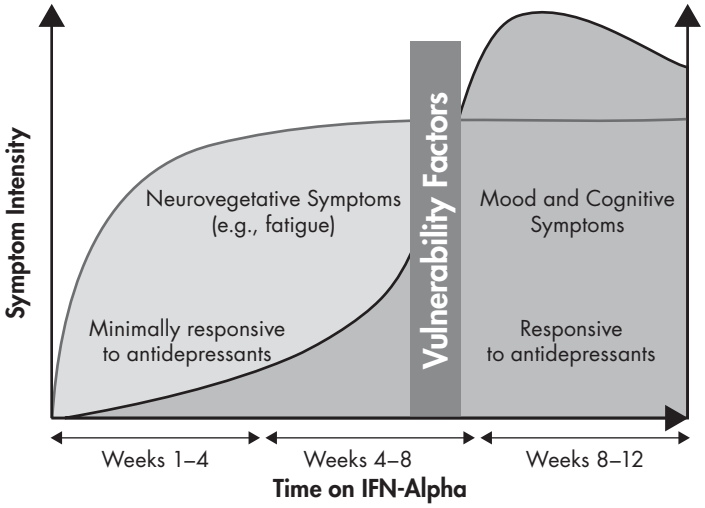
INTERFERON MODEL

Perhaps the most compelling data linking sickness behavior and depression stems from studies of cytokine therapy. Approximately 20% to 50% of patients treated with the proinflammatory cytokine, interferon-alpha, for hepatitis C or malignant melanoma will develop a clinical depression (4), and these rates can be dramatically reduced (approximately fourfold) following pretreatment with the antidepressant paroxetine (12).

Further analysis of patients receiving interferon-alpha therapy has revealed an acute phase neurovegetative syndrome, characterized by prominent malaise, sleep disturbance, and psychomotor slowing, followed by a mood and cognitive syndrome (typically 1–3 months post treatment initiation), characterized by anxiety, depressed mood, and disturbances in concentration and memory (see Figure 1) (13). Compared with the neurovegetative syndrome, the mood and cognitive syndrome is more responsive to antidepressants and more prevalent in patients with intrinsic vulnerability factors. For example, using the Montgomery-Asberg Depression Rating Scale (MADRS), Capuron and

Ravaud found that baseline mood ratings in patients with cancer could be used to predict the intensity of depressive symptoms induced by interferon-alpha (14); the same group also found that hypothalamic pituitary adrenal (HPA) axis hyperresponsiveness following the initial injection of interferon-alpha was associated with increased risk of developing depression during subsequent treatment (15). Additionally, researchers have now identified depressive subtypes among different cohorts receiving interferon-alpha therapy. A recent study found that patients treated with interferon-alpha for hepatitis C were more likely to develop depression with mixed features, including prominent irritability, anxiety, and dysphoria (16). This finding, perhaps, adds ecological validity to the interferon-induction model of depression, recapitulating the pleomorphic phenomenology of MDD found in clinical settings (17).

Figure 1. Neuropsychiatric Symptoms Seen With Interferon-Alpha Therapy



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MDD AND BIOMARKERS OF INFLAMMATION

The behavioral similarities between sickness behavior and depression have catalyzed research exploring potential immunological mediators of MDD. Proinflammatory cytokines, acute phase reactant proteins, chemokines, and adhesion molecules have been shown to be increased in individuals with MDD (18–20) or risk factors for MDD (stress, medical illness, obesity, sedentary lifestyle, diet, insomnia, social isolation, low socioeconomic status) (21) compared with healthy comparison subjects. High levels of inflammatory biomarkers have also been positively correlated with depression severity and negatively correlated with treatment resolution (22). There is also increasing evidence that elevations of proinflammatory cytokines represent a common factor underlying the bidirectional influence between major depressive disorder and chronic inflammatory disorders, such as cardiovascular disease, metabolic syndrome, and obesity (23, 24).

MECHANISMS

The following section will review how inflammatory processes in the central nervous system (CNS) may affect the pathophysiology of MDD.

PERIPHERAL CYTOKINE SIGNALS CAN ACCESS THE BRAIN

Historically, the CNS was viewed as an immunologically privileged site, sequestered from the immune system by the blood-brain barrier (25). However, in 1984, Ericsson discovered that peripheral IL-1 can stimulate catecholamine neurons projecting from the medulla to the paraventricular nucleus of the hypothalamus; additionally, the vagus nerve was shown to transmit peripheral cytokines signals directly to the brain (referred to as the neural pathway) (26). Several other neuroimmune communication pathways have also been elucidated, including a dynamic active transport system for cytokines to cross the blood-brain barrier (27, 28) (the cellular pathway); and the possibility that peripheral cytokines can penetrate circumventricular organs, leaky regions of the blood-brain barrier, and then stimulate neural elements projecting to the CNS (the humoral pathway) (29). Within the CNS, cytokine networks (consisting of microglia, astrocytes, and neurons) can influence behavior and mood through multiple mechanisms, including the modulation of neurotransmitter systems, neurotrophic factors, neuroendocrine activity, and mood-related neurocircuitry.

