Neurochem Res (2014) 39:1634–1639
DOI 10.1007/s11064-014-1372-5

OVERVIEW

Neuroimmunomodulation in Depression: A Review of Inflammatory Cytokines Involved in this Process

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Received: 29 April 2014 / Revised: 2 June 2014 / Accepted: 25 June 2014 / Published online: 5 July 2014

Abstract Depression is a debilitating mental disease that affects a large number of people globally; however the pathophysiological mechanisms of this disease remain incompletely understood. Some studies have shown that depression is associated with inflammatory activity, and the mode of action of several antidepressants appears to involve immunomodulation. In this case, the induction of a pro-inflammatory state in healthy or depressive subjects induces a 'sickness behaviour' resembling depressive symptomatology. Potential mechanisms of pro-inflammatory cytokines are effects on monoamine levels, disruption of the hypothalamic–pituitary–adrenal axis, activation of the pathological microglial cells, such as the macrophages and alterations in neuroplasticity and brain functions. Thus, this review will highlight the role of inflammation in depression, the possible mechanisms involved, and also explore effective treatments that act on the immune system.

Keywords Cytokines · Inflammation · Antidepressants · Depression

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Introduction

Depression is a mood disorder that may ultimately cause severe impairment in occupational, social, or other important areas of functioning. The disease also has high mortality rate, as the indexes of individuals who die by suicide reach 15 % [1]. The etiology of depression is associated with stressful life events, personality, gender, illness, family history, loneliness as well as alcohol and drugs abuse [2]. Although the pathophysiology of depression is not yet fully known, this disorder may be involved with changes in the expression of neurotransmitters, the hypothalamus–adrenal–pituitary (HPA) axis, genes and structural changes within the brain. Treatment of depression is generally safe and effective, but it is far from ideal, since only 60–70 % of patients using antidepressants are positive about their therapeutic efficacy, in addition to its various side effects [3]. Therefore it is necessary to look beyond currently characterized neurotransmitter systems to understand the pathophysiology of depression in order to produce more effective treatments in the long-term. Major depression has been shown to be associated with activation of the inflammatory response. These changes include increased numbers of peripheral leucocytes including monocytes and neutrophils [4]. Positive acute phase proteins including C-reactive protein are increased [5] while negative acute phase proteins are decreased, e.g. albumin [6]. This acute phase response is an integral part of the inflammatory response and its purpose is to enable protein mobilization, which serves to limit tissue damage and stimulate repair [7]. Smith [8] put forward the 'macrophage theory of depression' in which he proposed that excessive secretion of macrophage cytokines such as as interleukin (IL)-1, tumor necrosis factor (TNF-α) and interferon (INF-γ) were associated with major depression and these alteration

may contribute to the dysfunction of the serotonergic and noradrenergic systems. Thus, this review will highlight the role of inflammation in depression and the possible mechanisms involved, besides exploring any effective treatments that act on the immune system.

