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

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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-1Ra, 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[6]. 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]. 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[23-25]. 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 the nervous system and the immune system. Several kinds of cytokines and their receptors are synthesized and released within the brain[26]. Moreover, non-psychological disorders such as 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[50], 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 Ca2+ 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,