NEUROTRANSMITTERS

Serotonin. Beginning with research performed in the 1960s by Coppen, who found that MAOI efficacy could be enhanced by the addition of the serotonin precursor tryptophan, and later Ashcroft, who found that patients with MDD had lower CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid, serotonin has been viewed as a central neurotransmitter in the pathophysiology and treatment of MDD (30). In recent decades, the serotonin

deficit model of MDD (31) has evolved to include abnormalities of serotonin receptors, particularly 5HT-1A (32), and dysregulation of the molecular and cellular mechanisms downstream of serotonin binding (33). Additionally, a novel class of antidepressants (e.g. vilazodone), termed multimodal serotonergic agents, has emerged to target specific serotonin subsystems (34).

There is now strong evidence that high levels of proinflammatory cytokines are associated with decreased serotonergic neurotransmission. Proinflammatory cytokines can induce the enzyme, indoleamine 2,3-dioxygenase (IDO), which shunts tryptophan metabolism toward the production of kynurenine and quinolinic acid rather than serotonin (35). Similar to the serotonin depletion paradigm (36), studies of patients receiving interferon-alpha—an inducer of IDO—reveal a positive correlation between the development of depression and decreases in serum tryptophan, increases in kynurenine, and increases in the kynurenine to tryptophan ratio (a proxy for low CSF levels of serotonin) (37, 38). Interferon-alpha also stimulates p38 mitogen-activated protein kinase (MAPK) pathways, increasing expression and activity of the serotonin transporter, and, therefore, decreasing extracellular levels of serotonin (39, 40). Finally, two independent research groups have found that a polymorphism of the serotonin transporter gene (5-HTTLPR) is associated with interferon-alpha-induced depression severity (41, 42).

Dopamine. There is increasing evidence that the pathophysiology of depression involves abnormal functioning of the dopaminergic, cortico-basal ganglia reward circuitry (43). Findings of dopamine dysregulation in MDD populations include reduced concentrations of the dopamine metabolite, homovanillic acid (HVA), in cerebrospinal fluid (44, 45), reduced L-dopa uptake across the blood-brain barrier (46), reduced density of striatal dopamine transporters (47), and increased striatal binding to D2/D3 receptors (48, 49), with several conflicting studies also reported (50, 51).

Multiple animal studies have now shown that proinflammatory cytokines can decrease concentrations of dopamine (DA) and its precursor, tetrahydrobiopterin (BH4), in limbic regions of the brain (52–54). In a remarkable study using a mouse model, Qin et al. demonstrated that single exposure to systemic inflammation increased TNF-alpha production both peripherally and centrally, creating a cycle of neuroinflammation that persisted for 10 months and caused degeneration of nearly half (47%) of dopaminergic neurons in the substantia nigra (55). Interferon-alpha induced activation of the p38 MAPK pathway has also been linked to the severity of depressive episodes during cytokine therapy (56) and a putative mechanism of action, since activation of MAPK causes increased dopamine uptake, dropping synaptic levels (57).

Glutamate. Glutamate is an amino acid neurotransmitter, highly abundant in the central nervous system, which primarily functions to modulate excitatory neurotransmission. In 1990, Trullas and Skolnick first proposed the glutamate hypothesis of depression based on their findings that antagonism of NMDA receptors produced antidepressant-like effects and reversed behavioral deficits in mice exposed to inescapable stressors (58). Over the past two decades, this hypothesis has expanded from a focus on long-term potentiation and excitotoxicity to include multiple morphological and molecular mechanisms of synaptic plasticity, including neurogenesis (59). Increased levels of glutamate in the frontal cortex (60) and increased glutamatergic neurotransmission in the mesolimbic system (59) have recently been implicated in the pathophysiology of MDD.

Proinflammatory cytokines can increase glutamatergic transmission through multiple mechanisms: TNF-alpha has been shown to suppress glutamate transport and to reduce expression of the glutamate transporters, EAAT-1 and EAAT-2, leading to higher extracellular levels of glutamate (61); inflammatory cytokines also stimulate astrocytes to release glutamate (62); and quinolinic acid, a metabolite formed by activation of the IDO pathway (above) functions as a strong agonist of the glutamatergic *N*-methyl-D-aspartate receptor (63). Collectively, these changes increase net glutamate transmission, possibly contributing to excitotoxicity and loss of glial elements (64) relevant to the pathophysiology of MDD (65).

