

Phagocytes and fluid move into area

Phagocytes

TUMOR NECROSIS FACTOR- α

CYTOKINES

C-REACTIVE P

INFLAMMATION

DEPRESSION



DEPRESSION AND INFLAMMATION: Examining the link

Inflammatory conditions may precipitate or perpetuate depression, but the precise relationship is unclear

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Sneezing, coughing, and a sore throat are hallmark symptoms of a common cold, but what keeps you in bed are the accompanying fatigue, inattentiveness, loss of appetite, change in sleep pattern, heightened perception of pain, and apathetic withdrawal. This “sickness behavior” is induced by inflammatory markers released in response to illness.^{1,2} These symptoms are similar to the constellation of symptoms that define depression. Within the inflammatory response to illness, we see the shadow of depression, but the precise relationship remains murky.

Is depression part of a normal somatic inflammatory response run amok? Some researchers have argued that “sickness behavior” is adaptive, forcing the body into a constricted pattern in order to funnel energy into healing.^{1,3} If depression and inflammation are related, depression pushes past these adaptive roots and is less a forced pause than a debilitating withdrawal. Perhaps depression, or a subtype, is a sign of inflammation along with heat, pain, redness, and swelling. In some instances, depression may be a sign of an underlying inflammatory process.⁴

In our progression toward understanding depression’s pathophysiology, we see factors that point to a relationship between depression and inflammation:

- depression frequently is comorbid with many inflammatory illnesses
- increased inflammatory biomarkers are associated with major depressive disorder (MDD)
- exposure to immunomodulating agents may increase the risk of developing depression
- stress can activate proinflammatory pathways
- antidepressants can decrease inflammatory response
- inhibition of inflammatory pathways can improve mood.

continued



Depression and inflammation

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Depression is relatively common among individuals with inflammatory illnesses



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Table

Evidence linking inflammation and depression

Study	Sample	Comments
Dowlati et al, 2010 ¹⁴	A meta-analysis of 24 studies measuring cytokine concentrations in patients with MDD	Depressed patients had significantly higher concentrations of TNF- α and IL-6 compared with controls
Maes et al, 1997 ¹⁵	15 controls and 35 inpatients with MDD. Serum IL-6, IL-6 receptor, IL-1 receptor antagonist, Clara cell protein 16, and sCD8 were measured at baseline and at 5 weeks after antidepressant treatment	Serum IL-6 and IL-1 receptor antagonist were higher in individuals with depression or treatment-resistant depression compared with controls
Raison et al, 2005 ¹⁶	162 patients with hepatitis C infection were assessed for depressive symptoms at baseline and after 4, 8, 12, and 24 weeks of IFN- α 2b treatment plus ribavirin	Thirty-nine percent of subjects experienced moderate to severe depressive symptoms. Depression scores were increased by week 4 and remained elevated throughout the study
Capuron et al, 2003 ¹⁷	14 patients with malignant melanoma. ACTH, cortisol, and IL-6 were measured during the first 12 weeks of IFN- α therapy	ACTH and cortisol responses but not IL-6 responses to IFN- α were significantly higher in the 7 patients who developed depression
Eisenberger et al, 2010 ¹⁸	39 participants were randomized to placebo or low-dose endotoxin, which increases proinflammatory cytokine levels	Individuals exposed to endotoxin showed greater increases in self-reported and observer-rated depressed mood compared with placebo
Pasco et al, 2010 ¹⁹	A retrospective cohort study of 1,494 randomly selected women	The hazard ratio for depression increased by 44% for each standard deviation increase in high-sensitivity CRP
Raison et al, 2013 ²⁰	60 depressed patients who were on a consistent antidepressant regimen or medication-free were randomly assigned to 3 infusions of infliximab (5 mg/kg) or placebo at baseline and weeks 2 and 6 of a 12-week study	There was a significant interaction between treatment, time, and baseline high-sensitivity CRP and change in depression scores in infliximab-treated patients with baseline CRP concentration >5 mg/L
Martinez et al, 2012 ²¹	CSF levels of IL-1, IL-6, TNF- α , BDNF, and NPY were measured in 18 patients with MDD and 25 controls; depressed patients received 8 weeks of depression treatment	At baseline, depressed patients had higher NPY concentrations compared with controls; researchers found statistically significant correlations between elevated cytokine levels and depression severity

ACTH: adrenocorticotropic hormone; BDNF: brain-derived neurotrophic factor; CRP: C-reactive protein; IFN- α : interferon α ; IL: interleukin; MDD: major depressive disorder; NPY: neuropeptide Y; TNF- α : tumor necrosis factor- α

Exploring these factors and a possible pathway linking inflammation and neurobiologic changes found in depression allows us to look closer at the possible integration of the inflammatory process and depressive symptoms.

