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Review

The importance of cytokines and autoantibodies in depression ☆

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ABSTRACT

The relationship between depression and immunity has been widely discussed. Cytokines, such as TNF-α, play an important role in immune system; these cytokines interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity. Antibodies have also been implicated in the pathophysiology of depression. The association between decreased serotonin levels and excessive glutamatergic activity forms the first biochemical basis for cytokine-induced depression. Cytokines and antibodies (anti-ribosomal-P and anti-N-methyl-D-aspartate receptor antibodies) are deeply related to pathogenesis of neurodevelopmental disorders, especially depression. Tumor necrosis factor alpha (TNF-α) may underlie the mechanism of depression by an activation of the hypothalamo–pituitary–adrenocortical (HPA) axis, an activation of neuronal serotonin transporters and the stimulation of the indoleamine 2,3-dioxygenase which leads to tryptophan depletion. In the last 20 years since the initial reports of neural–immune interactions in depression, studies have shown a clear association between activation of the immune system mediated by proinflammatory cytokines. Genes encoding cytokines are highly polymorphic and single nucleotide polymorphisms, associated with increased or reduced cytokine production, have been described. To date, there are only few studies that investigated the relationship between depression and proinflammatory cytokines in patients with autoimmune diseases. Although an associative link between neuroinflammation and mood disorders is widely accepted, further studies are necessary to establish the cause–effect relationship. In this paper, we review the role of cytokines, focusing on TNF-α and antibodies in the depression and hypothesize how TNF-α may underlie and mediate the inflammatory process depression in patients with autoimmune disease.

Contents

1. Introduction

Mood disorders are a substantial cause of morbidity and the etiology of depression remains unclear [1]. Depression is a multifaceted disorder that is associated with disability and reduced quality of life, as well as a significant social burden [1]. It has a multifactorial

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etiology combining environmental and genetic factors and presents frequent comorbidity [2].

Evidences show that depression is an inflammatory disorder, accompanied by antibody-mediated immune activation [3]. The mechanism involved in depression has been proved to be mediated by proinflammatory cytokines, such as interleukin 2 (IL-2), IL-6, IL-12 and TNF alpha (TNF-α) [4,5]. The role of antibodies, mainly anti-ribosomal-P and anti-N-methyl-D-aspartate receptor (NMDA) antibodies in depression, has been supported by previous data that demonstrated that intravenous injection of these antibodies resulted in depression-like behavior [6,7]. Several studies showed a novel molecular relationship between immunity (cytokine/antibodies) and neural activity; this is of particular relevance to patients suffering from psychiatric or neurological diseases, and also autoimmunity disease. Interestingly, patients who suffer from depression have increased levels of proinflammatory cytokines, suggesting a potential link between depressive illness and activation of the inflammatory response [8–14].

In this paper, we review the role of cytokines and autoantibodies in depression, and hypothesize how TNF-α may underlie and mediate the inflammatory process of depression in patients with autoimmune disease.

2. Peripheral cytokines and central nervous system

Several studies have demonstrated that peripheral inflammation can lead to depression through several immune-mediated pathways that transmit the signal from the periphery to the central nervous system [15–17]. Infection and tissue damage stimulate the production of proinflammatory cytokines, such as TNF-α in the periphery. Cytokines are large molecules and circulating cytokines typically do not cross the blood–brain barrier (BBB). However, these molecules reach the brain through three main mechanisms. The first one is via a fast transmission pathway involving primary afferent nerves innervating the site of inflammation. Second, a slow transmission pathway involving cytokines originating from the choroid plexus and circumventricular organs diffuse into the brain parenchyma by volume transmission [5]. This passage only occurs with a high concentration of peripheral cytokines [15]. Third, cytokines can also be transported across the BBB by specific saturable transport systems [18,19]. Saturable transport systems from blood to the CNS have been described for IL-1 alpha, IL-1 beta, IL-1 receptor antagonist (IL-1ra), IL-6, and TNF-α. The blood-to-brain uptakes of IL-1 alpha, IL-beta, and IL-1ra are interrelated for most brain sites, but the posterior division of the septum shows selective uptake of blood-borne IL-1 alpha. The saturable transport systems for IL-6 and TNF-α are distinguishable from each other and from the IL-1 system; a transporter or a family of transporters is responsible for the blood–brain influx of each cytokine [19–21]. IL-2 is an exception; it is not capable to cross the BBB by this saturable transport system [22].

