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Review Article

Cytokines as Depression Underpinning

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Abstract:

Depression is a common illness worldwide, with an estimated 3.8% of the population affected; by 2030 it will be the leading cause of disease burden globally. Depression has been associated with more prolonged hospital stays, increased physical distress, poorer treatment compliance, lower quality of life, and increased desire for hastened death. A meta-analysis revealed that minor or major depression increases the rate of mortality by up to 39%; in addition, patients displaying even a few depressive symptoms may be at a 25% increased risk of mortality.

The monoamine hypothesis is the most extensively studied etiologic theory of depression and virtually all available antidepressants act, at least in part, by increasing monoaminergic transmission.

Keywords:

Monoamine; cytokines

Introduction:

With it all less than one-third of patients achieve remission with their first course of antidepressant pharmacotherapy and even after four systematically applied treatments, about one third of patients fail to achieve remission. Because the most existing antidepressants primarily target monoamine systems, there are grounds to support the exploration of alternative therapeutic targets. These include neuropeptides, amino acid neurotransmitters (e.g., glutamate), and neurotrophic and inflammatory factors (1). The latter claimed attention that dates back Nobel laureate Wagner-Jauregg who observed psychiatric symptoms due to malaria inoculation. Since his research the role of inflammation in the pathophysiology of depression has been increasingly recognized and is now described as the inflammatory or cytokine hypothesis of depression. Initially, cytokines were discovered and described as signaling protein molecules that are produced by immunocompetent cells to stimulate or inhibit the function of other immune cells. A presentation of mood disorders is accompanied by immune dysregulation with both immune suppression and immune activation being detected. With it all the production of proinflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, the soluble IL-6 receptor, and the IL-1 receptor antagonist increases.

The cytokine hypothesis has emerged as a predominant explanation for its underlying pathophysiology (2). Inflammation is usually a reflection of cell damage caused by infection, physical injury or the response of tissues to an antibody challenge. However, in recent years it has become apparent that psychological stress can also initiate the inflammatory response, thereby linking inflammation to both physical and mental ill health (3).

Immune activation influences brain functioning and the CNS modulates the immune response. Moreover, immune activation can lead to profound alterations in psychological status (e.g. mood and behavior). The most important link whereby the immune system influences the brain is established by the interactive cytokine network. Now it is clear that these molecules have pleiotropic functions that are far wider than solely participating the immune regulation. They reciprocally affect the expression of each other, with it all pro-inflammatory activity inherently trigger a compensatory anti-inflammatory reflex system, with the balance between the two determining impacts (2).

In addition to monoamine, norepinephrine (NE), neuroendocrine and growth factor variations it has been suggested that depressive symptoms may stem from activation of the inflammatory immune system, especially that of pro-inflammatory cytokines. Cytokines are important for development and normal brain function, and have the ability to influence neurocircuitry and neurotransmitter systems to promote several neurobiological changes that have been implicated in depression (4). These have included elevated circulating corticosterone levels, increased expression of corticotropin releasing hormone (CRH) and its receptors as well as changes of neurotrophins in brain areas that subserve stressor appraisal processes as well as depression (prefrontal cortex, hippocampus, amygdala, paraventricular nucleus of the hypothalamus, and nucleus accumbens) (5, 6). Biological stressors, such as infection, tumor cell burden, treatment-induced tissue destruction lead to damage-associated molecular patterns (DAMPs; also known as danger

associated molecular patterns) on damaged tissue, which bind to pattern recognition receptors on leukocytes, particularly macrophages, causing the expression of the transcription factor nuclear factor-κ-β (NFκβ) and the production of numerous pro-inflammatory cytokines, including IL-1, IFN-α, IL-6 and TNF-α. The combined impact of neural and neuroendocrine factors is usually named inflammatory activation; it contributes to depression (7). There is a strong interaction between the peripheral immune system and the central nervous system (CNS).

