Inflammation in Depression: The Role of Cytokines

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ÖZET

Depresyonda inflamasyon: sitokinlerin rolü

Son yıllarda yapılan çalışmalar majör depresyonun patolojisinde inflamatuvar mekanizmaların önemli rol oynadığını göstermektedir. Majör depresyonda, inflamatuvar sitokinlere verilen yanıt olan "hastalık davranışı"na benzer belirtiler görülmektedir. Depresif hastaların plazma ve beyin omurilik sıvılarında proinflamatuvar sitokinler ve inflamasyonla bağlantılı proteinlerin miktarında artış gözlenir. Hastalığın prognozu da sitokin değerlerindeki değişmelerle paralellik göstermektedir. Antidepresan tedavi ile sitokin seviyeleri normale çevrilebilmektedir. Depresyonun bu yeni hipotezi, tedavide de yenilikleri gündeme getirmiştir.
Anahtar sözcükler: Sitokin, inflamasyon, depresyon, antidepresan

ABSTRACT

Inflammation in depression: the role of cytokines

Recent studies support the concept that inflammatory mechanisms play a crucial role in the pathomechanisms of major depression. Major depression shares similarities with 'sickness behavior', a normal response to inflammatory cytokines. Elevations in proinflammatory cytokines and other inflammation-related proteins in major depression were found in plasma and cerebrospinal fluid (CSF). Clinical progress of the disease may also be predicted by the changes in proinflammatory cytokine levels. Antidepressant treatment can lead to a normalization of elevated cytokine levels in major depression. The new hypothesis of depression provided some new opportunities in treatment of depression.
Key words: Cytokine, inflammation, depression, antidepressant

INTRODUCTION

The "inflammatory" hypothesis of depression was based on findings on increased levels of proinflammatory cytokines produced by monocytes/macrophages, such as interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α (TNFα); and T lymphocytes, such as interferon-γ (IFNγ) and IL-2, and may be explained by 6 requirements (1,2):

1. Proinflammatory cytokines are increased in depression, e.g., IL-1β; IL-6, and IFNγ; and the acute phase response in depression is caused by increased levels of pro-inflammatory cytokines, such as IL-6 and IL-1β.
2. Proinflammatory cytokines may cause depressive-like behaviors.
3. Proinflammatory cytokines are able to explain the etiology of depression whereby psychosocial stressors and internal stressors may trigger depression.
4. Proinflammatory cytokines may result in serotonergic changes in depression.
5. Proinflammatory cytokines may be an explanation of disorders in the hypothalamic-pituitary adrenal axis in depression.
6. Antidepressants may reduce the production of proinflammatory cytokines.

All cardinal signs of inflammation, an increase in plasma levels of cytokines and an increase of cytokine receptor frequency in cerebrospinal fluid and plasma have been reached in depressed individuals. Additionally, plasma levels of inflammatory mediators, such as acute phase proteins, chemokines, adhesion molecules and prostaglandins also increase in depression (3). A variety of mechanisms are involved in "inflammatory" process in

depressive disorder. These include: 1) oxidative and nitrosative stress pathways, including damage to lipids, DNA and proteins; and lowered levels of antioxidants and antioxidant enzymes, including zinc (4); 2) the tryptophan catabolite (TRYCAT) pathway (5), 3) decreased levels of ω3 polyunsaturated fatty acids (PUFAs) (6), 4) a process of neuroprogression evidenced by structural brain changes, cognitive sequelae and signs of neurodegeneration, apoptosis and decreased neurogenesis (7,8).

Cytokines, polipeptides of 15-25 kD, could be either produced in the brain or in the periphery. Peripheral cytokines may be able to affect the cerebral tissue by different ways. These molecules have the ability to pass easily through leaking parts of blood-brain barrier and may be subjected to transport molecules mediated active transport. These molecules may also affect the brain via cytokine receptors which are connected to peripheral afferent nerves. As a result of this signal transduction, brain regions, such as hypothalamus may take part in this signaling process. The activation of perivascular macrophages and endothelial cells surrounding cerebral vessels results in production of cytokines in cerebral area (9).