NEUROGENESIS

A growing body of data suggests that changes in synaptic plasticity, defined as changes in the number of synapses and signal transmission through a synapse, and impairments in neurogenesis contribute to the pathophysiology of MDD. In animal models, brain-derived neurotrophic factor (BDNF) signaling in the hippocampus decreases under chronic stress conditions, and increases following ECT, or sustained treatment with several pharmacodynamically distinct antidepressants (SSRIs, NERIs, MAOIs) (66). Additionally, direct infusion of BDNF into the rodent hippocampus has been shown to induce neurogenesis and produce antidepressant-like effects (67, 68). Recently, Tfilin and colleagues demonstrated that intracerebral infusion of mesenchymal stem cells also resulted in

differentiation of new hippocampal neurons, and reduced behavioral measures of depression, such as immobility time on the forced swim test (69). In humans, atrophy of the hippocampus and other forebrain regions in patients with MDD have been linked to decrements in neurotrophic factors that also regulate homeostatic plasticity (66, 70).

Cytokines have a physiologic role in modulating neural development and synaptic plasticity in humans (64). However, pathological elevation of proinflammatory cytokines has been shown to disrupt these processes and to produce depression-like behaviors (71). In a particularly novel study, Ben Menachem-Zidon and colleagues established that chronically isolated mice demonstrated a significant elevation in hippocampal IL-1 associated with weight loss, cognitive impairment, and decreased hippocampal neurogenesis. They then delivered an IL-1 receptor antagonist (IL-1ra) into the brain, using transplantation of neural precursor cells (NPCs), obtained from neonatal mice with transgenic overexpression of IL-1ra; they found that, after 4 weeks, the transplanted mice demonstrated restored hippocampal neurogenesis and reversal of depressive-like symptoms, compared with isolated mice transplanted with wild type cells or sham operated (72). Similar results have been obtained by independent investigators, who found that blockade of the IL-1β receptor (also using IL-1ra in a mouse model) reverses the antineurogenic and anhedonic effects of stress (73). Additionally, a series of animal studies have demonstrated that IL-1 effects on synaptic plasticity follow an inverted U shaped curve: constitutive low levels of IL-1 are necessary for memory formation and maintenance of synaptic strength; however, the elevated levels found in proinflammatory states decrease cell proliferation in the hippocampus and impair memory formation (74, 75). Finally, as described in the glutamate section above, induction of IDO by proinflammatory cytokines increases concentrations of the glutamate agonist, quinolinic acid, which can inhibit BDNF expression via stimulation of extrasynaptic NMDA receptors (76).

NEUROENDOCRINE FUNCTION

Abnormalities of the HPA axis have been consistently observed in subsets of depressed patients (77). The physiologic stress response begins with activation of the sympathetic nervous system, which (within seconds) releases the catecholamines epinephrine and norepinephrine into the portal circulation. A slower activation of the HPA axis then follows, with secretion of corticotrophin-releasing hormone (CRH) by the hypothalamus stimulating the pituitary to secrete adrenocorticotropic hormone (ACTH), which activates the adrenals to release glucocorticoids (cortisol) (78). Unbound cortisol can cross the blood-brain barrier and bind to the glucocorticoid receptor, leading to changes in gene transcription that can acutely upregulate immune function prior to pathogen exposure (79). MDD, however, is characterized by both HPA hyperactivity and glucocorticoid receptor insensitivity, which results in impaired negative feedback inhibition of the stress response (77).

Consistent with the stress-diathesis model of MDD (80), proinflammatory cytokines may preferentially activate the HPA axis in patients vulnerable to depression. For example, in a study of patients receiving IFN-alpha therapy for malignant melanoma, Capuron and colleagues demonstrated that patients who developed MDD during treatment exhibited a higher production of ACTH and cortisol following initial infusion of IFN-alpha compared with those who did not develop a major depressive episode (15). In contrast, chronic exposure to elevated levels of proinflammatory cytokines has been associated with depressed mood and HPA axis abnormalities characteristic of MDD, including a blunted ACTH response to intravenous administration of CRH, flattened circadian cortisol variation, and reduced glucocorticoid receptor sensitivity (81–84). Glucocorticoid resistance in MDD has specifically been correlated with high levels of IL-1 (85) and TNF-alpha (86). It is possible that this relationship is mediated by increased activity of the cytokine signaling pathways, p38 MAPK and NF-κB, which can reduce glucocorticoid receptor activity through multiple intracellular mechanisms (87).

