Role of inflammatory cytokines in depression: Focus on interleukin-1β (Review)

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Abstract. According to the World Health Organization, major depression will become the leading cause of disability worldwide by the year 2030. Despite extensive research into the mechanisms underlying this disease, the rate, prevalence and disease burden has been on the rise, particularly in the industrialized world. Epidemiological studies have shown biological and biochemical differences in disease characteristics and treatment responses in different age groups. Notable differences have been observed in the clinical presentation, co-prevalence with other diseases, interaction with the immune system and even in the outcome. Thus, there is an increased interest in characterizing these differences, particularly in terms of contribution of different factors, including age, cytokines and immunotherapy. Research into the possible mechanisms of these interactions may reveal novel opportunities for future pharmacotherapy. The aim of the present review is to document recent literature regarding the impact of inflammatory mechanisms on the pathophysiology of the depressive disorder.

Contents

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1. Introduction

Major depression is set to become the leading cause of disability worldwide by the year 2030 (1). The pathophysiology of depressive illness has been extensively investigated over the past decades and a wide range of underlying mechanisms have been identified for therapeutic interventions (2). Major theories revolve around alterations in neuroamine metabolism and efforts have been made to halt these alterations (3). The most recently identified drug group, selective serotonin reuptake inhibitors, are one such example. Yet the prevalence and disease burden, in terms of quality-adjusted life years lost to depression, are increasing globally. Inflammation has recently been considered as a contributory factor. However, it remains to be seen which of various inflammatory cytokines may be considered for use in intervention strategies. Interleukin (IL)-1β is one such factor with notable implications. The following review describes the existing evidence.

2. Central and peripheral markers of inflammation in depression

Depression has been associated with inflammatory markers since 1985 (4-7). Reduced numbers of red blood cells, hematocrit and hemoglobin, and increased reticulocyte number and changes in iron metabolism that are consistent with the inflammatory process have been observed in individuals

presenting with major depressive illness. These observations are comparable with already established markers of inflammation (reduced levels of serum albumin and zinc) that are present during episodes of depression (8).

Research during the last two decades has revolutionized current understanding of depressive illness. Epidemiological studies have identified correlations between depression and degenerative, inflammatory, genetic, functional and various other types of disorder. Since Smith (9) presented a study of the implications of cytokines in depressive-like behavior, establishing the etiology and pathogenesis of depression has become a point of research. The majority of research has been dedicated to the co-prevalence of depression with vascular and inflammatory disorders. Numerous studies have reported these links and discussed their proposed mechanisms (10). Additionally, inflammatory disorders have been associated with alterations in behavior (6,11). As a result of these findings, inflammation in general and its individual components (such as inflammatory cytokines), associated genes and their polymorphisms, as well as the effect of environmental interactions, have become a point of focus for future research.

Sickness behavior, first reported by Hart (12), was characterized by hyperthermia, lethargy, sleep and appetite disturbances, and reduced grooming, which arose as a consequence of an infectious stimulus. Many of these effects were later attributed to IL-1, one of a variety of pro-inflammatory cytokines that is released during the course of infection (10). It was reported in the same experiment that central administration of an antagonist effectively inhibited the above-mentioned behavioral effects in an animal in which IL-1β was injected intraperitoneally; however, hyperthermia and reduction in food-motivated behavior were not affected (13). Hart noted sickness behavior as an evolutionary strategy to fight disease-causing organisms. Yet the observed link between mood and inflammatory alterations led to the hypothesis that a bidirectional association between cytokines and behavioral alterations exists, and the prospects were promising enough to further elucidate the pathophysiology of depressive illness.