Microglia cells are the first compartments that give a response to peripheral inflammatory signals. These cells start the inflammatory cascade which includes cytokines, chemokines, inflammatory mediators and reactive nitrogen and oxygen species. Afterwards, astroglial activation results in the amplification of the inflammatory signal. As a result, the main components of this cascade, IL-1, IL-6, TNF-alpha, IFN-alpha and IFN-gamma induce 2,3 dioxygenase enzyme, which catalyses tryptophan. This enzymatic process causes the production of quinolinic acid, which provides a potentialization of astrocytic function and a decrease in neurotrophic factor production as a result of glutamatergic dysfunction. The increase in astrocytic function followed by an augmented glutamate activity may result in excitotoxicity and apoptosis, which are mainly observed by the oxidative stress and the loss of neurotrophic support (Fig. 1) (9).

Psychosocial stressors may also contribute in the inflammatory process observed in depression. They may affect locus ceruleus, which provides release of corticotropin-releasing hormone and the activation of sympathetic nervous system. Catecholamines, secreted by sympathetic nerves, cause an increase in NF-kappa B activity in macrophages. This induces release of proinflammatory cytokines, followed by changes in monoamine metabolism, excitotoxicity and a decrease in neurotrophic factor production (Fig. 2) (9,10).

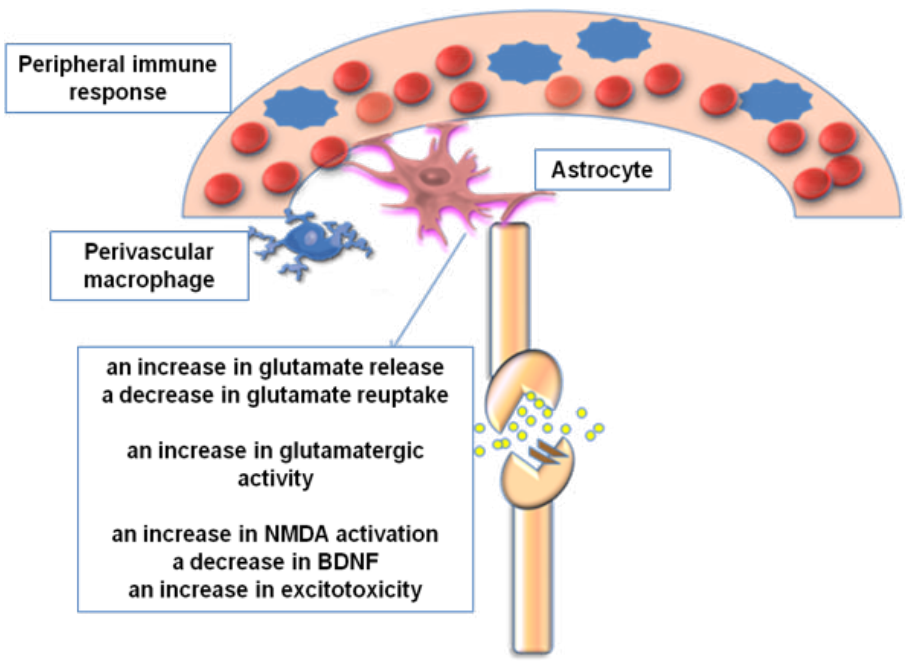

Figure 1: Contribution of peripheral immune response into the inflammatory response in depression

