Brain-immune interactions and implications in psychiatric disorders

Interações imunocerebrais e implicações nos transtornos psiquiátricos

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Abstract

Objective: This review will focus on the role of cytokines in the central nervous system and its implications to depressive disorder. We will then discuss the main findings of cytokine measurements in patients with major depressive disorder. Method: We searched Pubmed for studies published from 1999-2007, using the keywords depression and cytokine; and depressive disorder and cytokine. We have focused on pro-inflammatory cytokine measurements in patients with depression syndrome using DSM-criteria. Results: Several lines of evidence suggest that cytokines have effects on depression, such as the induction of sickness behavior; clinical conditions related to cytokines that also overlap depressive symptoms; and immunotherapy that can lead to depressive symptoms attenuated by antidepressant treatment. Finally, patients with depression exhibit increased levels of pro-inflammatory cytokines, although conflicting results have been described. Conclusion: Cytokines may play a role in the pathophysiology of some cases of depression, although a causal link has not been established yet. Further longitudinal studies are needed to determine patterns of cytokine in patients with major depressive disorder, taking into account confounding factors closely associated with the activation of pro-inflammatory cytokines. In addition, simultaneous measurements of multiple biomarkers could provide critical insights into mechanisms underlying major depressive disorder and a variety of common cytokine-related diseases.

Descriptors: Cytokines; Immune system; Depressive disorder; Antidepressive agents; Neurosecretory systems

Resumo

Objetivo: Nesta revisão será focado o papel das citocinas no sistema nervoso central e suas implicações para o quadro depressivo. Posteriormente, serão discutidos os principais achados sobre medidas de citocinas em pacientes com depressão maior. Método: Foi realizada uma pesquisa no Pubmed selecionando estudos entre 1999-2007, utilizando as seguintes palavras-chave: "depression, cytokine"*;* "depressive disorder, cytokine"*. Focou-se nos estudos de medidas de citocinas pró-inflamatórias em pacientes com síndrome depressiva que utilizaram critérios DSM. Resultados: Várias linhas de evidência sugerem que as citocinas possam exercer um papel na depressão. Entre elas, destacam-se: citocinas induzindo a "comportamento doentio"; doenças clínicas relacionadas com citocinas também apresentam associação com quadros depressivos; uso de imunoterapia levando ao desenvolvimento de depressão. Além disso, níveis elevados de citocinas pró-inflamatórias em pacientes com depressão foram relatados, apesar de resultados contraditórios. Conclusão: O papel das citocinas na fisiopatologia em alguns casos de depressão é descrito; porém, uma relação causal não foi ainda estabelecida. Novos estudos são necessários para determinar padrões específicos de citocinas em pacientes com depressão, levando em consideração outros fatores associados à ativação imunológica. Além disso, medidas simultâneas de múltiplos marcadores biológicos podem gerar informações importantes para a compreensão dos mecanismos fisiopatológico da depressão e em doenças relacionadas à produção de citocinas*

Descritores: Citocinas; Sistema imunológico; Transtorno depressivo; Antidepressivos; Sistemas neurossecretores

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Introduction

Studies on brain-immune interactions have revealed the bidirectional connections between the neural and neuroendocrine systems and the immune system.[1] Through neuronal and neuroendocrine pathways, the central nervous system (CNS) regulates the immune system and, in turn, the immune system signals the brain through neural and humoral routes. Immune organs are innervated by the sympathetic nervous system and immune cells express receptors for neurotransmitters including catecholamines, neuropeptides, and for hormones including those of the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-gonadal (HPG), hypothalamic-pituitary-thyroid (HPT), and the hypothalamic-growth-hormone axes (Figure 1).[2-3] In addition, the parasympathetic system, via the vagus nerve, contributes to the bidirectional connection between the brain and the immune system.[4] Through these pathways, the nervous system and the endocrine system can exert a direct effect on the immune system.

