Editorial

Bidirectional Inflammation-Depression Associations and the Dynamic Intersection of Inflammation with other Pathophysiological Correlates

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Major depression is a common disabling disorder that affects about 280 million people worldwide (1-3) and is predicted to become the main contributor to global Disability-Adjusted Life Years (DALY) by 2030 (4). The costs imposed by depression and its complications in the United States reach more than 200 billion annually - considering occupational problems and suicide of patients (5). There are effective treatments for depression, but about one-third of patients are resistant to treatment. In addition, Electroconvulsive Therapy (ECT) has been reported to be beneficial for only half of refractory patients (4,6). A better understanding of the neuropathophysiology of the disorder, which leads to more appropriate and useful classifications, preventions, and treatments, seems to be a solution.

After the monoaminergic system, the glutamatergic system and, recently, the neuroinflammation hypothesis have been proposed in the pathophysiology of major depression. Inflammation disrupts the regulation of the Hypothalamus-Pituitary-Adrenal (HPA) axis and the production of neurons in the hippocampus (7). Inflammatory cytokines disrupt the serotonin production pathway by decreasing Brain-Derived Neurotrophic Factor (BDNF) expression and increasing tryptophan oxidation (8). Decreased levels of BDNF and decreased signaling between it and its receptor in the hippocampus and prefrontal cortex cause depression (9). The result of the oxidation of tryptophan is kynurenine, whose compositions have agonistic and antagonistic effects on the N-methyl-d-aspartate (NMDA) receptor, a major player in the glutamatergic system (8,10). In general, the evidence shows the complexity and overlap of systems in the pathoetiology of inflammatory depression. Regarding this, even a subtype called Inflammatory Cytokine-Associated Depression (ICAD) has been suggested so that different treatment approaches can be considered for these patients (10).

There is clinical evidence for these proposed mechanisms. An imbalance in the levels of kynurenine metabolites in patients with depression and an increase in the levels of pro-inflammatory cytokines in patients with resistant depression have been reported. Another

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suggester is its higher prevalence in patients with chronic autoimmune connective tissue disorders and exacerbated activation times of the innate immune system (11). The administration of cytokine and interferon for the treatment of cancer and hepatitis C, respectively, has led to depression in patients (7,10,11). Moreover, anti-inflammatory compounds such as celecoxib, simvastatin, pioglitazone, and dexamethasone have shown antidepressant effects in various trials (8).

Blood levels of Interleukin-6 (IL-6) and C-Reactive Protein (CRP) are associated with depression, so that inflammation measured through these two predicts future depression (13). The levels of peripheral inflammatory cytokines have also been helpful in predicting patients' responses to antidepressant treatment. Specifically, lower baseline IL-8 levels have been reported to lead to a better response to antidepressants. Additionally, antidepressant responders had a significant reduction in Tumor Necrosis Factor-α (TNF-α) (10,12).

It seems that any primary neuroinflammation of the brain and any chronic inflammatory condition that produces markers crossing the blood-brain barrier and even chronic stress on the vessels can cause depression (7). Also, genetics, cellular damage, obesity, stress, diet, and gut microbiome can fuel chronic inflammation (10). Considering that inflammation predicts future depression and depression is a predictor of IL-6, it is possible to suggest a bidirectional relationship between inflammation and depression. The evidence promises an important therapeutic target for major depression treatment approaches. Also, more research is necessary to investigate the possibility of using inflammatory cytokines as biomarkers of response to pharmacological treatment and even other treatments.

Conflict of Interest
The authors have no conflict of interest.

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