Viewpoint

Neuroinflammation and Depression: Kynurenine Pathway, BDNF, and the Implications for Psychedelic Therapies

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Abstract
This article discusses the relationship between depression and neuroinflammation, which is a process in which the immune system responds to injury or infection in the brain, leading to the activation of immune cells and the release of inflammatory molecules. Recent research has suggested that neuroinflammation may play a key role in the development and progression of depression. Studies have shown that neuroinflammation interacts with the three neurobiological correlates of major depressive disorder: depletion of brain serotonin, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, and alteration of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus. The article also discusses the Kynurenine pathway, which is a critical metabolic pathway responsible for the conversion of tryptophan into several biologically active metabolites, including kynurenic acid, and quinolinic acid. Alterations in the kynurenine pathway may be associated with depression. The article also discusses the impact of brain-derived neurotrophic factor (BDNF) on depression and how psychedelics may offer more sustained benefits compared to other therapies due to anti-neuroinflammatory effects.

INTRODUCTION

Depression is a mental health disorder that affects millions of people worldwide. Recent research has suggested that neuroinflammation may play a key role in the development and progression of depression [1,2,4]. Neuroinflammation is a process in which the immune system responds to injury or infection in the brain, leading to the activation of immune cells and the release of inflammatory molecules [2]. This response can be triggered by a variety of factors, including chronic stress, infection, and injury [4].

Studies have shown that neuroinflammation interacts with the three neurobiological correlates of major depressive disorder: depletion of brain serotonin, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, and alteration of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus [1]. Inflammation can impact hippocampal neurogenesis by increasing extracellular glutamate levels and glutamate neurotransmission [1]. Patients with chronic inflammation are often associated with the emergence of depression symptoms, while diagnosed depressed patients show increased levels of circulating cytokines [2].

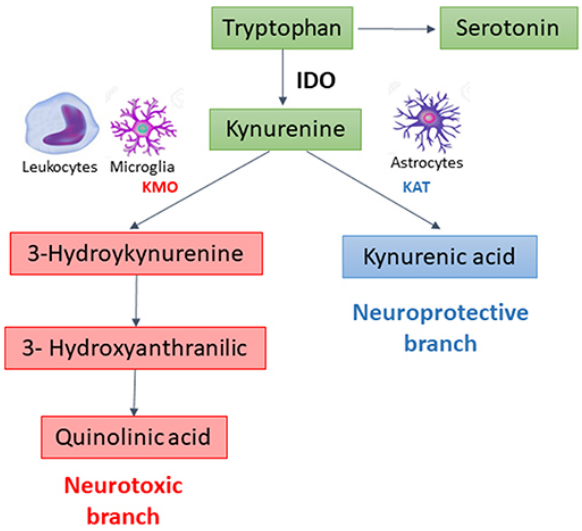
Further studies have revealed the activation of the brain immune cell microglia in depressed patients with a greater magnitude in individuals that committed suicide, indicating a crucial role for neuroinflammation in depression brain pathogenesis [2]. Animals subjected to different stress paradigms show glial cell activation and a surge in proinflammatory cytokines in various brain regions [4]. The concept of sterile inflammation observed in animal models of depression has intrigued many researchers to determine the possible triggers of central immune cell activation [4].

KYNURENINE PATHWAY

An interesting emerging area of clinical research supports interactions between the immune system and the Kynurenine pathway. Kynurenine pathway activation by pro-inflammatory cytokines results in a cascade of

metabolites as potential contributors to the pathophysiology of depression, psychosis, and cognitive deficits [5]. The Kynurenine pathway is a critical metabolic pathway responsible for the conversion of tryptophan into several biologically active metabolites, including kynurenic acid, and quinolinic acid.

Research has shown that alterations in the kynurenine pathway may be associated with depression. In particular, the imbalance between kynurenic acid and quinolinic acid can have neuroinflammatory and neurotoxic effects. Elevated levels of quinolinic acid have been linked to neuroinflammation and oxidative stress, which are associated with depressive symptoms. The initial enzymatic reaction in the Kynurenine pathway to convert tryptophan by indoleamine-2,3-dioxygenase (IDO) is activated by proinflammatory cytokines [6].



Microglia and macrophages produce quinolinic acid, which must release for enzymatic conversion to nicotinamide adenine nucleotide (NAD+) by astrocytes and neurons containing quinolinate phosphoribosyl transferase (QPRT). In physiologic conditions, quinolinic acid is catabolized into NAD+ with involvement in cellular respiration, energy production, DNA repair and transcriptional regulation [3].

In a pathogenic state, quinolinic acid accumulation can occur, stimulating NMDA receptors resulting in excitotoxic damage. Specific regions of the brain have been found to have variations in QPRT activity. Of interest, areas of lowest activity have been found within the frontal cortex, hippocampus, and the striatum. The hippocampus and striatum areas are particularly vulnerable to damage, with the combination of NMDA receptor density, paired with limited clearance of quinolinic acid, and calcium influx associated with oxidative stress.

