The Role of Immune System in Depression Disorder

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Abstract
In order to diagnose a major depressive disorder, patients must have at least 5 depressive symptoms out of 9 criteria, present for at least two weeks. Depressive symptoms include absence of concentration, fatigue and suicidal ideation. The intensity of depression symptoms affects the severity of depression and the degree of the impact on the quality of life. Major depressive disorders (MDD) are defined as a significant health problem, and are estimated to rise in prevalence in the future years. Immune cytokine, associated with major depression for instance, is the interleukin IL-6 and tumor necrosis factor (TNF-α) which is defined as pro-inflammatory cytokines, can activate an inflammatory response. The effects of other inflammatory cytokines on the central nervous system are of controversy. There is an increasing interest about the effect of cytokines derived from innate immune system on the brain and behavior. Cytokines are defined as large sized proteins, mainly produced by immune cells. Two subtypes of cytokines exist: pro-inflammatory cytokines, facilitating inflammatory responses and neural activities; and anti-inflammatory cytokines, inhibiting inflammatory processes. Besides microglia and astrocytes, immune cells such as monocytes, macrophages, and lymphocytes also produce cytokines. At the times of immunological alterations, infections or inflammation, cytokines will be in an activated form. The main goal of the current review study is to investigate the role of the immune system in the depression disorder.

Keywords
Depression, Cytokines, IL-6, TNF-α, Psychoneuroimmunology

1. Introduction
Depression, as a mental disorder, is a major public health concern. In some societies,
the prevalence of depression is about 20% [1] [2]. The estimations are showing rise of the depression’s incidence in the future [3]. Many studies have indicated a relationship between the immune system and the neural system.

Cytokines mediate immune system’s response to injury, infections and etc. [4]. They also have an important role in immune responses, neurogenesis and neuroprotection which are mediated by macrophages and monocytes [5].

Studies have shown that not only the increase of the immune cytokines can be a trigger to depression, but also, depression can stimulate the immune system and release cytokine and interleukins [3] [5] [6]. Although depression decreases proliferation of B cell and T cells and reduces natural killer cell activity, it up-regulates serum levels of interleukins and increases the cellular response of the immune system [1].

On the other hand, inflammatory cytokine can lead to a major depressive episode in the physically ill patient. Cytokine and interleukins that are raised in infections and trauma induce ill symptoms, like malaise, weakness and loss of interest in the physical activity, but more importantly it can trigger depressive symptoms [7].

Among the immunologic factors, interleukin 6 and the tumor necrosis factor α are increased more compared to other cytokines. The elevation of these cytokines in a normal functioning body is abnormal [8].

In this study, we review the relationship between the immune system and depression and then discuss the role of cytokines in the depression, and their effects on neuropeptides and neural growth factors.

2. Psychoneuroimmunology

There are two pathways between the brain and immune system namely, autonomic nervous system and neuroendocrine outflow mediated by the pituitary gland. The pathways are defined as bidirectional. For instance, Besedovsky et al. reported that immune system activation occurs concurrently with the alterations in the hypothalamic, endocrine and autonomic processes [9].

Data confirms that the signals produced by an activated immune system, are released and are received by the CNS (central nervous system). While immune cells activate, they generate cytokines. Besides their role in regulating cellular interactions, they also have some links with the CNS and thus, changes in the behavior. Some cytokines, including IL-1, IL-2, IL-6, Interferon-γ and tumor necrosis factor (TNF) lead to activation of the HPA-axis (hypothalamic-pituitary-adrenal) [10]. Cytokines affect the neurotransmitter system via various pathways [11] [12].

The pathways aforementioned are monoaminergic system impairments, HPA-axis dysfunction, growth factor changes, alteration in neuropeptides and neurogenesis decline, while inflammatory cytokines can impact on the sited approaches [13] [14] [15] [16] [17].

3. Inflammatory State and Depression

The relationship between cytokines and inflammatory model with depression has ex-
isted for a long time as an immune-based model of depression [7] [18] [19].

Based on mentioned model, a rise in the pro-inflammatory cytokines (PICs) and a decline in anti-inflammatory cytokines (AICs) are hypothesized as the pro-inflammatory state, which have been linked with depression-like behavior in both human and clinical animal experiments. The role of inflammatory state can be addressed in a number of ways such as hippocampal (HC) neuroplasticity impairment, HC oxidative stress enhancement, decrease in the levels of serotonin which will lead to the production of neurotoxic serotoninergic metabolites, including 3-hydroxykynurenine (3-HK) and Guinolinic acid (QA) [7] [19] [20] [21] [22]. Inflammatory model which has been defined in the depression, has hypothesized that, level of PICs such as TNF-α, IL-6, IFN-γ and IL-1B is correlated to depression in clinical and pre-clinical experiments [7] [18] [19]. Data on a rodent model illustrated that about 50 μg/kg of PICs (such as IL-1, IL-6, IL-2, TNF-α, IFN-γ) is defined as a threshold level for depression like behavior [21] [23].