Episodes of depression have been characterized by an increase in levels of various markers of inflammation, centrally and peripherally (14). In addition, cellular components of the immune system have demonstrated increased activity in certain classes of cells and decreases in others (15-17). Natural killer cells have been found to be reduced with augmented IL-6 release during depressive episodes (18,19). Serum levels of IL-6 and tumor necrosis factor (TNF) have been reported to be higher in depressed subjects when compared with non-depressed subjects (20). Furthermore, it has been stated that the three pro-inflammatory cytokines, IL-6, TNF and IL-1β are implicated in the pathophysiology of depressive illness (21). IL-6 has been proposed to be central in the systemic consequences of psychological stress, mediating with stress through the hypothalamic-pituitary-adrenal (HPA) axis and catecholamines leading to insulin resistance, coagulation abnormalities and endothelial dysfunction (22-24). Similarly, depression has been associated with systemic diseases involving induction of a pro-inflammatory state or upregulation of inflammatory markers. For example, levels of IL-6 have been found to increase with age (25) and be associated with cognitive wellbeing (26). In addition, depression caused an increase in fatty lesions in arteries in a mouse model, providing a potential link between psychological stress and vascular diseases (27). Chronic unpredictable stress was noted to induce a decrease in locomotor activity (depressive-like behavior), as well as favor atherosclerosis through activating various markers of inflammation, including C-reactive proteins, IL-6 and elevated concentrations of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 in the plaques and plasma of apolipoprotein knockout mice (28). Levels of positive acute phase proteins were found to be increased while negative acute phase proteins were decreased during an episode of depression, implying that depression initiates an inflammatory response in the body (29). Social stress in humans has been found to trigger an increase in the circulating levels of IL-6, eventually resulting in activation of the HPA axis and its metabolic consequences, such as diabetes mellitus and coronary heart disease (30). IL-6 was observed to be increased in the plasma and cerebrospinal fluid (CSF) of patients with post-traumatic stress disorder (31). Inflammatory changes have also consistently been reported with exposure to short durations of stress. Acute stress has been associated with an increase in the levels of IL-1β in rats (32). In addition, acutely depressed and previously unmedicated patients were found to have higher concentrations of pro-inflammatory cytokine, IL-1β in the CSF (33).

A DNA microarray analysis of the aging brain demonstrated a gene expression profile suggestive of a marked inflammatory response, oxidative stress and reduced neural plasticity and neurotrophic support (34). In this analysis half of those genes upregulated with age were found to be associated with inflammatory mediators.

HPA axis hyperactivity is the hallmark of major depression and accounts for the alterations in the immune system. A study, involving 16 females suffering major depression and 16 control subjects, found that the basal concentration of cortisol was significantly higher in depressed subjects than control subjects (35). Thus, central and peripheral inflammatory parameters have been documented to be associated with mood alterations.

3. Inflammatory cytokine concentration in depression

Cytokines are known to cause changes in the central nervous system when injected peripherally, as well as when secreted internally in response to various conditions, such as an endotoxin challenge or in a model of stress. Previous studies have investigated the concentration of pro- and anti-inflammatory cytokines in various models of depression. Pro-inflammatory cytokine, IL-1β has been found to be increased in depressed elderly subjects (age, >60 years), directly proportional to the severity of illness (36). In another study, IL-1β levels were found to be higher in women with symptoms of depression when compared with those who did not have any such symptoms 1 month post-partum (37). These statistics are, however, refuted by Ovaskainen *et al* (38) who observed that the concentration of IL-1β was not increased during an episode of depression. They observed an increase in the level of IL-1 receptor antagonists (IL-1 RA). Reduced levels of zinc during an episode of depression has been proposed to originate from increased levels of

IL-1, which results in sequestration of metallothionen, the zinc-binding protein found in the liver (39). An age-associated increase in IL-1β concentration and signaling was also accompanied by a similar decrease in concentration and signaling of anti-inflammatory cytokine, IL-4 (40). A recent study has reported that overexpressed inflammatory parameters are associated with suicidal ideation (41).

Conversely, anti-inflammatory cytokines modulate the initiation of depressive-like behavior in experimental animals. IL-10 knockout mice showed decreased latency to immobility in a forced swim test where administration of IL-10 was able to reverse behavior of helplessness (42). IL-10 receptor 1 is located on rat microglia, and responds to inflammatory stimuli, such as lipopolysaccharide (LPS) injection (43). It inhibits pro-inflammatory cytokine production by glial cells stimulated by LPS in a dose-dependent manner (44).