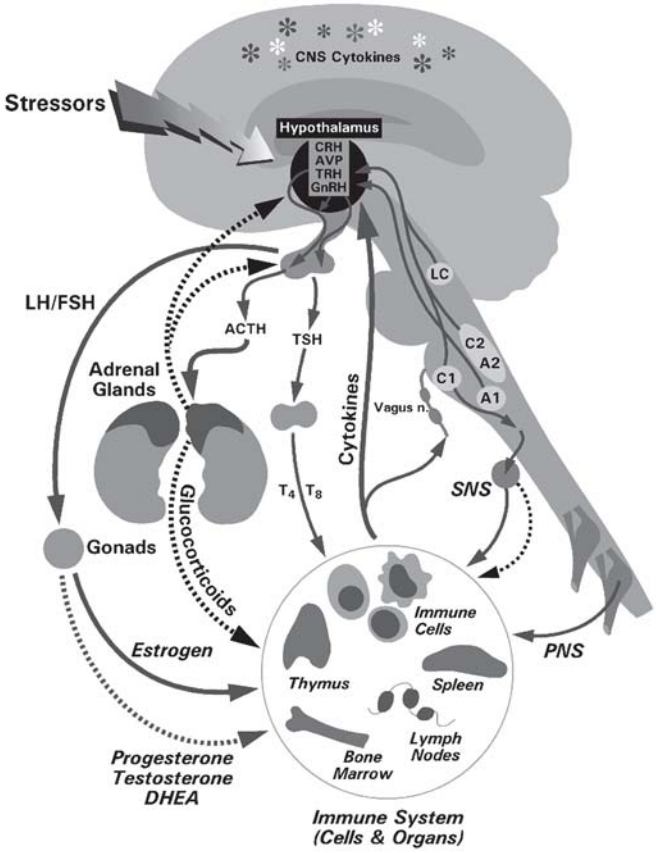

Figure 1 – Schematic illustration of neural immune connections including immune signaling of central nervous system via systemic routes and the vagus nerve (Vagus n.), and CNS regulation of immunity via the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and hypothalamic-pituitary-gonadal (HPG) axes, and the sympathetic nervous system (SNS), parasympathetic nervous system, and peripheral nervous system (PNS). Cytokine expression within the CNS is represented by asterisks within the brain. Dotted lines represent negative regulatory pathways, solid lines represent positive regulatory pathways. Reprinted with permission from Molecular Psychiatry, Volume 10, 2005.

CRH: corticotrophin releasing hormone; AVP: arginine vasopressin; ACTH: adrenocorticotropin hormone; TRH: thyrotropin-releasing hormone; GnRH: gonadotropin-releasing hormone; TSH: thyroid-stimulating hormone; T4: thyroxin; T3: triiodothyronine; LH: luteinizing hormone; FSH: follicle-stimulating hormone.

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The immune system can also signal the CNS through the action of cytokines.[5] In the last few decades, the growing understanding of the interaction between the immune system and the neuroendocrine system has shown that this interaction plays a role in many diseases such as sepsis, rheumatologic diseases, autoimmune diseases, cardiac diseases, neurological diseases, and psychiatric disorders.[6-7] Recently, cytokines have been approved to treat many diseases including TNF inhibitors for treatment of rheumatoid arthritis and Crohn's disease; IL-1 to increase platelets; erythropoietin to increase red cells; interferon alpha (INF-α) for hepatitis C and multiple scleroses; and IL-2 for melanoma and renal carcinoma.[8] This review will focus on the role of cytokines in psychiatric disorders. We will first review the role of cytokines in the CNS and the implications for psychiatric disorder. Finally, we will discuss the main findings of cytokine measurements in patients with major depressive disorder (MDD).

Immune system actions in the CNS – role of cytokines

Cytokines are regulatory proteins that can act in an autocrine, paracrine and also hormone-like way. Cytokines have a pleiotropic action (multiple target cells and multiple actions) and many cytokines have an overlapping spectrum of actions. They may also exert antagonistic or synergistic actions. Therefore, exposure to different cytokines simultaneously may result in qualitatively different responses in target cells. In addition, a cytokine may increase or decrease the production of another cytokine. Cytokines are rapidly cleared, and the half-life of most cytokines, which have been injected intravenously, is usually measured in minutes.[9]

Cytokines act by binding to specific high affinity cell surface receptors. Interestingly, cytokine actions can be antagonized by different pathways. One cytokine can decrease production of other cytokines (e.g. IL-10 decreases TNF's production). In addition, some cytokines have a natural antagonist that shares significant structural homology and binds to the same receptor (e.g. the IL-1 receptor antagonist (IL-1RA) is the antagonist of IL-1). Thus, whenever IL-RA binds to the IL-1 receptor, it does not stimulate the cell, thereby acting as an antagonist by blocking the biological activity of IL-1. Finally, soluble cytokine receptors may be shed from the surface of the cell and bind to cytokines in the circulation. This extra-cellular interaction serves to inactivate the actions of circulating cytokines. Therefore, the final effect of a certain cytokine will depend on the ratio of the soluble receptor concentration and their concentration, as only free cytokines are able to exert their effects.[8-10]