Psychological stress may also precipitate inflammation, activating the hypothalamic–pituitary–adrenal (HPA) axis, increasing peripheral sympathetic tone, stimulating pro-inflammatory cytokine release from immune cells and NFκβ expression. The social stressors also affected pro-inflammatory cytokines both peripherally and within stress-sensitive brain regions, supporting the view that activation of these inflammatory markers may contribute to the pathogenesis of stress-related disorders. Recent interest has been paid to the mechanisms by which psychological stress can translate into immune system activation and release of proinflammatory cytokines. On a cellular level, the immune system can detect danger signals in the absence of a pathogen through the release of DAMPs that are thought to be released during stress, and one key mechanism by which they may elicit an immune response is through the NLRP3 inflammasome, a multiprotein complex that is involved in the processing of IL-1β. DAMPs are known to stimulate the inflammasome in the presence of *lipopolysaccharides* to activate caspase-1, which cleaves the immature precursor of interleukin IL-1β and IL-18 into their mature releasable forms. This increase in IL-1β release can then induce the production of other inflammatory cytokines that are released during stress. The ATP purinergic type 2X7 receptor, a primary activator of the NLRP3 inflammasome, may be involved in inflammatory processes in cardiovascular disease, obesity, neurologic disorders, pain, and pulmonary fibrosis.

An attention is paid to the role of intestinal microorganisms in influencing the immune responses of an organism. The dense and complex community of gastrointestinal microbiota of an individual may be influenced by genetic and environmental factors. The intestinal lining also harbors immune cells, including dendritic cells and T cells, and serves as a source of circulating cytokines. Increased exposure to toxins, food allergens, and stress may promote a loss of protective microorganisms and increase inflammation in the gut, thus contributing to behavioral symptoms associated with increased inflammatory cytokines. Furthermore, manipulation of the gut microbiota of mice altered behavior and hippocampal BDNF content independent of changes in circulating inflammatory cytokines and neuroendocrine hormones, indicating a potentially direct gut to brain connection that can influence behavior.

The inflammatory hypothesis of depression postulated that elevated circulating levels of pro-inflammatory cytokines might promote the evolution and maintenance of depressive symptoms. Then other immune cells, including lymphocytes and neutrophils activate. Meta-analyses have, in fact, indicated that in the absence of infectious pathogens, peripheral concentrations of pro-inflammatory cytokines, especially that of IL-6, TNF-α and C-reactive protein (CRP), were higher in non-medicated individuals with depression than in non-depressed individuals; further, the associations with somatic symptoms of depression were higher than psychological ones (8).

A stress-activated production of these cytokines leads to metabolic and regulatory alterations that potentially contribute to the development of depression (9).

Proinflammatory cytokines are key mediators of a constellation of depressive-like signs and symptoms referred to as sickness behavior (alternative designation – "cytokine-induced depression"). This potentially adaptive response is viewed as a motivational state that promotes recovery and includes anhedonia, anorexia, cognitive impairment, hyperalgesia, fever, sleepiness, withdrawal from social activities and fatigue. The listed behavioral reactions to cytokines can benefit an organism by promoting conservation of energy and allocation of resources to combat infection or recovery from injury, along with behaviors that may elicit care-giving from others (10). However, under conditions of chronic exposure to elevated inflammatory cytokines, persistent alterations in neurotransmitter function and behavior can lead to the development neuropsychiatric dysfunction, and especially depression. For instance, patients with increased inflammatory cytokines due to a variety of medical illnesses have increased rates of depression compared to the general population. The related symptoms may have a profound effect on patients' quality of life.

The responses characteristic of sickness behavior can be elicited by systemic action of proinflammatory cytokines including IL-1, TNF-α, IFN-α, and IL-2, administered subcutaneously, intravenously, or intraperitoneally.

The feelings of anhedonia also results from reducing striatal dopamine (DA) release with

DA-2 receptor expression decreasing as IFN-α impact; the mechanisms behind this and any possible pharmacological strategies remain to be elucidated.

IFN-α also causes decreased conversion of phenylalanine to tyrosine and, further, reduced downstream formation of DA in the brain that potentially evolves depressive symptoms.