The Inflammatory System and Its Function

The immune system is well known for its function in defending a host against microbial invasion [9]. It is conceptually divided into the innate and adaptive immune systems [10], that consist of cells and molecules that work together, in concert, to fight against microbial infection and to maintain homeostasis. In this context, the innate immunity represents a rapid and stereotyped response to a large number of limited stimuli. It is represented by physical, chemical and biological systems, using specialized cells such as macrophages, neutrophils, dendritic cells, natural killer cells [11] and soluble molecules present in all individuals [12]. These release inflammatory mediators and activate the complement system, as well as stimulating the activation of acute phase proteins, that's when the pro-inflammatory cytokines are released, and the vascular system and inflammatory cells are activated, thus characterizing innate immunity [13]. In addition to this, these elements contribute to the activation of the adaptive immune system [10]. The response of the adaptive immune system serves to create and maintain the memory of the immune system [14]; furthermore, it is antigen-specific, and is based on the antigen-specific receptors on the surfaces of T and B lymphocytes [9]. T-lymphocytes produce the cellular response and maintain the immune response through the release of cytokines, mainly IL-2, to attract more macrophages, neutrophils and lymphocytes. Therewith, the B-lymphocytes are attracted and stimulated by these cytokines to induce a humoral response whereby antibodies are produced against the identified pathogens [15]. Cytokines comprise a heterogeneous group of messenger molecules that are produced by immunocompetent cells, such as lymphocytes and macrophages, which are secreted by astrocytes and microglia during human fetal development, suggesting a role of cytokines in the modulation of nervous system development [16, 17]. They are present at low concentrations in the nervous system under physiological conditions, however, in pathological conditions, they are able to increase their concentrations up to a hundred times [18]. Although their specific activities and concentrations may vary, cytokines can be divided into two groups, the pro-inflammatory and anti-inflammatory cytokines. The first group contains cytokines that are classified by being directly involved in the inflammatory process, such as interleukin (IL)—1β, IL -6, interferon (IFN) -γ and TNF—α. The second group includes IL-4, IL-10 and IL-13, which are known to decrease the inflammatory response by producing pro-inflammatory mediators. However, there are some cytokines, such as IL-8, which are able to perform both tasks, depending on the concentration in which this cytokine is synthesized [15, 16]. In the end, the cytokines and chemical factors produced during the inflammatory response serve as excellent biomarkers when investigating the potential relationship between inflammation and mood disorders.

The Role of Cytokines Produced by Innate Immunity in Depression

It has been established that cytokines that are produced peripherally can reach the brain through leakage regions of blood brain barrier, cytokine binding to specific molecules expressed on the endothelium of the brain, and other factors, that lead to the cytokines affecting brain functions [19, 20], and thereby causing the development of depressive disorder. The hypothesis that cytokines are related to depressive disorder was first proposed by Smith [8] and Maes [21]. These studies showed that in patients with chronic depression, there was an increase of inflammatory markers in the blood, but these results were overshadowed by the advancement and success of selective serotonin reuptake inhibitors and other monoaminergic-based treatments for depression. However, many studies have shown a relationship between an increased incidence of mood episodes and elevated levels of inflammatory markers, such as prostaglandin E2 (PGE2), TNF-α, IL-1β, IL-2, and IL-6 in peripheral blood and cerebral spinal fluid in major depression [22–27].

TNF-α is of particular interest as it's a pro-inflammatory cytokine that been shown to contribute to the pathogenesis of depression [28, 29], and may influence central serotonergic homeostasis through the modulation of glial localized serotonin transporter activity, allowing a possible link of depressive symptoms with chronic inflammatory diseases [30]. Moreover, Reichenberg et al. [31] showed that an experimental stimulation of TNF-α production leads to depression-like emotional and cognitive disturbances in humans. Furthermore, a considerable number of studies showed elevated serum levels of TNF-α in depressed patients [32–36], while one study reported unchanged levels of these cytokine [37]. In animals, intracerebroventricular injections of lipopolysaccharide (LPS) or this pro-inflammatory cytokine are sufficient to produce depressive-like behavior [38, 39]. Moreover, intracerebroventricular administration of TNF-α antagonist [40–43] is sufficiently capable of reversing sickness and depressive-like behaviors that usually occur in systemic inflammation. It has been postulated on the basis of in vitro as well as in vivo studies,

that the therapeutic action of antidepressants may be partially caused by their influence on cytokine production in addition to their direct effect on monoaminergic neurotransmission. In this way, some antidepressants have been shown to decrease TNF-α production in depressed patients [44, 45]. Still, Bayramgurler et al. [46] showed that in animals, etanercept, a TNF-α receptor antagonist, presented antidepressant and anxiolytic effects. In humans, the anti- TNF-α antibody, infliximab has been shown to reduce depressive symptoms in depressed patients that were resistant to antidepressant treatments [47]; and the potentially beneficial antidepressant effect of infliximab depends on the baseline of inflammatory levels [48]. Besides TNF-α, which is known to act in the immunoregulation of inflammatory processes, studies suggest that cytokine IL-1β is also involved in neuroinflammation [19, 49]. Indeed, it has been noted that the pathophysiological levels of IL-1β may regulate synaptic plasticity and behavioral systems, beyond having detrimental effects on hippocampal-dependent memory and learning processes [50–56].

