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·Review·

Inflammation: a mechanism of depression?

Qiu-Qin Han, Jin Yu

Department of Integrative Medicine and Neurobiology, State Key Laboratory of Medical Neurobiology, Institutes of Brain Science, Shanghai Medical College, Fudan University, Shanghai 200032, China

Corresponding author: Jin Yu. E-mail: yujin@shmu.edu.cn

In recent decades, major depression has become more prevalent and research has shown that immune activation and cytokine production may be involved. This review is mainly focused on the contribution of inflammation to depression. We first briefly introduce the inflammatory biomarkers of depression, then discuss the sources of cytokines in the brain, and finally describe the neuroimmunological mechanisms underlying the association between inflammation and depression.

Keywords: depression; inflammation; cytokines; hypothalamic-pituitary-adrenal axis; 5-HT; neuroplasticity

Introduction

The prevalence of major depression has increased dramatically over the past few decades[1], and women are nearly twice as likely as men to develop depressive disorder[2]. Depression is classified as a brain disorder, but its symptomatology includes some behaviors that also occur during chronic inflammatory stress[3]. Research has shown that immune activation and the production of cytokines may be involved in depression[4], so this relationship has received much attention. In fact, three causal pathways have been proposed: depression to inflammation, inflammation to depression, and a bidirectional relationship[5]. In this review, we focus on the impact of inflammation on depression and the underlying mechanisms. Cytokines are small cell-signaling proteins that mediate and regulate immune responses and inflammation, and can be divided into two categories: the pro-inflammatory cytokines interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α, and the anti-inflammatory cytokines IL-1Rα, IL-4, IL-10, and transforming growth factor (TGF)-β1. Generally, the pro-inflammatory cytokines promote systemic inflammation and are essential for the initiation of an inflammatory response to disease[6], while the anti-inflammatory cytokines antagonize these actions to reduce inflammation and promote healing[6, 7]. Moreover, some cytokines play dual roles[8]. In the central nervous system (CNS), the cellular source, function, and mechanisms of action of cytokines differ from those in the periphery. In the following, we briefly introduce the current research on inflammatory biomarkers of depression.

Inflammatory Biomarkers of Depression

So far, there are neither universally accepted or definitive biomarkers of depression[9], nor effective methods to assess the severity, endophenotypes, or response to treatment[10]. However, sufficient evidence has suggested changes in the circulating levels of cytokines in depressed patients, which can be reversed by antidepressant treatments[11, 12]. So, many studies have aimed to clarify the neurobiological changes in depression and to establish inflammatory biomarkers. The peripheral levels of IL-6, TNF-α, and IL-1β are increased in patients with depression[13-17], and antidepressant treatments reverse this effect[18-20]. These consistent results demonstrate that IL-6, TNF-α, and IL-1β are putative biomarkers for depression. However, due to the heterogeneity of depression, not all clinical studies have reported consistent results. For example, Jazayeri[21] showed that serum IL-6 and IL-1β do not change significantly after antidepressant treatments. Can

inflammatory biomarkers be used to predict or diagnose depression? Clearly a great deal of work is warranted in this area. Further research is needed to develop a biomarker panel for depression that can be used to identify its subtypes and treatment responses.

Sources of Cytokines in the Brain

Peripheral immune activation, such as that seen in psychological stress, induces the release of IL-1α, IL-1β, IL-6, and TNF-α[22]. Moreover, non-psychological disorders such as cardiovascular disease, diabetes, cancer, and rheumatoid arthritis can induce depression, which is also related to inflammation with elevated levels of plasma IL-6, IL-17, and TNF-α[23-25]. In addition, the new technology of optogenetics can be applied to understand the inflammatory process in psychiatric disorders and cardiovascular diseases, representing a potential dialogue between heart and brain[26]. All this evidence hints at a bidirectional relationship between peripheral immune activation and depression. Cytokines are signaling molecules mediating the immune response on activation of the peripheral immune system. They may also mediate the impact of inflammation on mood regulation. In support of this hypothesis, several kinds of cytokines and their receptors have been identified in the brain or in the cerebrospinal fluid of depressive patients and animal models of depression[3, 4]. Then, what is the source of these cytokines in the brain? Do they come from the periphery or are they endogenous to the brain? If the former, how do the peripheral cytokines access the brain? If the latter, which cell type produces cytokines, and how? Next, we review the recent research targeting these questions.