In some cases, cytokine antagonists can prevent some components of sickness behavior. For example, the LPS-induced inflammatory cascade leading to pain and other symptoms can be attenuated by antagonists of the IL-1 and TNF-α receptors.

In periphery cytokines are produced and released primarily by immune cells or adipose tissue. A potential association between obesity, inflammatory cytokines, and behavioral alterations has been postulated. Adiposity has been suggested as a link between depression, increased inflammatory markers, and increased risk of coronary heart disease. The cytokines from periphery can access the CNS to initiate local immune activation by several mechanisms, including 1) passage through leaky regions in the blood-brain-barrier at circumventricular organs; 2) active uptake mechanisms of cytokines across the blood-brain-barrier; 3) local actions at peripheral vagal nerve afferents that relay cytokine signals to relevant brain regions, including the nucleus of the solitary tract and hypothalamus (the so-called 'neural route'); 4) activation of endothelial cells, microglia and perivascular macrophages in the cerebral vasculature to produce local inflammatory mediators such as cytokines, chemokines, PGE2, and nitric oxide (NO) and 5) activated immune cells such as monocytes/macrophages and T-cells can be recruited from the periphery to the brain parenchyma, and these cells can in turn produce cytokines in the brain (11). Production of monocyte chemotactic protein-1 (MCP-1) recruits peripheral immune cells into the brain that produce even more cytokines and inflammatory mediators.

Peripheral cytokine signals are amplified in the CNS by local inflammatory networks, including inflammatory signal transduction pathways, cytokine production, and PGE2 release. In the brain, endothelial cells and perivascular macrophages respond to circulating cytokines to induce expression of COX-2 and release of PGE2. Cytokines in the brain are produced primarily by microglia, but can also be produced by astrocytes, oligodendrocytes and to some extent by neurons. Within

the CNS, proinflammatory cytokines have been shown to affect the brain and behavior through different ways. Following an acute inflammatory stimulus, increased CNS cytokines can confer protection to the brain (12), yet under conditions of chronic immune activation, microglia may be overactivated becoming a source of inflammatory mediators that influence brain neurotransmitter systems and neuronal integrity. An innate immune activation during chronic medical illnesses, as characterized by elevations in inflammatory cytokines, may contribute to the high rates of depression and other neuropsychiatric (e.g. cognitive or psychomotor) symptoms observed in medically ill populations (13). These cytokines are known to affect monoaminergic and glutamatergic systems. They play crucial roles in the stress response system and in the regulation of adult neurogenesis that focused at hippocampus. Insofar as the influence of inflammatory activity on this neurogenesis is considered largely inhibitory, the cytokines proved to be a key contributing mechanism in the pathophysiology and treatment of depression. With it all a decrease in neurogenesis can contribute to the reduction in both gray matter and whole hippocampal volume seen in depressive disorders. Such reduction seems to be parallel to pro-inflammatory cytokine involvement in these disorders. Activated microglia employs IL-6 as a key antineurogenic signal, which can interact directly with neural progenitor cells via IL-6 receptors (16).

Conversely, selective serotonin (5-HT) reuptake inhibitors (SSRIs) have been shown to upregulate the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus thereby exerting the protective impact. BDNF promotes the proliferation and survival of neural progenitor cells, it is considered to be crucial for neurogenesis. Further, SSRIs alleviate cytokine-induced depression, its affective symptoms appear to be most responsive, while fatigue and neurovegetative symptoms are less responsive (15). The differential responsiveness of symptom dimensions coupled with the association of specific gene loci with behavioral symptoms suggests that distinct mechanisms may mediate the various aspects of cytokine-induced depression, and understanding these mechanisms may improve treatment strategies.

Inflammatory cytokines are associated with increased oxidative stress and generation of reactive oxygen and reactive nitrogen species (ROS and RNS). Increased ROS and RNS contribute to oxidation of tetrahydrobiopterin, a cofactor required for the synthesis of monoamines. Furthermore, evidence exists indicating that TNF-α, IL-1, other inflammatory cytokines increase the activity and expression of 5-HT and NE reuptake transporters, through activation of the p38 mitogen activated protein kinase (MAPK). This effectively lowers synaptic concentrations of 5-HT and NE, and can lead to depressive behavior which is referred to as specific subtype of inflammatory cytokine-associated depression.