4. Data regarding the role of IL-1β in the pathophysiology of depression

Aging has a significant effect on brain function. Comparisons between two human brain tissue samples showed that microglia in the aged brain (68 years-old) were markedly different from those in the young brain (34 years-old). Changes occurred in the aged brain were dystrophic and characterized by loss of fine cytoplasmic processes, appearance of swellings, and twisted and shortened processes and pyknotic nuclei. The changes are described as senescence of microglia that may account for cognitive dysfunction in the ageing brain (45). Serum concentration of IL-1β was found to be increased with age. Prolonged depressive-like behavior has been documented in aged rats exposed to *Bacillus Calmette-Guérin* (42,46). As depression occurring in the later stages of life may present a different pathophysiological picture than that which occurs in younger age groups (47), an insight into the factors affecting IL-1β may lead to novel strategies for establishing a treatment plan.

5. Effects of IL-1β on neurogenesis

Neurogenesis is the birth of neurons in the dentate gyrus of the adult brain, which continues throughout life. An important aspect of neuroplastic changes during depression is the decrease in neurogenesis along with a reduction in the size of the hippocampus (48). A study investigating antineurogenic and anhedonic effects of stress found that many of these actions require IL-1β as the mediator and were not observed in the presence of an IL-1β antagonist (49). This study observed the following: i) A decrease in hippocampal cell proliferation under the influence of IL-1β that was abated by its antagonist; ii) blockade of the acute stress-induced decrease in neurogenesis, as well as antineurogenic and anhedonic effects of chronic unpredictable stress by the application of a potent antagonist of said cytokine; and iii) a significant decrease in cerebral levels of interferon (IFN)-γ and TNF-α in LPS-treated animals that were also injected with IL-1 RA.

6. Role of IL-1β in serotonergic metabolism

Serotonin is the most important neurotransmitter implicated in the pathophysiology of depression. The antidepressants, selective serotonin re-uptake inhibitors (SSRIs) have been developed in order to ensure the abundance of serotonin in synapses, based on the particularly dynamic association between serotonin availability and serotonin transporters, and receptor function and depression (50). In 1995, Ramamoorthy *et al* (51) found that IL-1β was a potent stimulant of the serotonin transporter in choriocarcinomatous cells and implied that experiments on nervous tissue reveal interesting data regarding its potential involvement in mood disorders. In an *in vivo* experiment, where LPS induced sickness behavior in mice, it also led to an increase in the extracellular concentration of 5-hydroxytryptamine and its metabolite, 5-hydroxyindoleacetic acid in the rat hippocampus. This effect was mimicked by intracerebral administration of IL-1β and was effectively attenuated by pre-treatment with IL-1RA (52). Recombinant human IL-1β, administered directly into the rat hippocampus, induced sickness behavior, caused an increase in serotonergic transmission, activated the HPA axis and raised the body temperature (53). Similar increases in concentration of serotonin and catecholamines have been observed in other brain regions, namely the anterior hypothalamus of animals exposed to IL-1β (54). IL-1β and TNF-α have also been observed to acutely activate the serotonin transporter, SERT via p38 mitogen-activated protein kinase (MAPK), thereby increasing the uptake of serotonin, which was effectively inhibited by SB203580, the specific inhibitor of p38 MAPK (55). Thus, the metabolism of serotonin remains under the influence of inflammatory mediators.

7. Receptors regulating IL-1β and their association with depression

IL-1 β, a key cytokine involved in depression in the elderly, is regulated by a purinergic ATP-gated cation channel of the P2X family, the P2X7 receptor (56). It has repeatedly been proven to be central in post-translational modification of IL-1β in microglial cells upon endotoxin challenge (56). Transgenic P2X7 gene knockout mice fail to produce IL-1 when injected with LPS (57,58), which also implicates its role in the eventual microglial activation and subsequent impact on behavior. Furthermore, certain single nucleotide polymorphisms that alter the function of P2X7 receptors have been found to be associated with depression in humans (59). P2X7 receptor blockade has been observed to exert an antidepressant-like effect in various models of sickness behavior (60), and a P2X7 knockout mouse model demonstrated an antidepressant-like profile in behavior tests (61). Furthermore, the results of a previous study stated that IL-1β converting enzyme was indispensible for the depressive-like effects following intracerebral administration of LPS (62). These receptors provide more insight into the proposed association between inflammation and depression.