How Do Peripheral Cytokines Access the Brain?

The CNS was traditionally considered as largely inaccessible by the immune system due to the blood-brain barrier (BBB), existing as an immunologically privileged site. However, immunologists noted that such immunological privilege is not absolute, suggesting the idea of neuroimmune communication[27]. Although cytokines are relatively large molecules that do not freely pass through the BBB, peripheral cytokines can still signal the brain *via* at least five mechanisms[28-30]: (1) passage of cytokines through leaky regions of the BBB, including the choroid plexus and circumventricular organs, so entering the brain by volume diffusion; (2) active transport by saturable cytokine-specific transport molecules on brain endothelium; (3) second-messenger signals from the endothelial lining of the BBB which in turn leads to an excess production of cytokines; (4) transmission of cytokine signals by afferent nerve fibers, such as the vagus during abdominal and visceral infections and the trigeminal during orolingual infections; and (5) entry of activated monocytes from the periphery into the brain, in which chemokines play a key role.

Can the Brain Produce Cytokines?

In the brain, cytokines can be produced by astrocytes, microglia, and neurons[31]. Most cytokines can be synthesized and released within the brain[8], such as interferon (IFN)-α, IFN-γ, TNF-α[32, 33], TNF-β, erythropoietin[34], granulocyte colony stimulating factor (CSF)[35], IL-1α, IL-1β[36, 37], IL-2[38], IL-3[39], IL-4[40], IL-5, IL-6[41], IL-8[42], IL-10[43], and IL-12[44]. Cytokines in the brain are referred to as one kind of gliotransmitter that acts on a number of receptors on neural cells and are thought to play key roles in some brain functions[28]. They are activated in various ways. For example, the human astroglial cell lines U87MG and U373MG produce CSF when stimulated by IL-1α and IL-1β[35]; and another human astroglial cell line, CH235-MG, when stimulated by IL-1β, induces the expression of TNF-α through protein kinase C (PKC) activator 4 β-phorbol 12 β-myristate 13 α-acetate (PMA) in concert with a Ca^{2+} ionophore[35, 45]. Human microglia synthesize IL-8 in response to pro-inflammatory stimuli, such as lipopolysaccharide, IL-1β, and TNF-α, while pretreatment with anti-inflammatory cytokines such as IL-4, IL-10, or TGF-β downregulates the stimulatory effects *in vitro*[42]. In addition, TNF-α is known to be synthesized by neurons in the CNS and is widespread in areas involved in autonomic and endocrine regulation in response to inflammation and infection[32].

Cytokines are also produced by endothelial cells of the BBB[46]. Low doses of endotoxin induce peripheral macrophages to produce IL-1β, which enters the circulation and activates brain endothelial cells to produce IL-1 and IL-6[46]. In contrast, high doses of endotoxin directly activate brain endothelial cells to produce IL-1 and IL-6[46]. These findings suggest that cytokines are produced in the brain itself.

Apart from this peripheral inflammatory induction of cytokine synthesis and release within the brain,

psychological stress or brain injury also has these effects. For instance, long-term light deprivation in the constant darkness paradigm induces elevated levels of IL-6 and IL1-R1 (interleukin 1 receptor, type I) in the hippocampus through the NF-κB signaling pathway, known to play a vital role in the cellular expression of pro-inflammatory genes[47]. Moreover, the expression of pro-inflammatory cytokines is induced by a high oxidative-stress status. In a rat model of brain injury caused by the intraperitoneal administration of kainic acid, reactive oxygen species (ROS) initiate an inflammatory response by up-regulating IL-1β expression[48]. Brain damage also increases the expression of pro-inflammatory cytokines[49]. TNF-α levels are elevated in various experimental models of brain injury[50], including the administration of kainic acid[51] or lipopolysaccharide[52], injection of the excitotoxin ibotenic acid[53], closed head injury[54], and traumatic head injury[55]. Specifically, IL-6 and TNF-α induced as a secondary event following brain damage exaggerate the neurodegeneration[49].