Cytokine interference with Tropomyosin receptor kinase B receptor signaling adversely influences neurogenesis and neuroplasticity; they also reduce levels of neural growth factors, e.g. BDNF, this decline is implicated in the pathogenesis of depression. Evidences of other growth factors' contribution are accumulated. A basic fibroblast growth factor, nerve growth factor, vascular endothelial growth factor, and erythropoietin are worthy to mention.

Increased circulating inflammatory cytokines and CRP are risk factors for the development of illnesses associated with inflammation, such as heart disease and type 2 diabetes, and individuals with major depression have a several fold greater risk of comorbidity and mortality (14). Numerous immune mechanisms are thought to underlie the increased risk of mortality of depressed patients compared with non-depressed patients (19). Depression in otherwise healthy adults reduces the number of circulating natural killer cells, which normally have a tumor surveillance role. Furthermore, patients who are resistant to antidepressant treatment demonstrate higher concentrations of circulating cytokines and acute-phase proteins than patients who respond to antidepressant treatment.

Beyond variations of the traditional pro-inflammatory cytokines IL-6, IL-1β, and TNF-α, depression has been associated with elevations of circulating IL-18, which is involved in cell-mediated immunity, and macrophage migration inhibitory factor, that is considered to be a pro-inflammatory cytokine with neurogenic actions.

Additional support for the inflammatory hypothesis of depression has come from reports showing that the prevalence of depressive symptoms was relatively elevated in non-medicated patients with chronic inflammatory diseases (e.g., chronic hepatitis C).

Meta-analytic result supports the involvement of IL-6 and TNF-α in major depression strengthens the evidence that depression is accompanied by activation of the inflammatory response system (17). Higher levels of TNF-α, IL-6 and IL-8 are associated with more severe depression.

They are potent activators of the autoregulatory hypothalamic-pituitary-adrenal (HPA) axis break central tryptophan and monoamine metabolism. Both these disorders are involved in depression's underpinning; tryptophan is additionally the primary amino-acid precursor of 5-HT.

A study of patients with advanced metastatic cancer showed that both plasma IL-6 concentrations and HPA axis dysfunction were markedly higher in patients with clinical depression. Furthermore, the cytokines engage in neuronal excitotoxicity, increase the secretion of CRH. The latter itself can induce behavioral changes observed in depression.

The circulating levels of pro-inflammatory cytokines are not increased in all depressed patients; for example, these levels remain normal in vascular, post-partum and peri-menopausal depression, hypothyroidism, depression secondary to cocaine withdrawal. The increased cytokine production may be related to certain subtypes of depressive disorders and/or the state of the patient. That is, not all subjects exhibiting increased inflammatory cytokines develop depression, and there are numerous vulnerability and resilience factors for cytokine-induced depression. Nonetheless, it is biologically plausible that inflammatory cytokines serve as mediators of both environmental and genetic factors that may trigger the development of depressive disorders. On the other hand, the patients with high serum levels of proinflammatory cytokines may be at significant risk factor for developing anxiety and depression, cytokine levels may be used as a marker for the manifestation of such psychological disorders in these patients. In patients where increased cytokine levels are apparent, antidepressant treatment may normalize this increase.

Monoamine neurotransmitters have long been known as mood regulators; such compounds as DA and NE were referred to this group but the most attention has garnered 5-HT, especially with the wide range of selective serotonin reuptake inhibitors (SSRIs) that have emerged as antidepressants. Cytokines and their signaling pathways (e.g., p38 MAPK) are reported to exhibit significant impacts on metabolism of multiple neurotransmitters such as 5-HT, DA, and glutamate; thus, influencing their synthesis, release, and reuptake. As mentioned above, TNF-α, IL-1 and other cytokines increase the activity and expression of 5-HT and NE reuptake transporters, through activation of the p38 MAPK. This effectively lowers synaptic concentrations of 5-HT and NE