Early studies linking the immune system to depression showed positive correlations between inflammatory biomarkers and depression indices in the absence of physical illness [23–26]. The administration of cytokines, mainly IL-1β and TNF-α, directly to the brain can induce sickness behaviors in rodents, including reduced locomotor activity, increased sleep, decreased social exploration, and reduced food and water consumption [23–26]. Similarly, intracerebroventricular injections of lipopolysaccharide or proinflammatory cytokines such as TNF-α and IL-1β are sufficient to produce depressive like behaviors [27–29], and intracerebroventricular administration of cytokine antagonists is able to reverse sickness and depressive-like behaviors that typically follow systemic inflammation [25].

3. The pathophysiologic role of TNF-α in depression

TNF-α may induce changes in brain structure and function, leading to the development of depression [30]. Three main different mechanisms might link the activation of the cytokine system, of which TNF-α is a part, to the pathophysiology of depression (Fig. 1).

First, the activation of the cytokine system might play a causative role in the depression-related activation of the hypothalamo–pituitary–adrenocortical (HPA) axis [31–33]. The stress response system is intricately linked with proinflammatory signaling. The release of TNF-α and IL-6 has been shown to increase the levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol which act directly on hypothalamic and pituitary cells [34–38]. The upregulation of the HPA axis is an important finding associated with depressive symptoms [39,40], highlighting the potential for direct clinical significance of raised proinflammatory cytokines, especially TNF-α [41] (Fig. 1).

Hyperactivity of this system has been attributed to glucocorticoid receptor (GR) resistance, secondary to either reduced expression of GR or decreased functionality of GR [30]. Cytokine signaling molecules such as nuclear factor kB (NF-κB), c-Jun N-terminal kinases (JNK), and signal transducer and activator of transcription 5 (STAT5) have been demonstrated to inhibit GR. Substantial evidence shows that TNF-α induces glucocorticoid resistance [42]. The functionality is inhibited by preventing the entry of the cortisol–GR receptor complex into the nucleus (by inducing JNK) and also by preventing the binding of the complex to the DNA (by inducing NF-κB) [43]. This in turn leads to altered expression of GR in cells. To restore the control of HPA axis and increase GR, antidepressants have been the best alternative [42,43].

Second, TNF-α activates neuronal serotonin transporters [32,44]. During the process of depression, the uptake of serotonin is diminished. Drugs like selective serotonin reuptake inhibitors (SSRI) are used in the therapy of depression, because SSRIs lead to recovery from depression via deactivation of serotonin transporters [32]. A remarkable study demonstrated that TNF-α stimulated serotonin uptake in both a rat embryonic *raphe* cell line and in mouse midbrain and striatal synaptosomes. These results provided evidence that TNF-α can acutely regulate neuronal serotonin transporter activity [44].

At least, TNF-α stimulates indoleamine 2,3-dioxygenase (IDO) leading to tryptophan depletion [31,32,45].The activation of IDO by proinflammatory cytokines, especially by TNF-α, additionally leads to the production of glutamatergic agonists (Fig. 1). The role of increased glutamatergic neurotransmission in the pathogenesis of depression is inconclusive [3,46]. The higher consumption of serotonin and its precursor tryptophan due to IDO activation may justify the reduced availability of serotonin in depression.

Another important point to note is IDO breaks down tryptophan into kynurenine (KYN), resulting in a reduction in the level of serotonin [47]. Reduction of serotonin is usually associated with depression, but depression resulting from IDO activation and KYN production has additional serotonin-independent effects. For instance, depressive behavior in mice has been demonstrated with administering KYN alone [48].

Moreover, KYN is further converted into quinolinic acid (QUIN) in microglia [47]. QUIN promotes glutamate release through activation of N-methyl-D-aspartate (NMDA) receptors as well as producing oxidative stress. The combination of these by-products leads to neurotoxicity [49].

4. Animal models

Animal studies have provided substantial evidences that support the role of cytokines in depression [50–54]. Animal studies showed that immune activation and administration of endotoxin (lipopolysaccharide) or the cytokines, such as IL-1β, IL-6 and TNF-α could induce a behavioral pattern resembling that commonly observed in sick animals. This behavioral pattern has been designated as sickness behavior. Sickness behavior and the symptoms of depression are very similar. Thus, it was suggested that cytokines could induce depression [51].

A study showed that early neonatal exposure to TNF-α increased anxiety and depression-related behaviors in male and female mice