8. Antidepressant therapy and variations in inflammatory cytokine concentration

Depressive symptoms have been frequently reported in patients undergoing chemotherapy, which often leads to treatment failure (63). Increased levels of pro-inflammatory cytokines have been implicated in the depressive, as well as

cachectic symptoms undergoing such treatment (64). Tricyclic antidepressants have been found to inhibit the release of pro-inflammatory cytokines IL-6, IL-1β and TNF-α in immune cells exposed to LPS (65). In another setting, a pretreatment with SSRI, paroxetine successfully prevented the onset of depressive symptoms in a significant number of patients undergoing high-dose IFN-α therapy for malignant melanoma as compared to those who were not pre-treated with the same antidepressant (66). IL-6 levels, found to be higher in depressed subjects, were successfully treated with antidepressant therapy, but coincided with the response to antidepressant therapy with regard to depressive symptoms. The non-responders to antidepressant therapy maintained the raised values of IL-6 (67). This evidence supports the hypothesis that the pathophysiology of depression has certain inflammatory components that should be taken into account. In addition, the idea that the efficacy of antidepressant treatment is partly influenced by inflammatory mediators requires further investigation. It should, however, be noted that inflammation does not happen in isolation. The genetic and epigenetic factors are also involved. Thus, these concepts remain complementary to the general understanding of depression pathophysiology.

9. Depressive-like behavior induced by chemotherapy

Anti-viral IFN-α therapy may induce depressive-like behavior in subjects. The incidence of these symptoms varies from 0 to 70% in different populations (68). Depression with varying severity and associated symptoms, such as insomnia, irritability, cognitive decline and suicidal ideation occur with IFN therapy (69-71). While certain studies have hypothesized that incidence of major depression remains the same in patients treated with IFN as compared to the general population (72), others indicate that major depression may be induced by the treatment, even in subjects without a previous history of major depression (73). This may lead to a cessation of treatment or reduction of dosage, which affects the course of recovery.

10. Cytokine-associated depressive symptoms and neurodegeneration

Numerous studies focusing on the association between depression and degenerative diseases have used pro-inflammatory cytokine levels as the basic criterion (74,75). These models have been somewhat conclusive in providing the evidence that depression precedes degenerative diseases. In addition, the studies indicate that degeneration is nothing but the consequence of neuroinflammation (70-78). In one such instance, a non-toxic dose of bacterial endotoxin that resulted in increased secretion of cytokines, as well as activation of microglia, also resulted in extended loss of dopaminergic neurons to a subsequent suboptimal inflammatory stimulus (6-hydroxydopamine). This effect, however, was effectively blocked by the administration of an antagonist of IL-1 receptors (74).

11. Neuroinflammation and its implication in the pathophysiology of depression

The evidence of depressive symptoms following cerebrovascular lesions is varied. The prevalence of major depression ranges from 18 to 61% in stroke patients, which is a 3-fold increase when compared with the general population (75). This association has been reported frequently (76,77). Patients with pre-existing depression have been identified to exhibit greater neurological impairment following a stroke, and stroke sufferers demonstrated a higher prevalence of depression at 6 months and 1 year following a stroke when compared with the general population (78).

Patients with depression are stated to have frequent hyperintensities of white matter observed on magnetic resonance imaging scans. The presence of white matter hyperintensities is associated with a prolonged course of depressive illness. The presence of these hyperintensities is also associated with weakened effect of antidepressant treatment, as well as long-term disability and neuro-cognitive decline (79). While the inflammatory response around the site of stroke is a well-known clinical observation (80) an animal model of focal ischemia demonstrated that inflammation extends far beyond the original site of ischemic injury, predominantly mediated by microglia (81). This is exactly the same manner by which stress has been attributed to the cause of neuroinflammation in various animal models (82), which has led to formulation of a neuroinflammatory hypothesis of depressive illness (83).

12. Conclusion

Depression is undoubtedly a multidimensional disorder. In addition to stress as the most important cause of depression, other disease processes are increasingly being implicated in the depression pathophysiology. Age-associated accumulation of inflammatory insults may support the role of disease processes in behavioral alterations. IL-1β exerts a multilayered effect on determinants of behavior, and understanding the role of IL-1β in the pathophysiology of depression may facilitate the elucidation of its effect on alterations in amine metabolism, neurogenesis and neuroinflammation. In addition, genetic and epigenetic phenomena may be taken into account when establishing a comprehensive treatment approach.

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