Illness and depression rates

Individuals with inflammatory illnesses—autoimmune diseases, cardiovascular disease, diabetes, and cancer—often struggle with depression. Nearly 1 in 5 persons with cardiovascular disease experiences MDD.⁵ A diabetes diagnosis doubles the odds of having depression.⁶ Up to 70% of patients with autoimmune diseases, such as rheumatoid

arthritis or systemic lupus erythematosus, experience depression.^{7,8} In a large-scale longitudinal study, having a prior autoimmune disease increased the risk of depression by 45% and history of hospitalization with infection increased a patient's risk by 62%; the risk more than doubled in individuals with both.⁹ Several studies show that 15% to 25% of cancer patients experience depression,¹⁰ compared with 9% in the general population.¹¹

Role of inflammatory markers

During an inflammatory episode the body releases cytokines, which are small, cell-signaling protein molecules. These inflammatory markers launch signaling cascades that incite

the immune system into action. Type 1 cytokines (interferon- γ , tumor necrosis factor- α [TNF- α], interleukin [IL]-1) enhance cellular immune responses, and type 2 cytokines (IL-6, IL-10, IL-13) engage antibody responses. These cytokines also induce acute phase proteins, such as C-reactive protein (CRP), which can activate the immune system. Significantly higher levels of inflammatory markers are associated with a range of depressive symptoms, which grants insight into disease severity and treatment response.^{3,12,13}

Multiple studies have explored the link between depression and inflammatory markers (Table).¹⁴⁻²¹ Peripheral inflammatory markers such as IL-6, IL-1 β , CRP, and TNF- α are elevated in inflammatory diseases and in otherwise healthy individuals with MDD.¹² In a meta-analysis of 24 studies measuring cytokines in depressed patients, Dowlati et al¹⁴ found individuals with MDD had significantly higher concentrations of TNF- α and IL-6 compared with controls. Increased peripheral inflammatory markers were found among antidepressant nonresponders more often than those who responded to treatment.^{15,22}

Cytokines and depression risk

Administering immunomodulating agents has been shown to increase the risk of developing depression. Injecting animals with IL-1 β or TNF- α causes sickness behavior in a dose- and time-related manner.¹ As these inflammatory signaling proteins increase, sickness behaviors become more pronounced.

In humans, a natural model arises in the use of the cytokine interferon- α (INF- α) for treating hepatitis C, multiple sclerosis, malignant melanoma, and some blood cancers. Patients receiving INF- α have higher rates of depression than those not administered interferon.¹⁶ Patients receiving chronic immunotherapy treatment show long-term changes in monoamine neurotransmitters and along the HPA axis; these changes mimic those seen in depressed individuals.^{17,23} Acutely administered immunotherapeutic agents, such as the typhoid vaccine, have led to depressive symptoms with brain changes similar to those seen in MDD.¹⁸ Low levels of IL-6 and CRP independently predicted development of depression over several years.¹⁹

Immunotherapy-induced depression looks similar to any other major depressive episode through our current diagnostic framework and at the molecular and anatomical level.

Stress and inflammation

Depression can develop in the absence of inflammatory illness. Knowing that depressive symptoms may be associated with increased peripheral inflammatory markers, what induces the inflammatory process in some persons who are depressed but medically healthy? One theory is that psychological stress can activate inflammation.

Acute and chronic stress is associated with increased availability of proinflammatory cytokines and decreases in anti-inflammatory cytokines.^{3,24} One theory looks to glucocorticoid response to stress as an explanation. Miller et al²⁵ found glucocorticoid sensitivity decreased among depressed women after exposure to a mock job interview stressor and increased among nondepressed controls. Because glucocorticoids normally stop the inflammatory cascade, this finding suggests depressed individuals may not be able to control inflammation during stress.²⁶ At the level of genetic expression, there is increased transcription of proinflammatory genes in response to stress as a result of increased activation of nuclear factor kappa B.^{3,27}

Shared pathways

If there is a relationship between inflammation and depression, what is the possible shared pathway?

