Inflammation, Stress, and Depression: An Exploration of Ketamine's Therapeutic Profile

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Abstract

Well-established animal models of depression have described a proximal relationship between stress and central nervous system (CNS) inflammation, a relationship mirrored in the peripheral inflammatory biomarkers of individuals with depression. Evidence also suggests that stress-induced pro-inflammatory states may contribute to the neurobiology of treatment-resistant depression. Interestingly, ketamine, a rapid-acting antidepressant, may partially exert its therapeutic effects via anti-inflammatory actions on the hypothalamic-pituitary-adrenal (HPA) axis, kynurenine pathway, or cytokine suppression. Further investigations into the relationship between ketamine, inflammation, and stress may provide insight into ketamine's unique therapeutic mechanisms and stimulate efforts to develop rapid-acting, anti-inflammatory-based antidepressants.

Keywords: ketamine, depression, stress, inflammation, treatment-resistant depression, anhedonia

Teaser: This review investigates the role of inflammation in chronic stress and depression, as well as how the rapid-acting antidepressant ketamine may exert some of its therapeutic effects via anti-inflammatory mechanisms.

1. Introduction

Depression is the leading cause of disability worldwide, affecting 322 million people [1]. In the United States, research suggests that approximately one-third of sufferers have treatment-resistant depression (TRD), broadly defined as non-response to conventional antidepressants [2]. One of the primary obstacles to understanding depression is its characteristic heterogeneity in course of illness, biomarkers, treatment response, and genetic polymorphisms. As such, recent efforts within psychiatry have sought to establish clinically-relevant biomarker and symptom-based subgroups under the umbrella of depressive disorders.

For over three decades, researchers have studied the relationship between depressive symptoms and inflammatory states [3]. This interest began with the observation that chronic administration of interferon-alpha (IFN-α)—a pro-inflammatory cytokine used to treat hepatitis C and other malignancies—precipitated depressive symptoms that responded to standard antidepressant interventions [4]. Preclinical studies also found that peripheral immune system activation via systemic administration of lipopolysaccaharide (LPS), an endotoxin, reliably triggered "depressive-like" behaviors in rodents [5]. Acute and chronic stressors that play an integral role in the etiology of depression [6] also reliably trigger inflammatory responses [7].

Indeed, emerging evidence from population-based studies supports the notion that chronic, low-grade inflammation—while not present in all individuals with depression—may nevertheless play a key role in the pathophysiology of depression for a subset of patients [8]. Data from longitudinal studies suggest that dysregulation of the inflammatory response is associated with a more severe course of illness, higher recurrence of depressive symptoms, and worse outcomes, including impaired brain connectivity within motivation and reward circuits

[9], increased suicidality [10], and—notably—greater resistance to conventional therapies [11]. Reward circuits may also impact a hallmark symptom of TRD, anhedonia, which has also been consistently linked to inflammation [12]. Other factors such as obesity and other conditions associated with chronic inflammation also appear to increase the development of inflammation-associated sickness and depressive symptoms, as well as their persistence [13].

Subanesthetic doses of the glutamatergic modulator racemic ketamine, as well as its enantiomers, have consistently been shown to exert rapid-acting antidepressant effects in patients with TRD and treatment-resistant bipolar depression (reviewed in [14]). Ketamine has also been found to successfully treat traditionally treatment-refractive symptoms domains such as anhedonia, suicidality, and amotivation [15,16]. Within the context of this review, it is important to note that although researchers primarily attribute ketamine's therapeutic effects to upregulated neuroplasticity induced via glutamatergic modulation [17], growing evidence suggests that it may also regulate acute and chronic inflammatory reactions and restore immune homeostasis [18,19].

This review of previous and emerging research: 1) discusses the links between depression, stress, and inflammation, particularly inflammation as an potential indicator of TRD; and 2) summarizes the preclinical and clinical evidence for ketamine's anti-inflammatory and immunomodulatory properties in the context of its antidepressant effects. Potential mediators of the process—including the kynurenine pathway and the hypothalamic-pituitary-adrenal (HPA) axis—are also discussed, as is the hypothesis that ketamine's unique ability to reduce depressive symptoms in TRD may in fact be due to its ability to reduce stress-induced inflammation.

2. Chronic Stress, Depression, and Inflammation: An Overview

Stress is an inherent physiologically or emotionally coordinated response that activates processes in the body to maintain homeostasis after threatening stimuli or, under acute stress conditions, helps anticipate challenges or respond to dangerous situations. Chronic stress is loosely defined as a sustained threat lasting at least several weeks that is accompanied by a resulting negative emotional state and deleterious effects on body systems. Under chronic, prolonged stress conditions, the brain and body lose their ability to restore homeostasis. The link between inflammation and chronic stress likely results from an evolutionary adaptation [7]. In prehistoric environments, this connection between the perception of danger and the risk of subsequent tissue injury or pathogen exposure was believed to be so reliable that evolution favored anticipatory inflammatory responses to many environmental stressors, including psychosocial stressors. In the context of the present review, chronic stress is known to be a major risk factor for depression [6].