Tryptophan (Trp) is the chemical precursor to 5-HT; therefore its destruction results in reduced 5-HT levels. It is well established that Trp levels are decreased relative to monoamine levels in the brains of depressed patients. There is body of evidence that not only Trp and consequent 5-HT depletion, but also induction of indoleamine 2,3-dioxygenase (IDO) and the detrimental neurotoxic effects of tryptophan catabolites (TRYCATs), including kynurenine (Kyn) and quinolinic acid (QUIN), play a role in the pathophysiology of depression. When the depressive symptoms develop by inducing inflammatory responses and acting on the immune signaling to the brain, the Kyn pathway are allocated a crucial position. In this pathway, Trp is converted to Kyn and is degraded leading to the production of nicotinamide adenine dinucleotide (NAD+) as the end product. The first step of the process is catalyzed by two heme-dependent enzymes: tryptophan 2,3-dioxygenase (TDO) and IDO. IDO-induced decreases in 5-HT synthesis in the brain are thought to mediate cytokine-induced depressive symptoms. TDO seems to be an important link between the Kyn pathway and inflammation, because of its activation by pro-inflammatory cytokines, particularly TNF-α. The Kyn pathway is involved in glutamatergic neurotransmission.

Cytokines can decrease synthesis of 5-HT via activating IDO which breaks the precursor of 5-HT (i.e., Trp) to Kyn instead of metabolizing to 5-HT; thus, leading to 5-HT depletion. The process of this depletion has been long associated with major depression. Moreover, cytokines can modulate 5-HT signaling via elevating the expression and function of monoamine transporters. These transporters are known to re-uptake 5-HT.

IL-6 directly controls the levels of 5-HT transporter (SERT) and therefore influences 5-HT reuptake. Indeed, the researchers concluded that IL-6-induced modulation of serotonergic neurotransmission through the signal transducer and activator of transcription 3 (STAT3) signaling pathway contributes to the role of IL-6 in depression. The activity of SERT forms serotonergic transmission which is implicated in depressive behavioral changes and pathophysiology of the disease. By intensifying DAergic and 5-HTergic turnover in hippocampus and frontal cortex, IL-6 influences neurotransmission of catecholamines. It seems that NE is not affected by IL-6; however, noradrenaline itself can induce expression of IL-6 in glial cells. IL-6 together with other pro-inflammatory cytokines can activate Kyn which is involved in glutamatergic neurotransmission.

In the brain, IDO activity is significantly increased at 24 hr and peaks at 48 hr in response to LPS administration, corresponding to the expression of some depressive-like behaviors. The IDO activation attains both during low-grade chronic inflammation and with administration inflammatory cytokine, e.g. IFN-γ, IL-6, TNF-α; both cytokine and LPS partake in the development of depression. Such activation reduces plasma Trp, promotes the release of neurotoxic metabolites and causes oxidative stress, culminating in depression. The occurrence of depressive manifestation during IFNα-based immunotherapy is strongly associated with IDO activation and lowered levels of Trp. Induction of IDO also causes the formation of TRYCAT, like Kyn and QUIN, they activate oxidative pathways; cause mitochondrial dysfunctions; have neuroexcitatory and neurotoxic effects that may lead to neurodegeneration. Increased QUIN levels correlate with increased depressive symptoms and might contribute to the apoptosis of astrocytes and certain neurons, resulting in decreased synthesis of neurotrophic factors. With less these factors, the astrocyte-microglia-neuronal network is weaker and thus is more likely to be affected by environmental factors such as stress. In addition, increased levels of QUIN could play a role in impairment of the glial-neuronal network, which could be associated with the recurrent and chronic nature of depression (18). In severe depression, levels of QUIN have been observed to be raised in several regions throughout the anterior cingulate cortex. Neurotoxicity and degeneration, particularly of the hippocampus, have been implicated in the development of depressive symptoms. The TRYCAT pathway is also activated following induction of TDO by glucocorticoids, which are elevated in depression. Women show greater IDO activation and TRYCAT production following immune challenge than men.