Production of cytokines and their concentrations in the circulation are usually low or absent, in contrast to hormones, which are normally present in circulation. Cytokines are produced in the periphery by a variety of immune cells such as monocytes, macrophages, activated T cells, B cells, natural killer (NK) cells, and fibroblasts.[10] In addition, production of cytokines has been described in many other cells types such as, smooth, muscle cells, endothelial cells, fibroblast,[9] keratinocytes, cardiac myocytes, and eccrine sweat glands.[11] In addition, cytokines are also produced in the CNS by microglia, astrocytes, vascular endothelial cells, and fibroblasts.[9]

Cytokines produced in the periphery can also signal the brain by several routes like active transport, as well as by passive entry through areas where the blood-barrier is weak or absent (circumventricular organs and choroid plexus).

However, since cytokines are relatively large and hydrophilic molecules, this mechanism has been rejected by some authors.[12] Furthermore, cytokines can bind to receptors on paraganglia cells near the vagus nerve. Thus, in turn, they activate the vagus nerve and the brainstem region where the vagus projects, the nucleus tractus solitarius. Cytokines can also exert effects on CRH-producing neurons in the median eminence, and can act on endothelial cells of brain vasculature or glia cells in circumventricular organs inducing synthesis and release of secondary messengers, which, in turn, activate hypothalamic neurons.[13]

In the periphery, cytokines coordinate complex components of the immune response including the innate and adaptive immune responses. Cytokines of the innate response, including TNF, IL-12, INF and IL-1 produced by macrophages and NK cells, help to activate neutrophils, NK cells and macrophages. During the later phase of adaptive response, the production of IL-1, IL-2, IL-6, mainly by T lymphocytes, helps to activate T cells, B cells, macrophages, neutrophils and eosinophilis.[10] Together these aspects of the inflammatory response provide immediate non-specific (innate) and later specific (adaptive) antibody and cellular defenses against infections or other insults.

In the brain, cytokines are responsible for neuroendocrine and neuronal activation. Cytokines regulate glial cell growth and proliferation, modulate activity of endogenous opioid peptides, and activate the HPA axis.[13-14] In addition, cytokines can affect noradrenergic, serotoninergic and dopaminergic system metabolism. For instance, IL-1 can induce serotonin, norepinephrine and dopamine synthesis; and IL-2 can increase norepinephrine and dopaminergic transmission in the nigrostriatal area.[15] Cytokine activation in the CNS leads to fever, induction of sleep, and many behavioral alterations associated with sickness, termed "sickness behavior".[16]

Multiple and diverse stimuli regulate the production of cytokines. Most pro-inflammatory cytokines are produced in response to invasive pathogens or to pathogens products such as lipopolysaccharide (LPS), derived from the cell walls of gram negative bacteria. Other classic inducers of pro-inflammatory cytokine production include viral infections, trauma, organ or tissue transplantation, ischemia, and reperfusion injury. Central cytokine production can be triggered by stress, physical exercise, ischemia, neurovegetative processes, autoimmunity, and infection. Interestingly, while peripheral cytokines mediate the inflammatory response, cytokines in the brain can be triggered in the absence of local inflammation. Therefore, cytokine expression in the brain is not necessarily an indication of inflammation.[17]