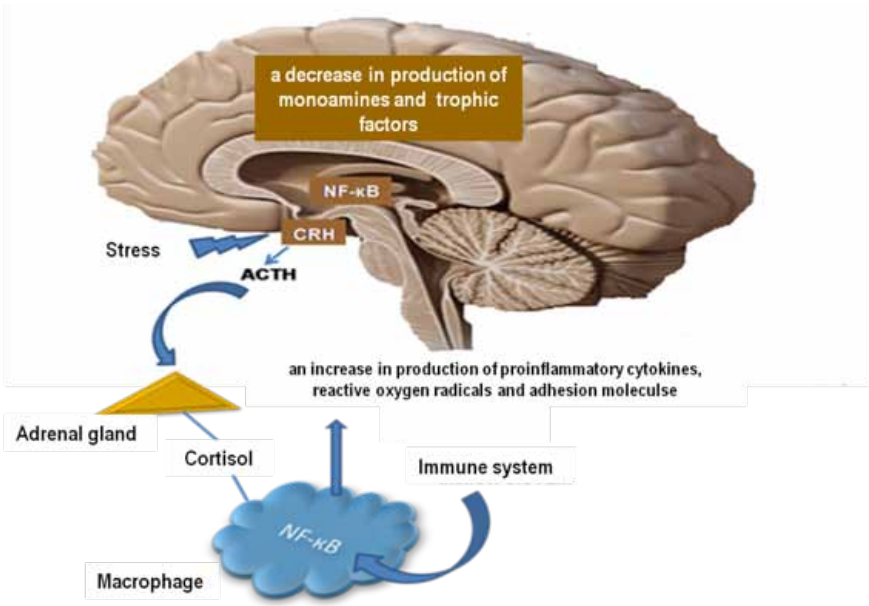

Figure 2: Contribution of stress into the inflammatory process in depression

Antidepressants and Cytokines

The action of mechanism of antidepressant drugs directly explains most popular theories of depression which include major neurotransmitters. However, therapy options have put some question marks in minds over time. The belief of that antidepressants quickly ameliorate the abnormal levels of neurotransmitters could not explain the time of two to three weeks following the first daily dose of the used drug. This latency in the appearance of the antidepressant effect has been tried to be explained by some additional mechanisms affected by antidepressants. Immune mechanisms have also been thought as a candidate target of antidepressant drugs.

In 1980's, rolipram, a phosphodiesterase-4 inhibitor, has been tested for its possible antidepressant effects. As an antiinflammatory agent, it does not have a direct effect on neurotransmitters in brain, but reduces the production of TNF, IF-gamma and lymphotoxin. These findings provided enough encouragement to investigate routinely used antidepressants for their effects on cytokines (11,12).

Imipramine, a tricyclic antidepressant drug, caused an increased production of interleukin 1 receptor antagonist. Since it has been used, imipramine was thought to affect mainly noradrenaline, but these recent discoveries showed its "anticytokine" effects. The time needed to show its therapeutic effect also equals the time needed to start the induction of anticytokine production (13).

A 40-day-treatment with one of imipramine, desipramine, clomipramine, amoxapine and mianserin was reported to reduce the production of substance P in rat brain. Although chosen drugs have different mechanisms of action, they have been found to reduce substance P levels as a common effect. Substance P stimulates astrocytes and monocytes to produce more IL-1, IL-6 and TNF. As a result, a decrease in production of substance P provides a reduction of cerebral and peripheral cytokine production (14).

Contradictorily, the late therapeutic effect of therapy by using antidepressants does not match with their rapid effects on neurotransmitters. It could be explained by their recently discovered late-occuring anticytokine properties. This provides a strong basis for the cytokine theory of depression.

Novel Treatment Approaches

Discoveries on depression and inflammatory process guided the scientists to new options of depression therapy. Antiinflammatory drugs have been the first targets. Celecoxib, a cyclooxygenase-2 inhibitor, may augment the efficacy of antidepressants (15). Statins, with antiinflammatory effects, reduce risks of depression (16). In

combination with SSRIs, non-steroidal antiinflammatory drugs (NSAIDs), such as acetylsalicylic acid, have an accelerating effect in the treatment of depression and in animal models of depression (17). Minocycline, an anti-inflammatory tetracycline derivative, augments the efficacy of antidepressants in depression (18). Eicosapentaenoic acid (EPA), one of the omega-3 polyunsaturated fatty acids (PUFAs), has a significant antidepressant activity by suppressing proinflammatory cytokines and Th-1-like cytokines (19,20).

TNF-alpha is another drug target in depression. Etanercept, a p75 TNF receptor/Fc fusion protein that blocks TNF-alpha functions, blocks IL-1b-mediated behaviours, including reduced glucose consumption and open-field activity (21). In animal models, administration of curcumin, a plant polyphenol and colouring agent/food additive commonly used in Indian culinary, results in antidepressive-like behaviours that may be explained by its strong anti-inflammatory properties targeting NF-kappa B and thus proinflammatory cytokines production (22). Ketamine, an NMDA receptor antagonist, produces rapid antidepressant effects. Ketamine is an anti-proinflammatory agent by limiting exacerbations of systemic inflammation (23). Vaccination is also thought to be effective against depression because of the inflammatory nature of the disorder (24).

CONCLUSION

The Immune-Cytokine Model of Depression is an entirely new concept for understanding the riddle of depression. This is the only model of depression to bridge the conceptual and diagnostic gap between physical and mental disorders. Today, it is known that antidepressants also have antiinflammatory activity, while antiinflammatory drugs are thought to be used in depression therapy. There are many up-and-coming treatment approaches arising from this hypothesis of depression.

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