The relationship between chronic stress and depression holds true in preclinical models, where chronic stress protocols (e.g. social defeat, unpredictable mild stress, and chronic corticosterone (CORT) administration) are the gold standard for producing depressive-like behaviors in animals, including symptom profiles such as learned helplessness and anhedonia [20]. In animal models, the upregulation of stress hormones was found to robustly increase inflammatory markers such as tumor necrosis factor alpha (TNF-α) and interleukin 1β (IL-1β) [21]. Preclinical studies also found that chronic stress induces central nervous system (CNS) inflammation characterized by the secretion of cytokines and neuroinflammation [22]. Interestingly, one study found that chronic social instability stress did not alter hippocampal pro-inflammatory cytokines; however, the study was conducted in females, suggesting potential sex differences in the links between chronic stress and inflammation [23].

Multiple clinical studies have reported elevated levels of pro-inflammatory cytokines in individuals with depression. For instance, meta-analyses found that elevated levels of C-reactive protein (CRP)—a common marker of inflammation—predicted subsequent depressive symptoms [24] and were strongly associated with a diagnosis of depression [25]. Another recent meta-analysis of individuals with depression found that a quarter of participants had low-grade inflammation (CRP >3 mg/L), and half had elevated CRP levels (CRP >1 mg/L) [26]. Other meta-analyses reported cerebrospinal fluid (CSF) and peripheral elevations of other pro-inflammatory markers such as IL-6, IL-8, and TNF-α [27,28]. Supporting the notion that higher levels of inflammation play a causative role in depression, one longitudinal study found that participants with elevated IL-6 and CRP levels at age nine were more likely to be evaluated as depressed at age 18 [29]. Nevetheless, many other studies have found no such association between increased levels of CRP and IL-6 (reviewed in [30]), suggesting that any putative relationship between depression and inflammation remains unclear. Thus, the presence of increased inflammatory markers may represent a distinct subgroup within the depressive diagnostic label, and the mixed results warrant further investigation.

It is also important to acknowledge the potential role of sex in the interplay between chronic stress, depression, and inflammation. Rates of depression have consistently been found to be two-to three-fold higher in females [31], and clinical research also suggests that women may be particularly vulnerable to the effects inflammation on depressive symptomatology [32]. In contrast, some preclinical models found that males were more vulnerable to developing depressive-like behaviors after inflammatory insult [33]. Throughout this review, sex differences will be discussed wherever possible.

3. The Relationship Between Inflammation and TRD

As noted above, evidence suggests that individuals with MDD with heightened inflammatory markers may constitute a subpopulation uniquely associated with treatment-refractory symptoms [34]. For example, body mass index (BMI)-corrected serum CRP levels were recently found to be significantly elevated in TRD participants relative to treatment-responsive MDD participants, unmedicated MDD participants, and healthy volunteers [35]. These findings are complemented by two randomized, controlled trials that found that baseline CRP levels predicted lack of response to conventional antidepressants [36,37]. Another study found distinct results in whole blood samples, with a significant upregulation in mRNA-indicated inflammasome activation and glucocorticoid resistance in the MDD population (untreated versus treatment-responsive versus TRD). Of the mRNAs identified, six (P2RX7, IL-1β, IL-6, TNF-α, CXCL12, and GR) differentiated between TRD and treatment-responsive subgroups [38]. In contrast, another study found no evidence of large inflammatory differences in the peripheral blood mononuclear cells (PBMCs) of healthy volunteers versus MDD patients (untreated versus treatment-responsive versus TRD), but did find strong evidence of increased biological aging in the MDD sample [39].

One study of unmedicated MDD participants found that those who, on average, had failed to respond to three or more antidepressant trials had significantly higher levels of CRP, IL-6, TNF receptor 2 (sTNF-R2), and TNF-α than those who, on average, had failed to respond to less than one trial [34]. A meta-analysis found that higher baseline levels of inflammatory markers in general were associated with poor treatment response, and that high TNF-α levels in particular were associated with TRD [40]. An analysis of participants with MDD and bipolar depression who participated in a randomized, controlled trial of escitalopram versus

nortriptyline found that cutoffs for absolute mRNA levels of IL-1β and macrophage migration inhibitory factor (MIF) in blood accurately predicted 100% of the non-responders in their study [41]. Interestingly, a randomized, controlled trial of the anti-inflammatory agent infliximab found that its antidepressant effects were specific to a subset of TRD participants with elevated baseline plasma CRP levels greater than 5mg/L [42]; because this impact was not consistent with results observed in individuals with bipolar I and II depression, it suggests a potential unique efficacy for TRD [43]. Finally, adjunctive use of the anti-glucocorticoid therapeutic metyrapone actually increased IL-6 levels in individuals diagnosed with TRD, an increase associated with poorer outcomes to treatment; this finding was hypothesized to result from potential glucocorticoid system overcompensation [44].