QUIN is a selective potent N-methyl-D-aspartate (NMDA) receptor agonist and is able to disturb the glutamatergic transmission; this substance induces lipid peroxidation in neurons by excitotoxicity, whilst Kyn has been demonstrated to be anxiogenic (19, 20). Inflammatory cytokines can affect the glutamate (Glu) system by activation of IDO. QUIN can directly activate the n-methyl-d-aspartate receptor (NMDAR), increase Glu release, and inhibit Glu uptake by astrocytes via the excitatory amino acid transporter (EAAT), thus allowing increased access of Glu to extrasynaptic NMDARs and contributing to both excitotoxicity and glutamate dysfunction in depression. QUIN serves as a potential candidate for a link between immune and neurotransmitter changes in depression (21). The fact that NMDA receptor antagonists possess antidepressant properties suggests that increased levels of microglial QUIN in patients with depression may overactivate NMDA receptors. The efficacy of NMDA receptor antagonist drugs, such as ketamine, in rapid antidepressant responses has prompted much attention to the role of glutamate in the pathophysiology of depression. Evidence obtained for an upregulation of QUIN in brain regions known to be responsive to infusion of NMDA antagonists.

In an alternative pathway to the NAD+ production, QUIN can be converted into kynurenic acid (KYNA), which is demonstrated to be neuroprotective, counteracting the effects of QUIN. KYNA can antagonize Glu receptors and decrease Glu release leading to decreased Glu neurotransmission. So, there is a balance between neurodegenerative and neuroprotective effects in the Kyn pathway, expressed by the QUIN/KYNA ratio, which is strictly related to immune activation. This process involves the microglia and the astrocytes cells, which are the primary site for Trp catabolism in CNS. KYNA is mainly produced by astrocytes, while microglia cells are responsible for QUIN production. QUIN/KYNA, as well as the most used (Kyn/Trp ratio), could be used as a measure of the pathway activity (22).

Clinical depression is accompanied by lowered levels of neuroprotective TRYCATs or increased levels or neurotoxic TRYCATs, and lowered plasma Trp, which is associated with indices of immune activation and glucocorticoid hypersecretion. Lowered Trp and increased TRYCATs induce T cell unresponsiveness and therefore may exert a negative feedback on the primary inflammatory response in depression. It is concluded that activation of the TRYCAT pathway by IDO and TDO may be associated with the development of depressive symptoms through Trp depletion and the detrimental effects of TRYCATs. Therefore, the TRYCAT pathway should be a new drug target in depression. Direct inhibitors of IDO are less likely to be useful drugs than agents, such as Kyn hydroxylase inhibitors; drugs which block the primary immune response; compounds that increase the protective effects of KYNA; and specific antioxidants that target IDO activation, the immune and oxidative pathways, and 5-HT as well.

Evidence suggests that inflammation significantly shifts Trp metabolism to Kyn production, carrying out several biological functions. The Kyn pathway is strictly related to the immune response. An increased Kyn pathway activity may therefore be associated with various clinical conditions linked to immune activation, such as depression and cancer. A long-lasting and/or uncontrolled immune activation, as observed in multiple chronic diseases, has been associated with clinically relevant behavioral symptoms, such as depression, and the Kyn pathway appears

to be strictly implicated in this association (13). Abnormalities of the Kyn pathway may be implicated in the pathophysiology of depression. Hence, this pathway could represent one of the links between depression and other clinical conditions.

In terms of immunologic mechanisms, an inflammatory pathway that may be involved in inflammatory cytokine-associated depression is the metabolism of polyunsaturated fatty acids involved in prostaglandin and resolvin synthesis. Omega-6 and omega-3 fatty acids have opposing effects on inflammatory signaling. The omega-6 fatty acid, arachidonic acid, is metabolized to form PGE2, while omega-3 fatty acids have anti-inflammatory properties and are metabolized to form 'resolvins' and 'protectins'. These can influence cytokine synthesis and resolve inflammation. As one example, docosahexaenoic acid (DHA) can be converted to 'neuroprotectin' which has potent inflammatory resolving activities in the brain (23). Resolvin receptors are newly being discovered and potentially include formyl peptide receptor 2 (FPR2). Conversely, arachidonic acid is both an intracellular second messenger and is also a substrate for the synthesis of prostacyclins and thromboxanes, which can stimulate inflammatory activity. Interestingly, omega-3 fatty acids are reduced in major depression and also predict vulnerability to cytokine-induced depression.