Behind the various factors associated with inflammation, cytokine IL-1β appears to have particularly strong associations with depression [57–60]. In fact, recent studies have reported the association between the polymorphism of IL-1β and major depression [49, 61], and they have even implicated the IL-β gene polymorphism (specifically its rs16944 variant, which results in the increased IL1-β levels) in the lack of response to selective serotonin reuptake inhibitors (SSRI) [62]. Furthermore, IL-1β cytokine is known to modulate the function of the HPA axis [60, 63]. For example, intra-hippocampal administration of recombinant IL1-β in rats leads to an increased plasma cortisol level [57]. In turn, the dysregulation of the HPA axis has been regarded as a neuroendocrine hallmark of chronic stress [64, 65] and has been used as a diagnostic tool in depression [66]. In this way, Goshen et al. [54] showed that chronic mild stress induced depressive-like symptoms concomitantly with an increase in IL-1β expression in the hippocampus, but in mice which possessed a deletion of the IL-1β receptor or a restricted overexpression of the IL-1β antagonist, exhibited no behavioral or neuroendocrine alterations after stress induction. Some studies also showed that administration of cytokines such as IL-1β, or the activation of macrophages and inflammatory cells via treatment with LPS causes behavioral and performance changes related with 'sickness behaviour' [54, 67–69]. In addition, in healthy human volunteers, depression, anxiety and memory impairment were associated with immune activation by the bacterial endotoxin LPS and were correlated with serum IL-1β and TNF-α levels induced by that treatment [70]. Also, Levine et al. [32] showed that depressed patients had higher IL-1β levels and no change in TNF-α compared with control group. IL-6 is a pro-inflammatory cytokine and different to TNF- and IL-1β. The highest levels of IL-6 production are found in adipocytes, highlighting the nexus between diet, obesity and depression, although central nervous system cells and immune cells are also a significant source [71]. Some pro-inflammatory cytokines such as IFN-γ and TNF-α can induce IL-6 in the inflammatory process [71, 72]. The increase of IL-6 in depression is associated with increased activity of the HPA axis, which in turn, increases the cortisol levels leading to activation of tryptophan 2,3-dioxygenase and decreased availability of tryptophan into the synthesis of serotonin, N-acetylserotonin and melatonin [71], thus, IL-6 has a role in the co-ordination of important biological pathways underlying stress and stress induced depression. In this case, some studies have shown elevated levels of IL-6 in the cerebrospinal fluid (CSF) and plasma of suicide attempters with a diagnosis of major depressive disorder and in patients who are refractory to selective serotonin reuptake inhibitor or serotonin–norepinephrine reuptake inhibitor treatment [24, 73]. However, treatment for the normalization of the high levels of this cytokine in plasma, blood and CSF yet seems contradictory.

Interestingly, several studies have been shown that in some cases, antidepressants reduce pro-inflammatory cytokines profiles and inflammatory markers in patients with depression [74, 75]. In fact, Himmerich et al. [76] found that blood levels of IL-1β became undetectable in patients with depression after treatment with antidepressants. Still, Ohgi et al. [77] observed that pretreatment with paroxetine, fluoxetine, venlafaxine and duloxetine in male BALB/c mice decreased the TNF-α levels in serum after the administration of LPS. Similarly, Réus et al. [78] showed that treatment with the antidepressant imipramine reduced the TNF-α and IL-1β levels in the serum and CSF induced by maternal deprivation in adult rats. In addition to antidepressants decreasing the levels of pro-inflammatory cytokines, the inhibition of production of pro-inflammatory cytokines, such as, TNF-α and IL-1β by celexocib, an anti-inflammatory, also induced a rapid antidepressant response and prevented cognitive decline in patients with major depressive disorder [79]. Besides celecoxib, other types of anti-inflammatory drugs have also been shown to have antidepressant-like effects associated with their anti-inflammatory actions, such as, minocycline, which is an antibiotic with an anti-inflammatory profile that has antidepressant like effects [80, 81]. Similar to the anti-inflammatory infliximab which is used in the treatment of psoriasis and related to chronic inflammation conditions, minocycline has mood-elevating effects before decreasing TNF-α levels [82].