Taken together, cytokines are produced in the brain by astrocytes, microglia, neurons, and microvessel endothelial cells in response to peripheral inflammation, psychological stress, and injury. In fact, many peripheral diseases and brain injuries can bring on secondary depression. Then, do the elevated cytokines participate in the pathogenesis of the associated depression? To sum up, the cytokines produced in the brain as well as those from the periphery may co-mediate the impact of inflammation on mood regulation and the pathogenesis of depression.

Hypothetical Mechanism of Cytokine-induced Depression

Brain cytokines can come from the periphery and can be produced by neural cells and microvessel endothelial cells. Then what effects do they have? How do they affect brain function and mood regulation? A number of studies have revealed an important role of cytokines in major psychiatric disorders. Actually, inflammatory cytokines have been found to influence many substrates in the etiopathogenesis of depression, including neuroendocrine function, neurotransmitter systems, and neuroplasticity.

HPA Axis Activation

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the pathophysiology of depression[56]. Recent research has shown that inflammatory cytokines such as IL-6, IL-1α, IL-1β, and TNF-α activate the HPA axis[57]. For example, an increase of IL-6 concentration is significantly correlated with disturbance of the HPA axis, which is generally displayed as elevated cortisol in depressive patients[24]. TNF-α and its soluble receptors released during infection and inflammation activate the HPA system, resulting in the release of cortisol[58]. Over-activation of the HPA axis contributes to both glucocorticoid receptor feedback insensitivity and the over-production of other corticotropin secretagogs insensitive to glucocorticoid feedback in depression[59]. In addition, chronic imipramine (an antidepressant drug) treatment significantly down-regulates the circulating plasma levels of adrenocorticotropic hormone and corticosterone[60], indicating that the HPA axis may be an important target for antidepressant treatment.

Changes in Neurotransmitter Systems

Similarly, cytokines can affect the neurotransmitter systems, such as the metabolism and function of serotonin (5-HT), norepinephrin (NE), dopamine, and glutamate; these effects may underlie the pathophysiology of inflammation-induced depression. It is widely accepted that standard antidepressant medication modulates the monoamine systems, including 5-HT, NE, and dopamine. Besides, currently the glutamatergic system is also a target for intervention in the treatment of depression.

5-Hydroxytryptamine Pro-inflammatory cytokines have profound effects on the metabolism of brain 5-HT[61]. Depression could be due to a stress-related increase in the production of cytokines such as ILs, TNF-α, IFN-α, IFN-β, and IFN-γ, which, in turn, up-regulate indoleamine 2,3-dioxygenase (IDO) expression[62-65]. IDO converts tryptophan, the precursor of 5-HT, to kynurenine; so IDO activation leads to reduced levels of tryptophan and thus reduced central 5-HT synthesis[66-68]. In addition, kynurenine metabolites such as 3-hydroxy-kynurenine (3-OH-KYN) and QUIN have neurotoxic and neurodegenerative effects. 3-OH-KYN induces oxidative stress by increasing the production of ROS, and QUIN is an agonist for N-methyl-*D*-aspartate receptors (NMDARs), causing overstimulation of NMDARs and leading to neurotoxicity[65, 69]. Thus, IDO amplifies the consequence of inflammatory states[70] so small-molecule IDO inhibitors may be considered to

negatively regulate the inflammatory program. These actions may be another means by which the effect of inflammation on depression is mediated.

Changes in the central 5-HT transporter (5-HTT) have also been implicated in depression[71]. The 5-HTT regulates 5-HT levels in the synaptic cleft by modulating its reuptake into the presynaptic cell[72]. Research has shown that the mRNA expression of IL-1β, IL-6, IFN-γ, TNF-α, and 5-HTT is higher in depressed patients than in healthy controls, suggesting that pro-inflammatory cytokines and the 5-HTT play critical roles in the pathogenesis of depression[73]. IFN-α, IFN-γ, TNF-α, and IL-1 upregulate the 5-HTT, causing a decrease of extracellular 5-HT[65, 74, 75]. It is generally agreed that regulation of the 5-HTT is a neurochemical mechanism underlying affective disorders.

Moreover, cytokines also have an influence on central 5-HT1A and 5-HT2 receptors[67]. IFN-α significantly reduces the affinity of the low-affinity 5-HT1A receptor site, which may be involved in IFN-induced psychiatric disturbances[76]. Besides, when administered intraperitoneally, IFN-α crosses the BBB to attenuate 5-HT2 receptor-mediated behavior in the CNS[77]. Therefore, agonists of the 5-HT receptor may be an option in the treatment of depression.