Human experiments and animal models have demonstrated that, “direct administration of the Th1 promoting cytokines IFN and IL-2 may lead to a phenotypically depression-like syndrome [24]”. Dowlati et al. found that there exists a relationship between clinical depression and a pro-inflammatory state. Based on this Meta-analysis, levels of TNF-α and IL-6 are higher in the group of patients with depression compared with the control group. Meta-analysis was performed by Hiles et al. shows higher concentrations of IL-6 in depression [25].

Additionally, rise of inflammatory markers such as CRP, IL-6, and TNF-α, have been reported in a cross-sectional study assessing 2415 participants [26]. Maes et al. have accomplished a cross-sectional survey showing a positive correlation between levels of inflammatory markers (TNF-α and IL-1) and the extent of depressive episodes [27].

Three major clinical courses after an episode of depression are full remission, partial resolution, and progressive trend in chronic depression. If full or partial resolution happens, anti-inflammatory or immune biomarkers have the ability to reduce the neuro inflammation [3]. Prospective cohort studies have compared cytokine’s profile in depressed subjects and a control group [28]. This study which included 50 medication-free MDD patients showed that they have higher serum concentration of IL-1B, IL-1Ra, IL-5, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF) and IFN-γ in comparison with control subjects. Some anti-depressants such as SSRIs, are able to reduce the levels of IL-6 and TNF-α that is raised in the patients with depression, however, other anti-depressants are not able to reduce PCIs [3].

Some cases of idiopathic depression with no co-morbid conditions showed an increase in the circulating pro-inflammatory biomarkers [8] [29] [30] [31]. Many studies done on idiopathic major depression showed that circulating biomarkers such as TNF-α, IL-6, their soluble receptors, and CRP have risen in this group of patients [29] [30] [31]. Furthermore, CSF examination in depressed patients showed an increase in the level of some cytokines [32] [33] [34].

Levine et al. assessed CSF concentration of IL-1B, IL-6, and TNF-α, IL-6, their so-
luble receptors, and CRP in depressed subjects and results showed there is a higher concentration of IL-1B, lower level of IL-6, and no change in TNF-α level compared with controls [32].

A study performed by Lindqvist and colleagues found that, there is increased level of CSF IL-6 in depressed cases [32] [33]. Elevations of prostaglandin E2 level as an inflammatory mediator have been reported in the depressed case’s saliva, plasma, and CSF [35] [36] [37] [38]. IFN-γ can lead to behavioral symptoms leading to depression, in 30% - 50% of treated patients; this effect is however, dose-dependent [39] [40] [41] [42].

Cytokines in Depression

Immune responses in injuries, infections or other stressful situations are regulated by cytokines and chemokines [43].

Cytokines as pleiotropic molecules, play a significant role in inflammatory responses. Except for this, they also have a remarkable role in the neurogenesis and neuro-protection processes. They are considered as an important factor for brain development. Furthermore, cytokines can support neuronal integrity, neurogenesis and synaptic remodeling [19] [44] [45]. However, chronic exposure to inflammatory cytokines with high concentration may lead to neuropsychiatric dysfunction with depression being a common one. Compared to the general population, patients with medical illnesses with elevated level of inflammatory cytokines were more prone to depression [46] [47].

Well known pro-inflammatory cytokines are IL-1B, IL-6, and TNF-α. On the other hand, most widely investigated anti-inflammatory cytokines are IL-4 and IL-10 [5]. During CNS injuries such as trauma, infections and ischemic attacks, cytokines will be activated via glial cells [48] [49].

The depression that is induced by IFN-α is closely similar to major depression. As an immunological marker, IFN-α can directly impact the central nervous system (CNS) or it may do so by activating central or peripheral pro-inflammatory cytokines [50] [51]. Pro-inflammatory cytokines are linked closely to the hippocampal glucocorticoid receptors (GRs) and the HPA axis. In the case of depression, elevated levels of pro-inflammatory cytokines and GR functional resistance are reported as the most investigated components.

Also, in depression, the neuro-inflammation is suggested as a factor making imbalance between oxidative stress and anti-oxidative processes. Based on the current research, cytokines and GRs, as the important factors in inflammatory and endocrine processes, have a major role in the depression [5].