There are 4 pathways by which cytokines effect changes in the CNS:¹²

- cytokines can activate primary afferent neurons (eg, vagal nerve)
- cytokines, released by macrophage-like cells in response to pathogens, diffuse through the brain's circumventricular organs
- cytokine transporters saturate the blood-brain barrier
- cytokine IL-1 activates receptors on perivascular macrophages and endothelial cells of brain venules, causing local release of prostaglandin E2.

Through these pathways, cytokines initiate a cascade of reactions that lower serotonin

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Immunomodulating agents have been shown to increase the risk of developing depression



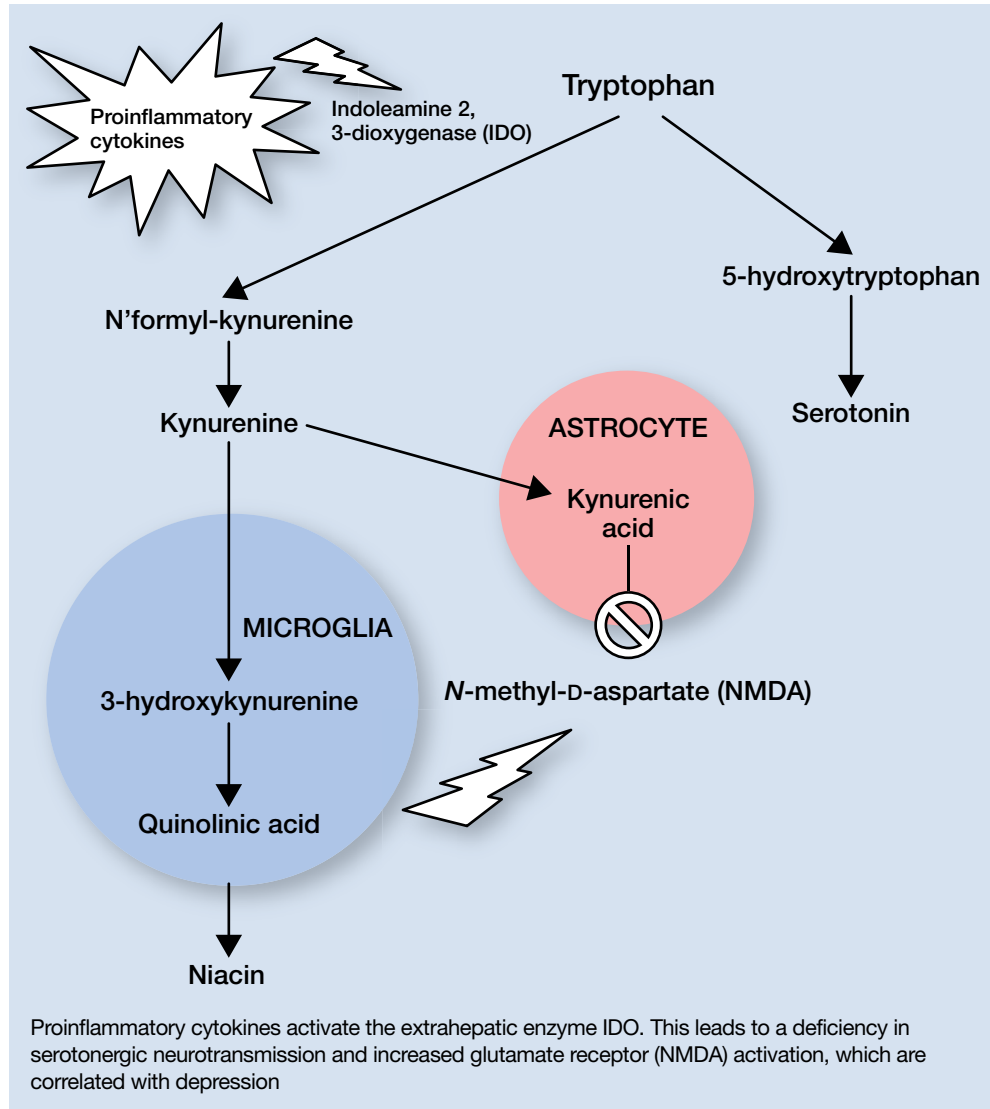
Depression and inflammation

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Cytokines initiate a cascade of reactions that lower serotonin levels and boost glutamatergic actions, possibly contributing to depression

Figure 1

Tryptophan metabolism



levels and boost glutamatergic actions, possibly contributing to development of depressive symptoms. Depression correlates with a deficiency in serotonergic neurotransmission and increased glutamate receptor *N*-methyl-D-aspartate (NMDA) activation.²⁸

Proinflammatory cytokines activate the extrahepatic enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan, a precursor to serotonin (Figure 1). Tryptophan is channeled increasingly toward production of kynurenine via IDO degradation, competing with the serotonin pathway. Within the microglia, which are preferentially activated over astrocytes during inflammatory states, kynurenine

is metabolized into quinolinic acid, which is an agonist of glutamatergic NMDA receptors.²⁸ Therefore, there is a serotonergic deficiency and glutamatergic overdrive in proinflammatory states that paves the way toward a likely depressive syndrome (Figure 2, page 30).