Norepinephrin The first catecholamine hypothesis of depression states that depression is related to a decrease in NE neurotransmission. Dysregulation of the NE system is important in the pathophysiology of inflammation-induced depression. Effects of IL-1, IL-2, and TNF-α on NE activity have been described[67]. In mice, IL-1 increases the 3-methoxy-4-hydroxyphenylglycol (MHPG)/NE ratio in the prefrontal cortex and hippocampus, while IL-2 increases the MHPG concentration and the MHPG/NE ratio in the hypothalamus[78]. Hurst and Collins reported that TNF-α inhibits NE release from the myenteric plexus[79], while Ando and Dunn found that TNF-α increases the MHPG/NE ratio in the hypothalamus at a higher dose[80]. These findings suggest that dysregulation of the NE system may be an intervention point in the treatment of inflammation-induced depression.

Dopamine The effects of cytokines on the dopamine system may also be responsible for the pathophysiology of inflammation-induced depression[22]. Pro-inflammatory cytokines impact dopamine synthesis and reuptake[81, 82]. Immune stimulation with IFN-α inhibits dopaminergic neuronal activity, which may be involved in depression[83]. A more recent study consistently showed that rhesus monkeys administered with IFN-α exhibit depressive-like huddling behavior and lower cerebrospinal fluid concentrations of a dopamine metabolite[84]. IFN-α administration has been related to depletion of tetrahydrobiopterin, a cofactor for tyrosine hydroxylase (the rate-limiting enzyme in the synthesis of dopamine), so dopamine could be depleted in this way[85].

Glutamate Many studies have shown that inflammation and glutamate dysfunction play an important role in the pathophysiology of depression. Inappropriate glutamate receptor activation leads to neurotoxic effects in the brain[86]. In more detail, their over-activation results in Ca^{2+} overload, which causes neuronal death. These receptors include NMDARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kaininate receptors[28]. Inappropriate activation of glutamate receptors can be induced by cytokines. For instance, IL-1β activates NMDARs by increasing tyrosine kinase function as well as inducing phosphorylation of the NR2A/B subunit[87]. Besides, as noted above, cytokines such as ILs, TNF-α, IFN-α, IFN-β, and IFN-γ up-regulate the expression of IDO, which then converts tryptophan to kynurenine. Importantly, one metabolite of kynurenine, QUIN, is an agonist for NMDARs and may cause their overstimulation, leading to neurotoxicity.

Moreover, cytokines can increase the release and reduce the reuptake of glutamate. For example, IL-1β and TNF-α both dose-dependently inhibit glutamate uptake by astrocytes through a mechanism involving nitric oxide[88].

Ketamine, primarily used as an anesthetic agent, is an NMDAR antagonist and shows rapid efficacy as an alternative medication for depression[89-92], tending to confirm the glutamate hypothesis of depression.

Altered Neuroplasticity

Pro-inflammatory cytokines including IL-1, TNF-α, and IFN-γ can impair neuroplasticity by neurotoxicity (excitotoxicity, oxidative stress, or glucocorticoid dysfunction), leading to apoptosis, which may ultimately participate in depression[93]. Besides, the hippocampal changes[94] and impairment of neurotrophic signaling cascades[95] greatly contribute to neuroplasticity and cellular resilience. In fact, neurotoxicity may be a contributing factor to the decreased hippocampal volume[96].

Hippocampal Changes Brain changes associated with major depression have been reported in different regions, such as the hippocampus, amygdala, caudate nucleus, putamen, orbital and medial prefrontal cortex, and anatomically related parts of the striatum and thalamus[94, 97]. All these structures are extensively interconnected, and the hippocampal changes are the most important.