MOOD NEUROCIRCUITRY

Neuroimaging studies of depressed patients have reported reductions in gray matter volume and glial density in the prefrontal cortex and the hippocampus (88); correlations between increased activity within the amygdala and subgenual cingulate cortex and dysphoric emotions (89); and abnormal functioning of the dopaminergic cortico-basal ganglia reward circuitry (43). Additionally, deep brain stimulation of the subgenual cingulate cortex has been shown to produce antidepressant effects in patients with treatment-resistant depression (90). Unfortunately, many published neuroimaging findings have been inconsistent (91) and limited by nonoverlapping study methodologies, heterogeneous study populations, and failure to establish causation (33).

There is now an emerging neuroimaging literature relating proinflammatory cytokines to specific changes in neurocircuitry (5). Two studies suggest

that IFN-alpha induces hyperactivity in the basal ganglia (thought to represent increased oscillatory bursts from depleted dopamine neurons), which parallels the metabolic changes found in Parkinson's disease (92, 93). Remarkably, patients treated with interferon-alpha have been found to develop Parkinson-like symptoms, which were relieved by treatment with levodopa (94). Additionally, multiple studies have shown increased activation of the dorsal anterior cingulate cortex (dACC) associated with elevated levels of proinflammatory cytokines (95–97); the dACC has been hypothesized to function as a "neural alarm system" for threatening social stimuli (98), and has also been found to be hyperactive in patients with high ratings of neuroticism (99), a robust risk factor for MDD (100).

EMERGING TREATMENTS

PHARMACOLOGICAL INTERVENTIONS

A number of antidepressant medications have shown anti-inflammatory properties: for example bupropion lowers production of TNF-alpha and interferon-gamma in mice (101), hypericum extracts have produced antiinflammatory activity in the rat paw edema test (102), and *S*-adenosylmethionine suppresses TNF-alpha production (103). In addition, there is growing evidence that immune-modulating medications may translate into a novel class of antidepressants. In a study of patients with psoriasis, Tyring and colleagues found that individuals randomly assigned to treatment with the TNF-alpha antagonist, etanercept, had significantly greater improvements in depressive symptoms (measured by the HAM-D-17) compared with controls; changes in core features of depression were only weakly correlated with objective measures of skin clearance and joint pain (104). In a proof-of-concept study, Müller and colleagues found that depressed patients randomly assigned to treatment with reboxetine combined with the COX-2 inhibitor celecoxib showed greater improvements in depression (measured by the HAM-D-17) compared with controls treated with reboxetine alone (105). Finally, a large randomized controlled trial of the TNF-alpha antagonist infliximab for treatment-resistant depression has recently been completed, suggesting that TNF antagonism may have preferential antidepressant effects for patients with high baseline levels of proinflammatory cytokines (106). Other potentially promising pharmacological agents include inhibitors of the inflammatory cytokines, IL-1, IL-6, and interferon-alpha; modulators of the cytokine signaling pathways NF-kB, p38 MAPK, and STAT5; and augmenters or agonists of the anti-inflammatory cytokines IL-10 and TGF (5).

POSSIBLE PREFERENTIAL RESPONDERS

Treatments specifically targeting inflammation may not be appropriate for every patient with depression. However, MDD patients with elevated inflammatory biomarkers (106) and/or comorbid chronic inflammatory diseases, such as autoimmune diseases, cardiovascular diseases, and obesity, may be more likely to respond to immune-modulating agents. For example, Howren and colleagues found positive correlations between body mass index (BMI) and circulating levels of IL-6 and CRP (107); and a recent study by Capuron et al. suggests the higher prevalence of neurovegative symptoms in patients with metabolic syndrome is associated with increased inflammation (108). Depressed patients experiencing acute psychosocial stress, and/or those with a history of child abuse, both of which are associated with hypersensitized innate immunity, may constitute additional subgroups of preferential responders (109, 110). Finally, insomniacs and men who are socially isolated also tend to have higher levels of inflammation and could, therefore, potentially derive greater mood benefits from CNS targeted anti-inflammatory compounds (111–113).

SUMMARY

This article is intended to provide a framework for understanding the inflammatory hypothesis of depression. We have covered the following key points:

- The acute immune response is mediated by diverse cytokines and cytokine signaling pathways
- Proinflammatory cytokines can also act acutely on the brain to produce "sickness behavior," characterized by symptoms that closely resemble the neurovegetative features of MDD
- The prevalence and phenomenology of depression associated with interferon-alpha therapy for medical illnesses have provided a human model of cytokine-induced MDD; research suggests that pretreatment with SSRIs has protective effects
- Increased inflammatory biomarkers are associated with MDD and may contribute to the high comorbidity between MDD and chronic inflammatory diseases
- Proinflammatory cytokines may contribute to the pathophysiology of MDD, and have been shown to modulate neurotransmitter systems,

neurotrophic factors, neuroendocrine activity, and mood-related neurocircuitry
- Immunological agents targeting proinflammatory cytokines and cytokine signaling pathways may represent a novel class of antidepressants

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