Will finding the depression–inflammation link lead to tailored treatments for MDD?

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There is an association between inflammation and depression: Patients with a major depressive disorder (MDD) have elevated levels of pro-inflammatory cytokines interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). Abnormal cell-mediated immunity and lymphocyte proliferation also have been reported in patients with MDD[1-2] (***Box, page 54***).[1,3-7]

What remains unclear is whether inflammation is *causative* in affective illness,[1-4] and how the association might be exploited for the benefit of a subset of MDD patients.

Underpinnings of pathophysiology

Immune system activation leads to production of cytokines, which 1) influences the synthesis, reuptake, and release of neurotransmitters and 2) stimulates the manifestations of depression.[1,2] Interferon-γ and TNF-α are involved in neuronal degeneration and inhibition of neurogenesis in the brain, especially the hippocampus—thereby explaining observed cognitive deficits in depression.

Production of cytokines in serum and cerebrospinal fluid can be triggered by psychosocial stress, administration of interferon-α or IL-2, and acute stimulation of the immune system after vaccination; this production of cytokines is associated with development of MDD.[1-3] Inflammatory disorders raise a person's vulnerability to MDD; affective illness is the most common psychiatric condition seen in association with multiple sclerosis, for example.[2]

Principal receptor targets

Glucocorticoid receptors. Synchrony between the hypothalamic-pituitary-adrenal axis and adrenal function occurs during stressful circumstances.[2] Down-regulation, or reduced activity, of glucocorticoid receptors in depression leads to glucocorticoid resistance, resulting in hyperactivity of this axis. TNF-α is associated with glucocorticoid resistance by its action in opposing the influx of the cortisol-glucocorticoid receptor complex into the nucleus and inhibiting its linkage with DNA. Cytokines increase levels of corticotropin-releasing hormone and adrenocorticotrophic hormone, leading to a higher-than-normal cortisol concentration in depressed patients.[8]

***N*-methyl-D-aspartate (NMDA) receptors** are involved in the monoamine and glutamatergic pathways that are associated with depression.[2] NMDA-receptor activation raises the intracellular calcium concentration, causing neuronal cell death. Inflammatory mediators, including TNF-α, induce activation of the kyneurin pathway. Thus, instead of serotonin production, tryptophan is diverted to the synthesis of the NMDA-receptor agonists kynurenine and quinolinic acid, which leads to apoptosis.

The glutamatergic pathway involves binding of IL-1β and IL-1R complexes to hippocampal NMDA receptors.[2] Persistent activation of these receptors results in calcium toxicity and neuronal death. Reuptake inhibition of neurotransmitters is explained by the action of IL-1β on reuptake of glutamate, which enhances its availability to stimulate NMDA-receptor activation.

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Psychosocial stresses initiate inflammatory responses that might result in affective illness

Box

What we are learning from clinical research

Two studies provided evidence that depression might precipitate inflammation, or result from it:

- An association between increased levels of IL-6 and C-reactive protein (CRP) and subsequent onset of depression was documented in a 12-year study[1,4]—revealing that inflammation can precede onset of affective illness and hasten relapse.
- Investigation of the CRP level in children who were followed to age 21 documented an elevated concentration after onset of depression.[1,5]

In addition:

- Children who were abused in early childhood—physically, emotionally, or sexually—are prone to persistently elevated concentrations of IL-6 and CRP and hyperactivity of the hypothalamic-pituitary-adrenal axis.[1,6,7]
- An elevated level of circulating cortisol and an abnormal dexamethasone suppression test have been observed in patients with MDD.[1]

Any prospects for therapeutics?

As described, an association exists between inflammation and depression. Psychosocial stresses initiate inflammatory responses that might result in affective illness. In treating depression and preventing its relapse, the question is whether psychotherapy provides clinical efficacy through stress reduction, thereby leading to potential anti-inflammatory action.[1]

Inflammation has a detrimental influence in a subset of MDD cases.[9] Identification of those patients through genetic research is ongoing, with the goal of establishing specific anti-inflammatory or antidepressant therapies.

Anti-inflammatory drugs such as aspirin, celecoxib, and etanercept do induce antidepressant effects and augment the antidepressant response to other therapies.[1,3] In the future, anti-inflammatory treatments might become an option for select MDD patients.

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