Antidepressants' effects

The symptoms of cytokine-induced depression are no different from MDD with unknown etiology²⁹ and both are effectively treated with antidepressants. Even sickness behavior can be improved with antidepressant treatment.³⁰



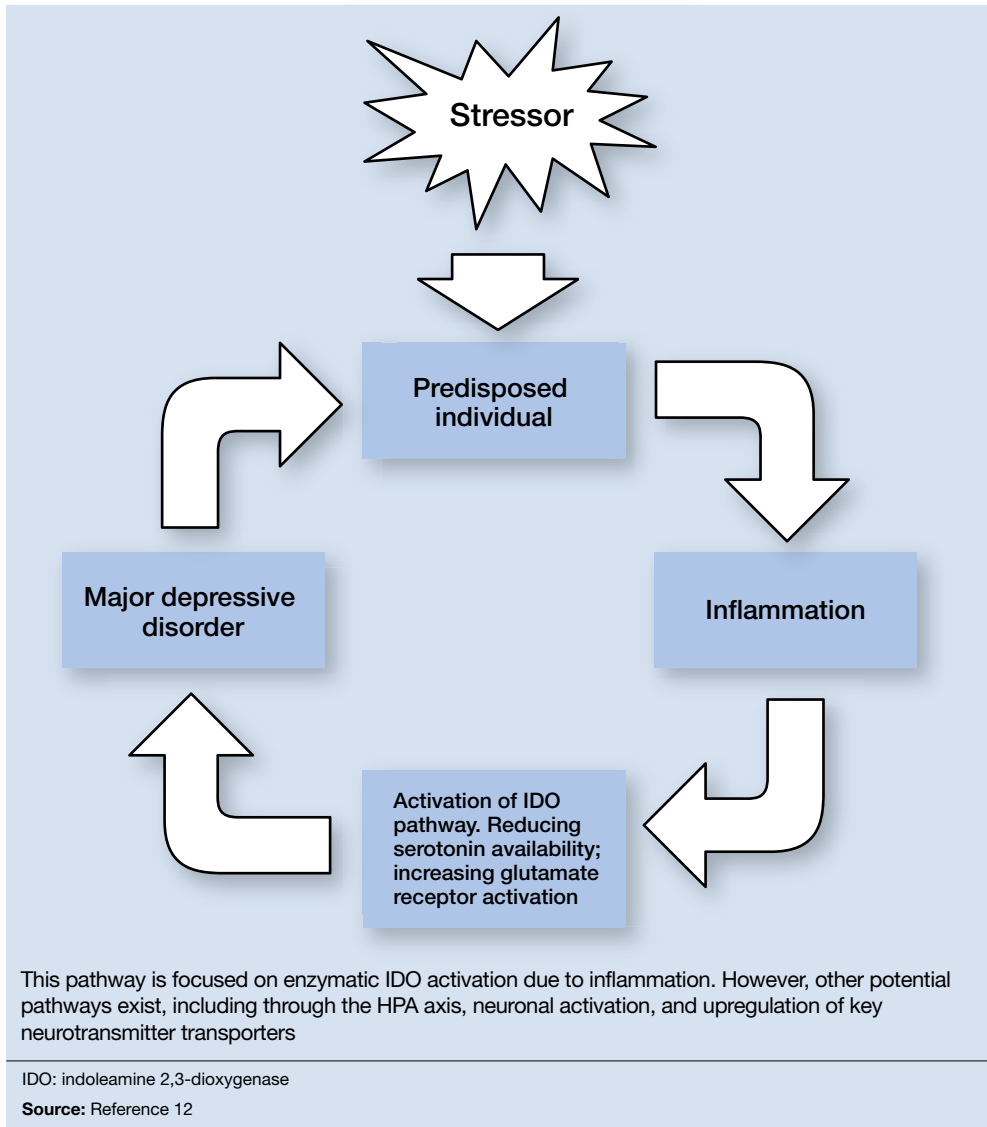
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Antidepressants decrease inflammatory response and lower proinflammatory factors