Data from a study carried out in Boston, on patients suffering from MDD, depicted an elevation in the levels of cytokines such as MCP-1, IL-1a, IL-1B, IL-2, IL-6, IL-8, and IFN-γ in this group of patients [52]-[61]. This survey also showed a rise in the levels of granulocyte-macrophage-colony-stimulating factor (GM-CSF), MIP-1a, pro-inflammatory cytokines such as IL-7, IL-15 and anti-inflammatory cytokines such as IL-4, and IL-10 [4] also, in a meta-analysis study, concentrations of IL-4 didn’t have significant
difference between depression group and non-depressed group. IL-6, TNF-α, have a significant different between two groups however, IL-1B, IFN-γ, IL-2, IL-8 and IL-10 has no significant different between two groups [8].

Smith et al. have reported inflammation resulted from macrophages, plays an important role in pathophysiology of the depression. Macrophage secret some cytokine like IL-6 and TNF-α that some evidence showed that these cytokine increase in MDD [62].

Evidences suggested a close relationship between depression and pro-inflammatory changes [63]. Levels of IL-1B, IL-6, and TNF-α have been reported to be increased in patients suffering from MDD [64].

Results published in a meta-analysis, showed significant raise in the levels of IL-6 and TNF-α in the MDD patients compared with the healthy individuals, but the levels of IL-1B, IL-2, IL-4, IL-10, and IFN-γ have not shown any notable change [65]. IFN-α, as an exogenous factor, can cause depression [66].

Based on several reports, rise of the anti-inflammatory cytokines and a decline in the pro-inflammatory cytokines levels happen following administration of glucocorticoids [67] furthermore, HPA regulation can be affected by pro-inflammatory cytokines, by the mean of GR counter-regulation [68]. MDD patients have been found to have higher levels of IL-6 and TNF-α [8] [69].

TNF-α as a major pro-inflammatory cytokine could prevent neurogenesis and; It has two receptor sub-types: (TNFR)-1 and (TNFR)-2. Previous evidence has shown that (TNFR)-1 could have a negative effect on the neurogenesis of adult’s hippocampus. On the other hand, TNFR-2 has been reported to have a positive impact on the neurogenesis process. IL-1B level is correlated with brain neurogenesis including the hippocampal site [69]-[75]. Elevation in levels of IL-6, IL-7, IL-8, IL-10, IFN-α and G-CSF have been demonstrated in recent evidences [28].

4. Cytokine Effects on the Monoamines

4.1. Serotonin (5-HT)

Among all approaches in neurotransmitter process associated with depression, serotonin (5-hydroxytryptamine, 5-HT) is known to be the most investigated neurotransmitter. SSRIs are the most commonly prescribed drugs for depression [76] [77].

In the case of depression disorders, the altered aspects of serotonin system are presented as a modification in turnover of serotonin, related receptors, and the transporter binding [78]-[83].

An acute increase in serotonin level resulted from administration of inflammatory cytokines by enhancement of 5-hydroxyindoleacetic acid (5-HIAA) or 5-HIAA/5-HT ratios, in the cerebral cortex and the nucleus accumbency [84] [85] (Figure 1).

Furthermore, changes in 5-HT turnover occur concurrently with the later and more persistent depressive-like behaviors [86] [87].

During the IFN-α treatment, lower 5-HT concentration in the plasma and higher levels of circulating TNF-α were correlated with somatic symptoms in the depression
Expressions of 5-HT1A receptors have been reported to increase during the administration of IFN-α [89]. “The relationship between the 5-HTTLPR and IFN-α-induced depression was observed to depend on a functional polymorphism in the IL-6 promoter [90].” Besides, there is a positive association between the functional effects of 5-HT and the increase in the level of IL-6. Furthermore, evidence shows that expression and function of 5-HTT is elevated as a response to IL-6 cytokine [91] [92] [93] [94].

Based on studies performed around the cytokine-induced depression therapeutic strategies, the role of 5-HT has been assessed, although SSRIs are useful for anxiety, depressed mood, and cognition therapy associated with cytokine-induced depression but not efficacious in fatigue and neurovegetative symptoms [95] [96] [97].

### 4.2. Dopamine (DA) and Norepinephrine (NE)

The main residual symptom, that occurs after SSRI treatment is fatigue. Fatigue is the underlying symptom of cytokine-induced depression. In the patients suffering from both idiopathic major depression and IFN-induced depression, the activity of basal ganglia has been modified [98] [99] [100] [101]. Evidence shows that peripheral cytokines influence the function of basal ganglia, leading to many inflammatory processes, thus related to fatigue-like symptoms [102] [103] [104].

DA neurotransmission, especially synthesis of DA, can be modified by cytokines and inflammatory signaling pathways, via various means [105].