Steiner and colleagues [7] found increased quinolinic acid concentrations in the anterior cingulate gyrus in human subjects during acute depressive episodes. Also noted increased serum IL-1, IL-6, and TNF-α in the same population compared to healthy controls. These pro-inflammatory signaling proteins have been found to activate the

In 2013, Erhardt, et al. [8] compared CSF from people who attempted suicide to healthy controls and found significant elevation in Quinolinic Acid, but not Kynurenic acid. Similar to results found by Steiner, elevated Quinolinic acid was associated with higher IL-6 levels in the CSF. Scores from the Suicide Intent Scale also correlated with Quinolinic acid levels.

New onset depressive symptoms, in previously psychiatrically healthy, with cancer or viral treatments involving Immunotherapy with cytokines has been found in multiple studies. Capuron [9] characterized the progression of cytokine therapy, beginning with sickness behavior; symptoms include anorexia, fatigue, pain, malaise, and fever. A third of the treatment participants were found to have symptoms consistent with depressive disorders, and some developed suicidal ideation.

Additional studies have found sickness disease symptoms include lethargy, depressed mood, disrupted sleep, impaired

concentration, anorexia, social isolation, and loss of interest in personal hygiene. Evidence of elevated proinflammatory cytokines, such as IL-1, IL-6, and TNFα compared to healthy controls [10] Dantzer.

In contrast to quinolinic acid, kynurenic acid is produced primarily by astrocytes, which acts as an antagonist on N-Methyl-D-aspartate (NMDA) and alpha7 nicotinic acetylcholine receptor (α7nAChR) with neuroprotective properties. Kynurenic acid shares some similarities with Ketamine and its derivatives that is already used to treat depressive symptoms via NMDA modulation.

Specifically, Ketamine has been shown to suppress pro-inflammatory cytokines and affect both pro- and anti-inflammatory cytokines in animal models [11]. Microglia are involved in the secretion of cytokines and chemokines as well as other pro-inflammatory mediators after infection or brain damage, and ketamine may regulate microglial activation through inflammatory signaling pathways [12].

Brain Derived Neurotropic Factor

Brain Derived Neurotropic Factor (BDNF) is a protein that plays an important role in neuronal survival and growth, serves as a neurotransmitter modulator, and participates in synaptic plasticity and cognitive function [13-15]. BDNF is highly regulated, and changes in its expression are associated with both normal and pathological aging, psychiatric disease, and structures important for memory processes such as the hippocampus and parahippocampal areas [16]. Studies have shown that BDNF levels are decreased in patients with depression [13, 15]. Antidepressant medication, such as the selective serotonin reuptake inhibitor Fluoxetine have been shown to increase BDNF levels [13, 17,-19]. Additionally, Quinolinic acid has been shown to decrease BDNF levels in the hippocampus and prefrontal cortex which may be mediated by quinolinic acid's effects on glutamate receptors and oxidative stress [13, 17].

Other factors known to impact BDNF include Butyrate, Lion's Mane, Omega 3, and Exercise are all known to impact Brain Derived Neurotropic Factor (BDNF) levels in the brain. Butyrate is a short-chain fatty acid produced by gut bacteria during the fermentation of dietary fiber. Studies have shown that butyrate can increase BDNF levels in the hippocampus and prefrontal cortex, possibly through its effects on histone acetylation and gene expression [20]. Lion's Mane is a mushroom that has been shown to have neuroprotective effects and to increase BDNF levels in the hippocampus and prefrontal cortex [21]. Omega 3 fatty acids are essential fatty acids that are important for brain function and have been shown to increase BDNF levels in the hippocampus and prefrontal cortex [22]. Exercise has also been shown to increase BDNF levels in the hippocampus and prefrontal cortex, possibly through its effects on neurogenesis and synaptic plasticity [23].

IMPLICATIONS FOR PSYCHEDELIC COMPOUNDS

Psychedelics have been shown to have anti-inflammatory effects in the brain, which may be one of the mechanisms underlying their therapeutic potential for neuropsychiatric disorders [24]. Psychedelics have been shown to decrease kynurenic acid levels in the brain, possibly through their effects on serotonin receptors and the kynurenine pathway [24, 25]. Additionally, studies have shown that psychedelics can increase BDNF levels in the brain, possibly through their effects on serotonin receptors and the mTOR pathway [24, 26]. A single dose of psilocybin has been shown to decrease levels of the inflammatory biomarker C-reactive protein (CRP) in healthy humans [27].. Lastly, Psychedelics may exert significant modulatory effects on immune responses by altering signaling pathways

involved in inflammation, cellular proliferation, and cell survival via activating NF-κB and mitogen-activated protein kinases [28].

Psychedelics likely offer more sustained benefits compared to other therapies, including transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES), electroconvulsive therapy (ECT), photobiomodulation (PBM), transcranial ultrasound stimulation (TUS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS), which have also been reported to attenuate neuroinflammation and reduce the symptoms of depression [3].

In conclusion, neuroinflammation is a key factor that interacts with the three neurobiological correlates of major depressive disorder, leading to the development and progression of depression. Further research is needed to fully understand the mechanisms underlying this relationship and to develop effective treatments for depression that target neuroinflammation.

AUTHOR INFORMATION

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