Figure 2

Pathway linking stress, inflammation, and depression



Antidepressants not only decrease immunotherapy-induced depressive symptoms but have been shown to decrease inflammatory response and lower proinflammatory factors (IL-2, IL-6, TNF- α , and INF- γ).³¹⁻³³ Electroconvulsive therapy has been shown to normalize elevated TNF- α levels.³⁴

Enhancing depression treatment

Researchers are investigating whether treatment with anti-inflammatory agents can ease depressive symptoms. In animal studies, normal behavioral reactions to a stressor—similar to sickness behavior and overlapping

with several features of depression—were reduced with administration of cytokine antagonists or anti-inflammatory cytokines directly into the brain.³⁵ However, there have been few successful trials in humans. Both anti-inflammatory agents such as cyclooxygenase-2 (COX-2) inhibitors, acetylsalicylic acid (aspirin), and TNF receptor antagonists can enhance depression treatments. Persoons et al³⁶ found that Crohn’s disease patients who had higher pretreatment CRP levels and MDD had greater remission of depressive symptoms after treatment with the TNF- α antagonist infliximab. In studies, depression within the context of other autoimmune

disorders or any condition with increased inflammation has responded to treatment with TNF- α antagonists.^{37,38} COX-2 inhibitors added to a standard antidepressant regimen improved depressive symptoms in medically healthy individuals during an acute depressive episode.³⁹ Aspirin has shown some benefits as an adjuvant agent in persons who have failed selective serotonin reuptake inhibitor monotherapy.^{40,41}

These anti-inflammatory agents have shown benefits in treating depression in some persons, but not in all. The key difference between those subsets of patients is elusive, mired in the complex interactions of the many systems that contribute to the symptoms we label as depression.

Future clinical applications

The association between depression and inflammation raises the possibility of a tantalizing line of future theories and treatment options. However, when considered individually, these pieces are limited in defining the precise relationship—a task nearly impossible for such a diffuse symptom as inflammation and such a complex disease as depression.

It is evident that inflammation and depression form a strong relationship to each other in individuals, which suggests the possibility of an inflammatory subtype of depression. At least within that limited group, there is the possibility of successful intervention and treatment of depression by directly treating inflammation with anti-inflammatory agents.

Perhaps once the relationship between depression and inflammation is further defined and a high-risk population identified—maybe even by genotype—depressive symptoms might be used to flag a provider's attention to a possible disease process and serve as a new tool for identifying dangerous inflammatory activity at an early stage. Managing stress and depression may become the next tool to prevent inflammatory diseases.

Given our current knowledge, clinicians treating patients with inflammatory conditions should be aware of the increased risk of depression and ensure that depres-

Related Resources

- The Emory University Mind-Body Program. www.psychiatry.emory.edu/PROGRAMS/mindbody/index.html.
- Gabriel B. The evolutionary advantage of depression. The Atlantic. October 2, 2012. www.theatlantic.com/health/archive/2012/10/the-evolutionary-advantage-of-depression/263124.

Drug Brand Names

Infliximab • Remicade Ribavirin • Rebetol, Virazole
Interferon- α • Intron

Disclosure

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sion screening is routinely completed and treatment is initiated or referrals made as needed. Ensuring appropriate depression treatment may help improve patients' quality of life and ease the inflammatory response itself.

For psychiatrists seeing patients with an inflammatory condition, brief explanations of the known links between depression and inflammation can provide patients—particularly those ambivalent about seeking mental health care—support for engaging in treatment and adhering to medication. Describing the links between inflammation and depression also can help encourage regular exercise and healthy diets rich in fruits, vegetables, and omega-3 fatty acids. In cases of treatment-resistant depression, particularly in those with known high inflammatory factors, it may be worthwhile to consider anti-inflammatory agents, such as infliximab, as an adjuvant treatment.

The relationship between inflammation and depression is rapidly unfolding, but the full intricacies have not yet described. However, this beginning awareness of the interplay among stress, inflammation, and depression can broaden our approach to care and treatment.

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Anti-inflammatory agents, such as COX-2 inhibitors, have shown benefits in treating depression in some persons, but not all



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Depressive symptoms might signal a possible disease process and serve as a tool for identifying inflammatory activity

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Bottom Line

Depression and inflammation are linked in many ways, although neither appears to be wholly necessary or sufficient for the other. Most likely there exists a particular subset of patients for whom inflammation will precipitate and perpetuate depression.