Cytokines in the physiopathology of depression

ABSTRACT: This paper presents a bibliographical review on the relevance of the possible role of cytokines in depression. There is a consideration of the existing approaches to detection and diagnosis of depression; they are classified according to different criteria such as design methodologies and applications. Although the etiology of depression is still an issue, the focus of this paper is to highlight the various studies regarding the interactions of the immune system and brain activity linked to depression. These interactions are particularly important when trying to find a correlation between proinflammatory cytokines (such as IL-1, IL-6, and TNF-α) and depression. This includes a brief comparison of results obtained by different studies.

Keywords: depression, cytokines, inflammation, TNF-α, IL-1, IL-6

ABSTRACT: Este artículo presenta una revisión bibliográfica sobre la relevancia del posible rol de las citoquinas en la depresión. Se tienen en cuenta los enfoques existentes para la detección y el diagnóstico de la depresión, estos han sido clasificados según diferentes criterios, como las metodologías de diseño y las aplicaciones. Aunque la etiología de la depresión sigue siendo un problema, el objetivo de este documento es mostrar los diferentes estudios sobre las interacciones del sistema inmune y la actividad cerebral relacionada con la depresión. Estas interacciones son particularmente importantes cuando se trata de encontrar una correlación entre las citoquinas proinflamatorias (como IL-1, IL-6 y TNF-α) y la depresión. También se incluye una breve comparación de los resultados obtenidos en diferentes estudios.

Palabras clave: depresión, citoquinas, inflamación, TNF-α, IL-1, IL-6

Introduction

Depression is a mental health disorder characterized by a group of affective, cognitive and somatic symptoms. Depression boards a broad spectrum of clinical presentations, for this reason, depressive disorders are classified into three main subclasses: Major Depressive Disorder, Dysthmic Disorder and Depressive Disorder NOS (No Otherwise Specified). Each of them is characterized by the presence to greater or lesser degree of different features such as psychotic, catatonic, atypical and chronic. The fourth version of the Diagnostic and statistical manual of mental disorders (DSM-IV) is used to diagnose depression, and tests like the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Asberg Depression Rating Scale (MADRS) are used in several studies in order to rate depressive symptoms to determine the severity of depression. Cognitive and sleep disturbances, fatigue, appetite suppression and depressed mood (sickness behaviour) are recognized as the most common symptoms of this disorder. However, to determine the etiology and physiopathology of depression is still an issue because of its heterogeneity and the fact that depression appears concomitantly with many other diseases such as diabetes, rheumatoid arthritis and coronary heart disease.

Major depressive disorder (MDD), the most severe in the classification of depressive disorders, is considered a major public health concern with 4% of the adult population. However, to determine the etiology and physiopathology of depression is still an issue because of its heterogeneity and the fact that depression appears concomitantly with many other diseases such as diabetes, rheumatoid arthritis and coronary heart disease.

Currently, there are several studies regarding the interactions between the immune system and the brain activity focused on finding a more accurate representation of depression physiopathology. In particular, there is an increased interest in the consequences of inflammation in depression and the role of proinflammatory cytokines such as IL-1, IL-6, and TNF-α. The consideration of a new approach regarding inflammation is based on the fact that illnesses promoting inflammatory responses are associated with higher rates of depression, the administration of cytokines induces depressive episodes in non-psychiatric patients, the therapeutic administration of cytokines has led to depression in up to 50% of the patients, and that cytokines induce behaviors that are commonly present as symptoms of depression.

The study aims to review the existing information about the relevance of the possible role of cytokines in depression and the underlying mechanisms.

Cytokines

Cytokines are large polypeptide regulatory mediator proteins secreted by white blood cells and other cells in the body. They play a role in the immune system specifically in inflammatory responses, the regulation of growth, differentiation, and function of cells. The most common classification of cytokines is into families of interleukins, tumor necrosis factors (TNF), interferons (INF), chemokines, haematopoietins and colony stimulating factors (CSF).

Interleukin-1 (IL-1) is the prototypical proinflammatory cytokine. It appears in two forms: IL-1alpha and IL-1beta. It functions as an immunoadjuvant as it is primarily under immune system control and it is highly inflammatory. The lea-
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...of preclinical research has indicated the presence of a potential "multiple network model" in the etiology of depression, where multiple factors including genetic, environmental, and neurochemical factors interact. This model suggests that depression can be understood as a complex disease with a multifactorial etiology.

The role of cytokines in depression has been extensively studied, and it is now well established that cytokines play a crucial role in the pathophysiology of depression. Cytokines are involved in the regulation of inflammatory responses, and they can affect the immune system, the central nervous system (CNS), and other organs and tissues.

