Review Article

Anti-inflammatory Effects of Ketamine in PTSD: A Review

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is a mental health condition that affects people who have experienced a significant traumatic event. Current pharmacotherapies offer small to modest benefits over placebo, and residual symptoms are to be expected. In recent years, ketamine has been studied as a potential treatment for PTSD. Clinical trials have found that ketamine can provide relief from PTSD and PTSD-related conditions with minimal side effects.

The pathophysiology of PTSD involves dysregulation of the stress response pathway. Ketamine has been shown to modulate the stress response pathway, which may contribute to its therapeutic effects in PTSD. This review aims to explore the current literature surrounding ketamine's potential to reduce PTSD symptoms through modulation of the stress response pathway.

BACKGROUND
PATHOPHYSIOLOGY OF PTSD-STRESS RESPONSE PATHWAY

PTSD is a psychiatric disorder that can develop after experiencing or witnessing a traumatic event, characterized by symptoms such as intrusive thoughts, avoidance behaviors, and hyperarousal. Symptoms of PTSD are hypothesized to represent the behavioral manifestation of stress-induced changes in brain structure and function.

Stress regulates and can cause dysregulation of the stress response pathway, which includes the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS), and the immune system. These systems interact extensively to maintain homeostasis in the face of stress on the individual. PTSD symptoms result when an acutely traumatic event causes an over-reactive adrenergic response, creating abnormal and maladaptive neurological patterns in the brain. These patterns can persist long after the event that triggered the fear, making an individual hyper-responsive to future fearful situations.

HPA AXIS CORTISOL

Although it is colloquially known as the "stress hormone," cortisol regulates the body's response to stress, affecting several aspects of the body. Individuals with PTSD following a single traumatic event tend to have lower basal cortisol levels than healthy or trauma-exposed individuals without PTSD [1]. This is in contrast to those suffering from depression or chronic stress, for whom cortisol levels are found to be higher than the average population [2].\

Amongst its many functions, cortisol is responsible for negative feedback on the HPA axis, downregulating the production of corticotropin-releasing hormone (CRH) from the hypothalamus and adrenocorticotropic hormone (ACTH) from the pituitary. Studies of individuals with PTSD find low secretion of cortisol and high secretion of catecholamines in urine, with a norepinephrine/cortisol ratio consequently higher than comparable non-diagnosed individuals [3]. Due to cortisol's negative feedback functions in restoring homeostasis, a lower level of cortisol perpetuates a longer and more distressing response to trauma, increasing the likelihood of developing PTSD. The blunted cortisol response in PTSD is attributed to an enhanced HPA feedback function [4]. Lower basal levels of cortisol increase the sensitivity of glucocorticoid receptors (GR) in PTSD, leading to a progressive sensitization of the HPA axis [5].

PTSD INFLAMMATION

Cortisol plays a role in suppressing immune and inflammatory reactions, protecting from an excessive immune response, and reducing inflammation-related tissue damage. Dysregulation leads to hyperactivity of the immune response in the face of a stressor. Furthermore, Immune signaling contributes to regulating the HPA axis and other neurobiological processes that modulate affective behavior in the face of stressor exposure. Elevations in proinflammatory cytokines, including interleukin 1β, interleukin 6, tumor necrosis factor α, and interferon γ, are associated with PTSD [6].

Cortisol binds GR on immune cells, inhibiting further transcription of pro-inflammatory cytokines and limiting inflammatory damage. However, stress-induced HPA disruption may result in decreased cortisol-mediated inhibitory feedback of cytokine production with subsequent prolonged exposure to inflammatory cytokines and disruptions to multiple neuronal functions [7]. Another consequence of the combined HPA axis dysregulation and pro-inflammatory state may be to compromise the glia function responsible for maintaining synaptic glutamate homeostasis, resulting in neurotoxic elevations of extrasynaptic glutamate levels [8].

KYNURENIN PATHWAY

The kynurenin pathway is responsible for the production of coenzyme (NAD+). Tryptophan is one of the primary metabolites in this pathway, accounting for 95% of tryptophan catabolism [9]. Inflammation, as seen following an acute traumatic event, induces activation of the kynurenine pathway, resulting in less availability of tryptophan for the biosynthesis of serotonin and, instead, a shift towards the production of kynurenine and downstream neurotoxic metabolites. This leads to decreased available serotonin and neurodegeneration.

Inflammatory cytokines, including IL-1β, IL-6, and TNF-α, are known to upregulate the enzyme indoleamine-pyrrole 2,3-dioxygenase (IDO), which converts tryptophan into kynurenin [10]. The activation of IDO results in a decrease in tryptophan concentration and an increase in several metabolites, including neurotoxic quinoline acids [11].

KETAMINE IS AN EFFECTIVE AGENT IN THE REDUCTION OF PTSD SYMPTOMS.

Ketamine is a dissociative anesthetic that has been used for decades as a pain reliever and anesthetic. It is a non-competitive inhibitor of the glutamate N-methyl-D-aspartate (NMDA) receptor. In recent years, ketamine has been studied as a treatment for mental health conditions. While a majority of research involving ketamine as a psychopharmacological agent has explored the treatment of depression, several clinical trials have investigated the use of ketamine in the treatment of PTSD.

Clinical studies of ketamine for the treatment of PTSD have found a significant reduction in PTSD symptoms with minimal side effects. A proof-of-concept, randomized clinical trial (RCT) published in 2014 found that ketamine infusion was associated with a significant and rapid reduction in PTSD symptom severity, compared with midazolam, when assessed 24 hours after a single IV infusion [12]. A follow-up RCT in 2021 examined repeated ketamine administration for chronic PTSD, which found that sixty-seven percent of participants in the ketamine group were treatment responders. Among ketamine responders, the median time to loss of response was 27.5 days following the 2-week course of infusions [13]. PTSD symptoms reduced by ketamine in these trials include hyperarousal, avoidance behaviors, and intrusive thoughts. Furthermore, ketamine has been found to be protective against recurrences of PTSD [14].

