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Editorial

The Inflammatory Mechanism in Depression and Some Possible Effective Agents

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Depression is a debilitating psychiatric disorder that affects more than 264 million people worldwide and is one of the main contributors to global Disability-Adjusted Life Years (DALY) (1). Limitations in psychosocial functioning, propensity to use drugs and alcohol, reduced quality of personal and professional life, and suicide in patients are alarming (1,2). The economic costs of the disorder and its individual and social effects in the United States are more than $ 200 billion annually (3).

The combination of psychotherapy and pharmacotherapy is the first line of treatment for depression (2). Tricyclic Antidepressants (TCAs) and Mono Amine Oxidase Inhibitors (MAOIs) are the first generation of antidepressants introduced in the 1950s. The second generation of antidepressants is Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs). Because of the reported efficacy and tolerability, SSRIs are the first line of pharmacotherapy, and TCAs and MAOIs are in the second and third lines, respectively (2,3).

Conventional drugs have moderate efficacy, clinically significant delay to the onset of therapeutic effects, and relatively low response and remission rates (4), in which cases sub-syndrome symptoms persist and reduce patients' quality of life (5). To overcome this resistance to treatment, scientists and researchers have suggested various ways, including a closer study of neuropathophysiology and the use of new therapies, drug repositioning, and combination and adjunctive therapies (4).

In the pathophysiology of depression, most attention has been paid to the serotonergic system; however, recently, the glutamatergic system has also been considered (6). However, none have been sufficient for treatment so far, and there have been some doubts about the effectiveness of drugs that work on these mechanisms (7). Another mechanism proposed is the inflammatory mechanism and cell-mediated immune activation, which, although there is evidence in favor of inflammatory activity in this disorder, is usually neglected in the treatment of the patients due to fewer high-quality clinical studies (8,9). Herein, the inflammatory mechanism in depression with molecular and clinical approaches and provide novel examples of agents that may be effective

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through this mechanism are briefly explained.

Pathophysiology of inflammation in depression

Administration of Lipopolysaccharide (LPS), a bacterial endotoxin used to build an inflammation-related depression model, activates pro-inflammatory cytokines that highly induce the ubiquitous In D Oleamine 2,3-dioxygenase (IDO) activity (10,11). IDO reduces tryptophan *via* oxidation and increases tryptophan-derived metabolites, the main of which is kynurenine. Tryptophan is a precursor of serotonin. The consequence of decreased serum tryptophan levels, which results in decreased serotonin synthesis in the brain, is depression. 3-hydroxykynurenine, quinolinic acid, and kynurenic acid compose kynurenine, which are inducers of oxidative stress and lipid peroxidation, the N-Methyl-D-Aspartate (NMDA) receptor agonist, and the NMDA and α 7 nicotinic acetylcholine receptors antagonists, respectively. Changing the balance of this path can cause depression (11).

Administration of LPS and pro-inflammatory cytokines also reduces the expression of the Brain-Derived Neurotrophic Factor (BDNF) gene (10,12). Tropomycin receptor kinase B (TrkB) is a BDNF receptor. Decreased signaling between BDNF and its receptor in the hippocampus and prefrontal cortex has been reported to cause inflammation and depression. In contrast, BDNF levels have been shown to increase in the ventral tegmental area-nucleus accumbens pathway in depression. As a result, TrkB agonists in the hippocampus and prefrontal cortex and its antagonists in the ventral tegmental area-nucleus accumbens may have antidepressant effects (12).

Agents

This section discusses examples of medications and supplements that may have antidepressant effects through anti-inflammatory mechanisms. table1 summarizes the mechanism of action of each.

Celecoxib is an inhibitor of the enzyme cyclooxygenase-2 (COX-2), which although the antidepressant action of drugs with this mechanism is unclear, it has been suggested that they may exert their antidepressant effect by reducing the levels of pro-inflammatory cytokines. In a six-week placebo-controlled double-blind randomized trial, Müller *et al* reported that the combination of reboxetine and celecoxib (400 *mg* daily) was superior to reboxetine plus placebo in reducing Hamilton Depression Rating Scale (HDRS) scores and had no different side effects (13).

S-Adenosyl Methionine (SAMe) is a metabolite derived from the amino acid methionine and the precursor of glutathione and is formed naturally in the human body (14). It has been reported that SAMe, a primary methyl donor, can compensate for the decrease in BDNF levels by demethylation in one of the eight promoters of one of the eight BDNF exons (15). Indeed, SAMe exerts neuroprotective effects by increasing the expression of endogenous BDNF in the hippocampus (14). A systematic review of eight randomized controlled double-blind clinical trials with eleven arms reported that SAMe was better than placebo in three trials, not different from imipramine and es-citalopram in four trials, was better than placebo in accelerating the response to imipramine from day 4 to 12, and performed better in a trial in combination with different SSRIs than placebo (16).

Carnosine (beta-alanyl-L-histidine), an imidazole dipeptide, can cross the blood-brain barrier inducing brain cells to express and secrete BDNF, and can also activate the cAMP-response element-binding protein CREB and CREB-related pathways (17).

Table 1. Proposed anti-inflammatory mechanism in depression for exemplified agents

Agents	Proposed anti-inflammatory function in depression
Celecoxib	Reducing the levels of pro-inflammatory cytokines
S-adenosyl methionine	Increasing the expression of endogenous BDNF
Carnosine	Enhancing the BDNF pathway and activating CREB

BDNF: brain-derived neurotrophic factor; CREB: cAMP-response element-binding protein.

In a six-week placebo-controlled double-blind randomized clinical trial, Araminia *et al* found that combination therapy with citalopram and carnosine (400 *mg* twice daily) was more effective and faster than citalopram and placebo without significant side effects (18). The observed rapid-onset antidepressant effect may be in line with the fact that a decrease in serotonin synthesis following a decrease in tryptophan levels induces depression within hours (19). As mentioned, the effect of carnosine on the inflammatory mechanism of depression is through the BDNF pathway (17). BDNF is effective on the enzyme tryptophan hydroxylase. BDNF infusion has been reported to induce mRNA expression of this enzyme in the rat brain as early as 24 hours (20). Also, in a clinical study, tryptophan depletion resulted in increased BDNF levels in healthy individuals (21).

Conclusion

After serotonergic and glutamatergic systems, each of which has had significant success in treating depressed patients, research has focused on the inflammatory mechanism in depression. Small sample size, limiting the inclusion of patients, for example, in terms of age (excluding the elderly) and disease severity, not investigating the effectiveness of monotherapy, relatively short treatment period, and lack of follow-up of patients after the end of the treatment period are examples of limitations of a significant number of studies. Although studies in this area still have significant limitations, this mechanism has a reasonable molecular backing supported by clinical evidence. Because of the prevalence, burden, and resistance to treatment of depression, it is recommended that further high-quality studies fill the gaps in the current literature.

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Conflict of Interest

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