Some depressed patients showed a decrease in the levels of IL-6 with antidepressants, but others who are resistant to treatment with antidepressants retained elevated levels of IL-6 in their plasma, suggesting a potential role for IL-6 in the

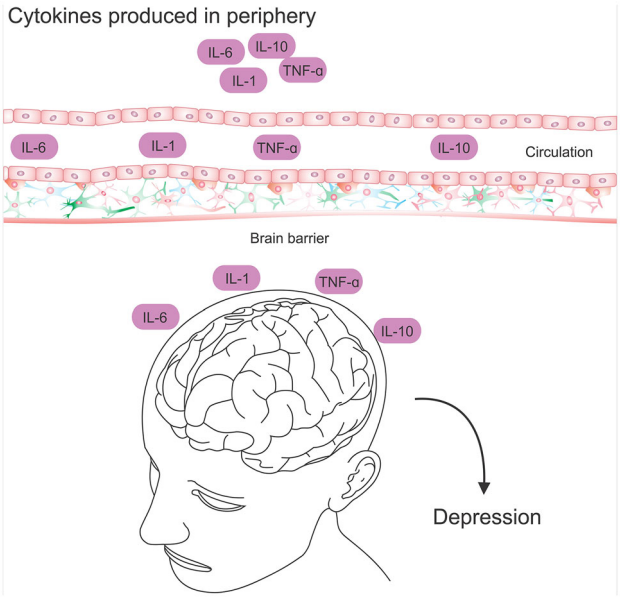

Fig. 1 Representation of how cytokines lead to the development of depressive disorder. Cytokines that are produced peripherally can reach the brain through leakage regions of blood brain barrier, with cytokine binding to specific molecules expressed on the endothelium of the brain, and other factors, which lead to the cytokines affecting brain functions. This in turn, leads to the development of depressive disorder

treatment of treatment resistant depression [83–85]. IL-6 levels also appear increased in animal models of depression [86] and antidepressants decrease the levels of the pro-inflammatory cytokine IL-6 in animal models, as well as in brain cultures and in humans [87]. Furthermore, Anderson et al. [71] suggests that monitoring IL-6 levels may provide an indicator of emerging alterations in the biological basis of depression.

Futhermore, in addition to these antidepressant effects, recent studies have reported anti-inflammatory effects in murine models of autoimmune disease like collagen induced arthritis or EAE [88]. SSRI and SNRI (selective serotonin/norepinephrine inhibitors) have been demonstrated to ameliorate clinical autoimmune disease and to decrease inflammation and inflammatory cytokine production in this context [89, 90].

Conclusion

A number of studies have shown an association between markers of the inflammatory process and major depressive disorder. In this way, disturbances in HPA function that lead to inflammatory system alterations, increasing the levels of the cytokines IL-1β, IL-6 and TNF-α, have long been recognized in depression. However, more studies are needed to characterize the mechanisms that lead to these alterations in the inflammatory markers within depression and their participation in antidepressant mechanisms, and so, further research in this area could reveal the great potential for the identification of new therapeutic targets for the development of antidepressant drugs.

Acknowledgments Laboratory of Neurosciences (Brazil) is a center within the National Institute for Translational Medicine (INCT-TM) and is also a member of the Center of Excellence in Applied Neurosciences of Santa Catarina (NENASC). This research was supported by grants from CNPq (JQ and GZR), FAPESC (JQ), Instituto Cérebro e Mente, UNESC (JQ and TB), and and ĹOréal/UNESCO/ABC Brazil Fellowship for Women in Science 2011 (GZR). JQ and TB are CNPq Research Fellows. HMA has CAPES studentships. We thank Allan M. Colladel for making the Fig. 1.

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