Recently, a study indicated that in IFN-α-induced depression, IFN-α suppresses cell proliferation in the dentate gyrus, and IL-1β participates in this[98]. As noted above, over-activation of NMDA as well as non-NMDA receptors results in Ca^{2+} overload, which causes neuronal death. The kynurenine metabolites 3-OH-KYN and QUIN have neurotoxic and neurodegenerative effects. QUIN may overstimulate hippocampal NMDARs resulting in excitotoxicity, which ultimately leads to apoptosis and hippocampal atrophy[65]. In addition, oxygen-radical damage and excess glucocorticoids can also mediate neurotoxicity that contributes to the overt loss of neurons in the hippocampus[96]. Increased activation of glutamate receptors leads to neurotoxicity not only through Ca^{2+} overload but also through oxygen free-radicals[97]. 3-OH-KYN induces oxidative stress by increasing the production of ROS, as noted above. Worth mentioning is that IFN-α induces an increase in ROS leading to neurotoxicity and apoptosis[99]. Reduced hippocampal volume may be related to glucocorticoids, which are frequently elevated in depression[100]. Glucocorticoids may elevate free cytosolic Ca^{2+}, and corticoids activate NMDA and AMPA receptors to exacerbate the excitotoxic processes[101]. Further, glucocorticoids reduce the capacity of antioxidant enzymes, resulting in free-radical accumulation[96]. Taken together, excitotoxicity, oxidative stress, and glucocorticoid dysfunction can interact to ultimately cause neurotoxicity.

Impairment of neurotrophic signaling cascades Neurotrophins such as nerve growth factor, brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3, NT-4/5, and NT-6[102] mediate neuronal survival and differentiation through many intracellular signaling pathways, such as the Ras, the Cdc42/Rac/RhoG protein family, and the mitogen-activated protein kinase, phosphatidylinositol-3-OH kinase and phospholipase C-γ pathways[103]. Interplay may exist between NTs and cytokines. NTs such as BDNF may be influenced by cytokines through their actions on 5-HT. 5-HT enhances BDNF expression, which in turn enhances the growth and survival of 5-HT neurons. On the contrary, reduced 5-HT causes reductions of BDNF and Bcl-2, leading to the impairment of neuroplasticity[93]. Therefore, impaired 5-HT and BDNF signaling pathways may be the key to depression and other mood disorders[104].

Conclusion

In this review, we describe the role of inflammation in the pathophysiology of depression, including the inflammatory biomarkers for depression, the sources of cytokines in the brain, and the various underlying mechanisms of cytokine-induced depression. A significant number of studies provide evidence for the important role of inflammation in the etiopathogenesis of depression by regulating HPA axis activation, neurotransmitter systems, and neuroplasticity (Fig. 1).

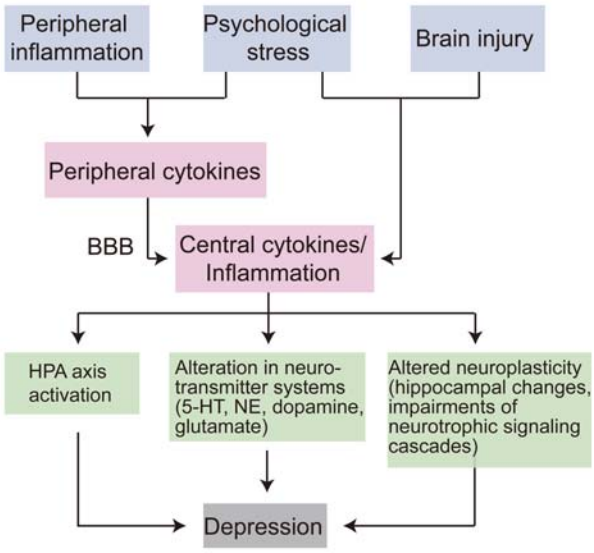

Fig. 1. Sources of cytokines in the brain and underlying mechanisms of cytokine-induced depression. Peripheral inflammation and psychological stress induce elevated levels of peripheral cytokines, which access the brain through the BBB. Besides, cytokines are produced in the brain itself when induced by psychological stress or brain injury. To sum up, cytokines produced in the brain as well as those from the periphery co-mediate the impact of inflammation on depression. The neuroimmunological mechanisms underlying the association between inflammation and depression include activation of the HPA axis, modulation neurotransmitters, and alternation of neuroplasticity.

While inflammatory dysfunction is increasingly recognized in depression, some important questions remain. For example, the precise relationships between inflammatory dysfunction and neuroendocrine function, neurotransmitter systems, and neuroplasticity need further clarification. Besides, biomarker panel to predict or diagnose depression is urgently needed. Identifying the underlying mechanisms can provide alternative treatment options targeting inflammation to treat depression, a very promising direction.

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