The inflammatory hypothesis of depression marks a significant shift away from monoamine-based approaches and is a major step towards developing novel treatments that directly target causal factors of depression (2).

If depression (or most likely specific depressive subtypes) is driven by inflammation, then traditional antidepressants would be expected to improve mood through cytokine-dependent mechanisms, and anti-inflammatory treatments would be effective in attenuating symptoms. However, this would only occur in those patients in whom depressive symptoms were precipitated by inflammatory factors. Indeed, the identification of specific cytokine markers that might be aligned with particular symptoms or subtypes of depression could be especially useful in the prediction of treatment efficacy.

Accumulating evidence has been published that antidepressants modulate cytokine production.

Assuming that pro-inflammatory cytokines are a causal factor of depressive disorders, they conclude that antidepressants should suppress these cytokines or hinder their action. Antidepressants are used to prevent depression in patients receiving high-dose interferon for adjuvant therapy of malignant melanoma. The rationale for this approach is that treatment with high-dose interferon is associated with a particularly high rate of depression in this patient population, and proinflammatory cytokines implicated in the biological changes that result in depression may be directly reduced by antidepressants.

Studies suggest that non-steroidal anti-inflammatory drugs (NSAIDs) given solely or as adjuncts to antidepressants are more effective than placebo in treating the symptoms of depression. Whereas NSAIDs are broad-acting agents, inhibitors targeting specific cytokine pathways such as TNF-α and IL-6 have been shown to improve the symptoms of depression in patients with rheumatic and other inflammatory conditions.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5713706/ - b38-ndt-13-2903

The most commonly used agents to block inflammatory signaling are cyclooxygenase (COX) inhibitors, which have been shown to inhibit depressive-like behaviors.

COX inhibitors have been administered as adjuvant to antidepressant therapy. The selective COX-2 inhibitor, celecoxib, improved the efficacy of the NE reuptake inhibitor, reboxetine, in depressed subjects. Addition of both celecoxib and acetylsalicylic acid (which blocks COX-1 and COX-2) augmented treatment responses to fluoxetine. Omega-3 fatty acids have increased the antidepressant efficacy of fluoxetine and citalopram, and a meta-analysis reported direct antidepressant effects when combining all sources of omega-3 fatty acids (e.g. docosahexaenoic acid, fish oils).

Nevertheless, the anti-inflammatory drugs with obligatory efficacy in limiting depressive disorders aren't still revealed. Anti-inflammatory approaches and treatment strategies that inhibit the release or activity of proinflammatory cytokines (usually in relieving from symptoms of sickness behavior) are being evaluated (24).

Some studies have also suggested that antidepressants potentially have anti-inflammatory properties, and antidepressant response has been associated with reductions in pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 (25).

Diet and the gut microbiome may influence inflammation and Trp metabolism by several ways. Reduction of the gut microbiota by antibiotics prevented the stressor-induced cytokine elevations, indicating that bacteria that live in the gut were necessary for an inflammatory stress response to develop. Given that microbiota may have immunoregulatory effects through actions on immune cells, it was suggested that probiotic bacteria (i.e., "good" bacteria that when ingested confer a benefit for the host), by their interactions with commensal gut bacteria, may also influence inflammatory responses. Probiotic supplementation with *Lactobacillus plantarum* in combination with SSRI treatment improved cognitive performance and decreased Kyn concentrations in patients with major depression (compared to SSRI treatment alone). Beneficial effects of probiotics on fatigue or depression might be due to alterations of Trp metabolism or anti-inflammatory effects.

confusion

The spotting of processes that are associated with inflammation, and their correlation to quality evidence linking those processes to increased risk of depression, will permit to substantiate the role of inflammation as one of the mediating pathways to both risk and neuroprogression in depression.

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