Cytokines are signaling proteins that are produced by immune cells and other cells in the body. They are involved in the regulation of immune responses, inflammation, and the formation of immune responses against pathogens. The expression and secretion of cytokines are regulated by various factors, including stress, infection, inflammation, and psychological factors.

In depression, the imbalance in cytokine production and function has been implicated in the pathophysiology of the disease. Cytokines can affect mood, sleep, appetite, and other behaviors, which are all important factors in the development and maintenance of depression.

The role of cytokines in depression is multifaceted. They can act as stressors themselves, as mediators of immune system function, and as modulators of other inflammatory processes. The complex interplay between cytokines and other immune system and neurochemical factors is essential for understanding the pathogenesis of depression and developing effective therapeutic strategies.

In conclusion, cytokines are intimately involved in the pathophysiology of depression, and understanding the role of cytokines in the disease is crucial for the development of new therapeutic strategies. Further research is needed to elucidate the complex interplay between cytokines and other factors in the etiology of depression and to identify new targets for the development of innovative treatments.
β are also present when there is an increase of TNF and IL-1, highlighting the possible neuroprotective role of IL-641. In the other hand, TNF-α may be necessary in brain development and as a modulator of synaptic plasticity when present in low concentrations. Synaptic plasticity is a fundamental mechanism of neuronal adaptation that becomes modified in depression, models of stress in animals and other conditions that alter mood. Increased levels of proinflammatory cytokines, in particular, TNF-α and IL-1 are able to damage synaptic plasticity and cognition promoting the progression of depressive disorders. Patients diagnosed with MDD show large deficits in declarative memory and cognition, mental processes that rely on the ideal functioning of the hippocampus and medial temporal lobe45.

Depression and other illnesses

High rates of depression are usually associated with diseases that involve upregulation of inflammatory processes37,46,47. Medical illnesses that enhance the appearance of inflammatory markers such as Alzheimer’s disease, MS, obesity, rheumatoid arthritis and gastrointestinal inflammation, promote the development of depression in patients suffering from these diseases at higher rates than in healthy patients33,40,48. Furthermore, treatments for conditions that include the use of proinflammatory agents such as interferon-gamma (IFN-γ) or IL-2 induce depression. This was proved in patients suffering from chronic infectious hepatitis C and cancer47-49,50. Cancer patients with depression show elevated levels of IL-6 compared to cancer patients without depression43,51. Cardiovascular diseases that are principally caused by atherosclerosis and the associated inflammation of arteries wall can promote the development of depression and vice versa. The use of anti-inflammatory medications (aspirin) to prevent cardiovascular events are associated with the reduction of the symptoms of depression. Exercise also downregulates TNF-α and inflammation43,53. However, healthy patients presenting depression and no comorbidity show elevation of cytokines and its receptors in the CSF, so cytokine levels are not more strongly associated with somatic than psychological symptoms of depression49,54.

Clinical Trials

The NCT00463580 study evaluated the effect of anti-inflammatory monoclonal antibodies in patients with treatment-resistant depression (TRD). It was a single site, parallel-group, randomized, double-blind controlled trial of infliximab versus placebo. Participants were patients with major depression, non-respondent to antidepressant therapies55. Infliximab is a monoclonal antibody TNF-α antagonist that suppresses the body’s response to this cytokine. This study aimed to test the efficacy of infliximab (Remicade®) in reducing symptoms of depression compared to the effects of placebo. High sensitivity c-reactive protein (hs-CRP), TNF-α, sTNFRII, and sT-NFRI were considered as biomarkers of inflammation and measured at baseline. The results showed that inhibition of TNF-α activity could not be regarded as a valid therapeutic strategy for TRD because infliximab did not show improvement of depressive symptoms. However, subjects with an elevated baseline of hs-CRP (hs-CRP>5mg/L) responded better to infliximab, showing a correlation between high inflammation and subsequent response to treatment. Of note, high levels of CRP are due to the increase of IL-6 concentration in stress-linked diseases that are principally caused by atherosclerosis and the associated inflammation of arteries wall can promote the development of depression and vice versa. The use of anti-inflammatory medications (aspirin) to prevent cardiovascular events are associated with the reduction of the symptoms of depression. Exercise also downregulates TNF-α and inflammation43,53. However, healthy patients presenting depression and no comorbidity show elevation of cytokines and its receptors in the CSF, so cytokine levels are not more strongly associated with somatic than psychological symptoms of depression49,54.
Conclusion

Throughout this review, we overviewed the role of cytokines in the immune system, its relationship with serotonin and tryptophan and the conditions that support the inflammatory hypothesis in the physiopathology of depression. Depression is without a doubt a complex disorder and understanding the roles of different processes that contribute to this disorder is a first step to achieve adequate treatment. The importance of this study lies in raising the possibility of finding psychotropic drugs that have a central anti-inflammatory action and that could provide a new generation of antidepressants.

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