Cytokines can be classified by their actions or properties, such as pro-inflammatory or anti-inflammatory actions, or their role as growth factors, or hematopoietic effects, etc. In this review, we will focus on pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-12, TNF-α and IFN-γ) promote activation of the inflammatory process, helping to eliminate pathogens and to speed resolution of inflammation. Increases in pro-inflammatory cytokines lead to activation of macrophages, neutrophils, NK cells, T cells, and B cells, proliferation of T cells and B cells; and proliferation and secretion of immunoglobulins. At a systemic level, cytokines have been shown to induce fever and increase synthesis of acute phase proteins. Locally, they promote recruitment of inflammatory cells to inflammation sites. Some cytokines, namely chemokines, are responsible for recruitment, activation and retention of leukocytes at local inflammation sites. Anti-inflammatory cytokines (IL-4, IL-10, IL-13, TGF-β) reduce the inflammatory response by decreasing pro-inflammatory cytokines and suppressing monocyte activation. Some cytokines exert their effects depending on the site of action. For instance, IL-8 has a pro-inflammatory action at local inflammation sites, while at high concentration, it exerts an anti-inflammatory action in the intravascular compartment.[8] Cytokines can also be classified by the source of lymphocyte T helper production: whether produced by T helper 1 (Th-1) or T helper 2 (Th-2) lymphocytes. Th-1 lymphocytes release cytokines and their inhibitors that activate macrophages, NK cells, neutrophils, cytotoxic lymphocytes, thus enhancing the cell-mediated immune response (e.g. IFN-γ, IL-1, IL-6, TNF-α, IL-2). Whereas, Th-2 cytokines (e.g. IL-4, IL-5, IL-6, IL-10, IL-13, TGF-β) enhance the humoral response by activating cells to express antibodies. Th-1 cytokines are mainly pro-inflammatory, while Th-2 cytokines are mainly anti-inflammatory. Equilibrium between pro- and anti-inflammatory is essential to maintain the homeostasis in the system. Dysregulations of the pro- versus anti-inflammatory (Th1 versus Th2) are involved in the pathogenesis of many human diseases, such as allergic and autoimmune diseases, chronic infections and sepsis. In addition, recent evidence also indicates that such dysregulations occur in atherosclerosis, visceral type obesity, metabolic syndrome, sleep disturbance, and major depression.[18]

Cytokines and major depression - evidence for the role of cytokines in MDD

Much evidence supports the role of cytokines in depression. Cytokines have been shown to affect many behaviors, including effects on sleep, appetite, sexual behavioral, memory and motor activity. In fact, cytokines are responsible for behaviors displayed during infectious disease, referred to collectively as sickness behavior. Interestingly, the constellation of symptoms in sickness behavior, such as lethargy, somnolence, fatigue, lack of interest, lack of appetite, decreased concentration, is similar to many symptoms described in the depressive syndrome.[16]

In addition, many other conditions associated with the increase in pro-inflammatory cytokines, such as allergies, excessive athletic training, and autoimmune inflammatory diseases also exhibit symptoms that overlap major depression. Recently, increased inflammatory processes have been shown in cardiovascular disease. Interestingly, patients with depression have an increased risk for cardiovascular disease, and, conversely, depression increases morbidity and mortality in patients with heart disease.[6]

Further direct evidence supporting a role of cytokines in mediating depression is the fact that administration of interferon-a in humans for treatment of infectious disease or cancer can lead to mood disorders including depressive syndromes, manic states, hypomania, and mixed states.[19] In cases in which depression is induced by these cytokines, symptoms resolve after the cessation of the treatment, or with the use of antidepressants. Interestingly, the effect of antidepressants in patients who develop depression after cytokine exposure is described to have a better action in selected symptoms such as depressed mood, anxiety, cognitive dysfunction, and pain, whereas the action is less effective in neurovegetative symptoms (fatigue, psychomotor slowing, altered sleep, and anorexia).[19] In addition, prophylactic treatment with antidepressants have prevented

depressive episodes in patients receiving cytokines for cancer and other diseases.[19] Moreover, increased risk for depression and reduced responsiveness to antidepressant therapy have been associated with polymorphism of IL-1β and TNF-α genes.[20-21] Results have also been reported showing no correlation between polymorphism of IL-10, IL-6 and TNF-β genes and depression.[22]

Finally, pro-inflammatory cytokines have been described to be elevated in patients with MDD who are otherwise medically healthy. In the next section, we will discuss the results from studies that have focused on the measurement of cytokines in patients with depression syndrome (medically healthy) using DSM-criteria.

Cytokine measurements in patients with depressive syndromes

Depression has been associated with activation of the immune system characterized by higher levels of pro-inflammatory cytokines and positive acute-phase proteins.[23] Some studies have shown that levels of pro-inflammatory cytokines (e.g. IL-1β, IL-6, IFN-γ; TNF) are increased in patients with depression;[24-27] however, conflicting results also have been described.[28-32] Moreover, recently, abnormal IL-6 production across the circadian cycle (between 10-12 am) has been reported, although the 24h mean remained normal.[33]