Conversion of tyrosine (Tyr) to L-DOPA by an enzyme called Tyr hydroxylase is linked with DA synthesis. Phenylalanine (Phen) is a major source for Tyr. Phen hydroxylase (PAH) converts Phen to Tyr. Tetrahydrobiopterin (BH4) is known as co-factor for both Tyr hydroxylase and PAH. NE concentration in the CSF of patients with major depressive disorder has been reported to be elevated [106] [107].

Cytokines, besides their role in Immune activation, lead to an increased activity in the locus coeruleus and elevation of NE in hippocampus and hypothalamus. Dunn et al. showed that there is a link between the increased activity of NE and the HPA axis [108] [109]. “5-HT and DA metabolites in the CSF have been found to correlate with IFN-alpha-induced depressive and fatigue symptoms, respectively [105] [110]” (Figure 1).

### 5. Cytokine Effects on Neuropeptides and Growth Factors

#### 5.1. Brain-Derived Neurotropic Factor (BDNF)

Both the neuronal development and their apoptosis are controlled by inflammatory cytokines [111] [112]. The activities of the subsequent and the stress inflammatory cytokines have a relationship with neuroplasty and neurogenesis [113]. Furthermore, IFN-α is able to decrease proliferation of cells in hippocampus area; this process is mediated by IL-1. In the case of BDNF, IFN-α administration has decreased the level of systemic BDNF among human [114].

Remarkably, the link between the pre-existing low concentration of BDNF and the risk of cytokine-induced depression has been reported [115] [116] (Figure 1).
5.2. Corticotrophin-Releasing Hormone (CRH)

The roles of HPA axis and CRH have been studied in patients with major depression and cytokine-induced depression. Study performed by Arborelius and coworkers, have demonstrated increased concentration of CRH in the CSF of patients with MDD [117]. Depression is considered as a public health problem. MDD prevalence is reported up to 20% among individuals, but medically ill subjects have prevalence up to 50% [118].

Depressive patients who do not respond to antidepressant therapy have been shown to have higher levels of inflammatory cytokines and CRH in the circulation, compared with patients who are not resistant to this therapeutic procedure [119] (Figure 1).

Two studies carried out in 2011, showed that after antidepressant therapy the level of circulating BDNF has increased, but a study showed that the level of IL-6 has declined after antidepressant therapy. Additionally, the individuals with a trauma experience in childhood have higher levels of inflammatory biomarkers and demonstrate higher rates of depression [120] [121].

5.3. Acute Phase Proteins in Major Depression

Several documents claimed that there exist a link between depression and the immune system. A study performed on the acute phase proteins in major depression, has demonstrated that levels of C4, IL-6, and C-reactive protein were significantly elevated in the patients with depressive disorder [122]. Evidence suggests that the level of acute
Phase proteins change during depression. Such studies found an increase in the level of a1-acid glycoprotein [123]. MDD has been correlated with activation of immune system, cellular activation, rise in positive acute phase proteins, and decline of negative acute phase proteins [124] [125] [126].

Rise in the serum levels of acute phase proteins and IL-6 were significantly documented [124] [127]. Some publications reported that complement proteins C3 and C4 were not affected, but some studies showed a raise in the level of this molecules [128] [129]. The biological marker, IL-6, has the ability to stimulate acute phase protein generation by the hepatocytes [130].

Several studies investigated the relationship between immunity and clinical depression, reported a reduced level of natural killer cells and reduced activity of neutrophils lymphocytes [125] [131]-[136]. Other studies have reported an increase in the level of acute phase proteins, C3, C4, immunoglobulin M and cytokines [123] [137] [138] [139].

Enhancement of acute phase proteins, complement proteins, and IL-6 could be defined as a link for the association of major depression and immune response activation [122] (Figure 1).

6. Conclusions

While positive and negative findings of elevated cytokines have been outlined above, there seems to be a relation between levels of pro-inflammatory cytokines such as TNF-α and IL-6 in the patients suffering from a major depressive disorder. In the case of acute phase proteins, there are some reports on the elevation of C4 and CRP levels in the MDD cases.

However, many clinical studies perform to evaluate the relation of inflammatory factors and depression but most of them are cross-sectional studies and therefore answering the question about whether inflammatory markers are one of the causes of depression or the depression increases these factors is unclear for this reason; observational studies like cohort should be necessary to determine exact effects of cytokines on happening of depression. Even though, various research on cytokines reported a higher concentration of IL-1β, IL-5, IL-15, IL-7, IL-8, IL-4, IL-10, G-CSF, MIP-1a, IFN-γ, MCP, GM-CSF and IL-1a, most of the reviewed studies showed that TNF-α and IL-6 were the cytokines which showed a significant raise in concentration.

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