KETAMINE

There are several mechanisms by which Ketamine may reduce PTSD symptoms through effects on the stress response pathway.

KETAMINE DECREASES HPA SENSITIVITY

Research has shown that ketamine can modulate the hypothalamic-pituitary-adrenal (HPA) axis, which may contribute to its therapeutic effects. In mouse models, Ketamine increased GR expression in the hippocampus of stressed mice, thus normalizing HPA axis responses [15]. Recent separate pre-clinical studies have reported how ketamine reduces HPA axis hyperactivity by decreasing the corticosterone response in male mice [16] and that ketamine (but not fluoxetine) reverses stress-induced GR receptor impairments and dendritic branching loss in the ventral and dorsal dentate gyrus regions [17]. Ketamine also increased cortisol levels in a double-blind, placebo-controlled study. In this study, low-dose ketamine produced a dose-dependent increase in cortisol production, with a twofold increase at a concentration of 165 ng ml−1 [18].

KETAMINE MODULATION OF THE INFLAMMATORY PATHWAY

Studies have found that Ketamine can decrease heightened inflammation in animal models and human blood in vitro [19]. Rodent studies provided strong support for ketamine-induced decreases in pro-inflammatory cytokines, namely in interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α [20]. In human models, Ketamine was shown to inhibit immune reaction-induced proinflammatory cytokine production, including nuclear factor κB, and to decrease blood levels of tumor necrosis factor-α, interleukin 6 (IL-6), C-reactive protein, and inducible nitric oxide synthase [21]. Ketamine exerts its anti-inflammatory actions by directly affecting immune cells and inhibiting the production and release of inflammatory biomarkers, including pro-inflammatory cytokines [22].

KETAMINE KYNURENINE PATHWAY

Studies have examined the effects of ketamine on the kynurenine pathway, which reduces available tryptophan for serotonin synthesis and produces neurotoxic metabolites. Findings suggest that ketamine's anti-inflammatory properties reduce the activity of the kynurenine pathway. Ketamine-induced reductions of inflammatory markers were observed most commonly for the cytokines IL-1β, IL-6, and TNF-α. The effect of ketamine in decreasing pro-inflammatory cytokines leads to the dampened activity of IDO and other enzymes in the kynurenine pathway, leading to increased availability and synthesis of neuroprotective kynurenic acid and a decrease in neurotoxic quinolinic acid [11].

A systematic review of the effect of ketamine on inflammation and the kynurenine pathway in depression found that ketamine appears to induce anti-inflammatory effects in at least a proportion of depressed patients [23].

DISCUSSION

Ketamine has emerged as a safe and effective treatment option for those suffering from PTSD. While the mechanisms by which ketamine alleviates PTSD are a topic of ongoing research, current models suggest a large contribution from ketamine's modulation of the stress response pathway, aiding in the restoration of homeostasis between the HPA axis, autonomic nervous system, and the immune system.

Ketamine regulates the stress response at several points. Low basal cortisol levels are implicated in sensitization of the HPA pathway, i.e., increased glucocorticoid receptor sensitivity, following an acutely traumatic

event. This leads to the upregulation of subsequent inflammatory activation in PTSD. Ketamine, in mouse models, has been shown to effectively "reset" the sensitivity of the HPA axis by decreasing the corticosterone response. Ketamine has been shown, in a double-blinded, placebo-controlled study, to increase cortisol levels, which may contribute to the downregulation of GR sensitivity. With decreased HPA axis sensitivity comes an attenuation of the unregulated feedback loop of neurotoxic inflammation and adrenergic response.

Ketamine has also been found to exert anti-inflammatory actions by directly affecting immune cells and inhibiting the production and release of inflammatory biomarkers, including pro-inflammatory cytokines. By binding GR on immune cells, ketamine inhibits further transcription of pro-inflammatory cytokines and limits inflammatory damage.

The kynurenine pathway, which forms the coenzyme NAD+, is the primary metabolic pathway of tryptophan metabolism. This pathway is upregulated with increased inflammatory signaling, as seen in PTSD, which leads to the depletion of tryptophan necessary to synthesize serotonin and increases the synthesis of quinolinic acid, an endogenous neurotoxin with multiple targets [24]. Ketamine is implicated in the downregulation of cytokine-induced activation of the kynurenine pathway, leading to increased serotonin and decreasing quinolinic acid, improving the neurochemical imbalance in individuals who have PTSD.

While this review focuses primarily on ketamine's modulation of the stress response pathway seen in PTSD, there are several other mechanisms by which ketamine may reduce PTSD symptoms. Other areas of investigation include ketamine's effects on the glutaminergic system, BDNF release, and cholecystokinin release [25]. At the same time, efforts to elucidate the underlying mechanisms of ketamine continue trials press on to examine the full therapeutic effects, risks, and optimal dosing to treat PTSD.

CONCLUSION:

In conclusion, ketamine has shown promise as a safe and effective treatment for PTSD in several clinical studies, with the underlying mechanisms of these effects under investigation. PTSD pathophysiology is driven by dysregulation in the homeostasis of the stress response pathway. Ketamine may improve symptoms of PTSD by modulating the stress response pathway in the brain at several points, including desensitization of the HPA axis by regulating GR sensitivity, inhibition of pro-inflammatory cytokines, and regulation of the kynurenine pathway. While more research is needed to fully understand the effects of ketamine on the stress response pathway in PTSD, ketamine represents a promising avenue for the treatment of this debilitating disorder.

AUTHOR INFORMATION

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