Studies have shown that the association between cytokine levels and MDD is attenuated when potential moderating factors such as age, gender, body mass index (BMI), smoking habits, recent and ongoing infectious diseases, prior medication, depression, characteristics of the sample, and clinical and psychiatric comorbidities have been included in the analysis.[29,32,34] Therefore, in addition to controlling for many confounding factors, a more detailed psychiatric characterization of the patients with depression (melancholic versus non-melancholic; dysthymia versus MDD; psychiatric and clinical comorbidities) has been described to be helpful towards identification of immune patterns in some studies, although the results are still unclear. Taking into account distinct symptomatology and neuroendocrine patterns in melancholic and non-melancholic depression, some authors have reported unchanged/decreased cytokines in patients with melancholic depression versus an increased/unchanged cytokines in atypical depression,[25,35] although, contradictory results have been shown.[36-38] Studies have also shown different cytokine patterns in patients with dysthymia compared to patients with MDD,[28,39-40] but these findings were not replicated in all studies.[37,41-42] In addition, some studies have reported that cytokines remain elevated in patients with depression after clinical remission,[27,33] although conflicting results have also been described.[30,43] This findings have important implications, as maintenance of increased pro-inflammatory cytokine levels increases the risk for development of osteoporosis, diabetes, and atherosclerosis.[18]

Furthermore, a distinct pro-inflammatory cytokine profile may distinguish antidepressant treatment responders from non-responders.[44]

Antidepressants have been shown to inhibit the production of pro-inflammatory cytokines and to stimulate the production of anti-inflammatory cytokines.[45] Conversely, controversial results on the change of cytokine patterns before and after treatment have also been reported in patients with depression. Some studies have reported a normalization of cytokine levels after treatment,[24-25,37,44,46-48] although that pattern was not consistent in the literature.[29,38,40-41,46,49-54]

In addition, positive correlations between some pro-inflammatory cytokines and the presence and intensity of depressive and anxiety symptoms have been described,[27-28,33-34,48,55] although conflicting results have also been described.[24,35,37,42,47] Indeed, even in patients who did not meet criteria for major depression, the presence of single depressive and anxiety-related symptoms such as fatigue, cognitive function, insomnia, and anger have been associated with cytokines.[56] Finally, the role of stress in inducing depression and as the link between depression and increased pro-inflammatory cytokine cannot be ruled out. It is well known that psychological stress is related to and can trigger depression. In addition, psychological stress has been associated with increased pro-inflammatory cytokines in human and animal studies.[57] Based on this evidence, an immune hypothesis regarding the pathophysiology of depression has been debated in the literature, although the role of cytokines in depressive disorder is complex and must still be clarified.[58-59] Identification of confounding factors and characterization of distinct phenotypes of depression will contribute to a better understanding of this interaction. Moreover, due to the complexity of cytokine network, simultaneous cytokine measurements within the same sample could also be helpful. Finally, we recently developed a novel methodology using recycling immunoaffinity chromatography (RIC) and sweat patches to collect and simultaneously measure multiple biomarkers in sweat in subjects under ambulatory conditions. Sweat measurements of cytokines were strongly correlated with plasma levels.[60] The use of sweat patches is an unobtrusive methodology that minimizes pain and stress related to blood collection and provides approaches that could help to clarify the role of cytokines in patients with depression.

Conclusion

Studies on brain-immune interactions have revealed the bidirectional connections between the neural and neuroendocrine systems and the immune system. Through neuronal and neuroendocrine pathways, the central nervous system (CNS) regulates the immune system and, in turn, the immune system signals the brain through the action of cytokines. Dysregulation of the pro- versus anti-inflammatory cytokines (Th1 versus Th2) has been reported to be involved in the pathogenesis of many human diseases such as allergic and autoimmune diseases, chronic infections, and sepsis. In addition, recent evidence indicates that such dysregulations can also be involved in atherosclerosis, visceral type obesity, metabolic syndrome, postmenopausal osteoporosis; sleep disturbance, and major depression. Several lines of evidence suggest that cytokines play a role in various depressive conditions such as: cytokines inducing sickness behavior; clinical conditions related to cytokines that also overlap depressive symptoms; and immunotherapy that can lead to depressive symptoms attenuated by antidepressant treatment. Moreover, depression has been associated with the activation of the immune system characterized by higher levels of pro-inflammatory cytokines and positive acute-phase proteins, although conflicting results have been described. These conflicting findings indicate that, although there is clear association between cytokines and symptoms of depression, and that cytokines may play a role in the pathophysiology of some cases of depression, a causal link cannot be established yet. Further longitudinal studies are needed to determine the

cytokine patterns in patients with MDD, taking into account confounding factors closely associated with the activation of pro-inflammatory cytokines. In addition, in light of the bidirectional connections between the neuroendocrine and immune systems and the cytokine network itself, simultaneous measurements of multiple biomarkers within the same sample could provide critical insights into the mechanisms underlying depressive disorders and a variety of common cytokine-related diseases.

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