Imaging studies are also beginning to confirm that this peripheral inflammation is mirrored in the brain itself. Positron emission tomography (PET) studies of translocator protein 18 kDa (TSPO)—a biomarker of neuroinflammation—have typically reported greater TSPO binding in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) of individuals experiencing a major depressive episode [45]. In an open-label trial of TRD participants who received the anti-inflammatory agent celecoxib, investigators plotted the reduction in Hamilton Depression Rating Scale (HAM-D) score against baseline TSPO volume in the PFC and ACC and found that HAM-D scores rapidly dropped post-treatment as baseline TSPO distribution volume decreased [46]. A recent parallel study measured the impact of minocycline, a tetracycline antibiotic with anti-inflammatory properties, on TRD participants experiencing a major depressive episode; minocycline did not significantly impact TSPO binding [47], though another study found that it significantly decreased HAM-D scores in participants with elevated CRP levels (CRP ≥3mg/mL) [48]. Other studies investigating minocycline as an adjunctive

treatment for TRD found no significant change in depressive symptoms [49]. Finally, increases in immune factors after ex-vivo LPS stimulation of PBMCs were associated with reduced reward anticipation in the ventral striatum, as measured via functional magnetic resonance imaging (fMRI) [50]. This builds on previous research that found that endotoxin administration to healthy volunteers significantly increased depressed mood over time and reducted ventral striatum responses to reward [51]. This effect may also be sex-dependent, given that females demonstrated greater reductions in ventral striatum activity in response to reward [52].

Inflammation may mediate motivational behavioral responses by dampening dopamine activity within reward circuits, resulting in disrupted fronto-striatal functional connectivity [53]. Inflammatory processes are therefore well-situated to influence the neural circuits underlying motivational symptoms related to anhedonia. This is particularly critical because behavioral responses to reward and social stimuli in patients with anhedonia have been associated with both suicidality [54] and treatment resistance [55]. Interestingly, depressive symptoms such as reduced motivation and anhedonia correlate significantly with central IL-6 soluble receptor (IL-6sr) [56] as well as peripheral CRP levels [9,56]. A resting-state fMRI study of depressed participants found that plasma CRP levels correlated with decreased connectivity between the ventral striatum and ventromedial PFC (vmPFC), and that this change in connectivity was itself correlated with the severity of anhedonia [9]. Consistent with this finding, administration of IFN-α for four to six weeks in 14 individuals with hepatitis C not only induced anhedonia but also reduced bilateral activation of the ventral striatum in an fMRI reward task [57]; change in striatal activity again correlated with anhedonia scores.

Relatedly, reduced motivation has been correlated with central levels of TNF-α [56]. Anhedonia, anergia, and amotivation all fall under the symptom interest-activity dimension of

depression; in the large Genome-Based Therapeutic Drugs for Depression (GENDEP) (n = 811) and Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (n = 3637) studies, this dimension was shown to best predict poor antidepressant response [58].

Glutamate may also modulate the interplay between inflammation and depression. Higher glutamate release from microglial cells appears to increase concentrations of extracellular glutamate, promote maladaptive glutamate metabolism, contribute to loss of synaptic fidelity, and decrease the specificity of neurotransmission—all of which can worsen depressive-like behaviors and increase circuit dysfunction [59]. While most research in this area has focused on chronic stress, acute traumatic stress can similarly provoke glutamatergic signaling dysfunction [60]. Administration of the pro-inflammatory cytokine IFN-α increased glutamate concentrations in the dorsal anterior cingulate cortex and basal ganglia [61,62]. Notably, individuals with depression who also had high concentrations of plasma CRP and high levels of basal ganglia glutamate were significantly more likely to have more severe symptom presentations of anhedonia and cognitive slowing [63]. Despite these intriguing findings, the role of glutamate in depression remains unclear. As an example, magnetic resonance spectroscopy (MRS) [64] studies found decreased levels of glutamate, or no differences at all [65] in individuals with depression. Other studies found that the glutamatergic neurons of individuals with depression exhibited decreased mitochondrial energy production [66]. One important caveat is that glutamate is often measured using Glx—a composite measure that includes both glutamate and glutamine. At least one study that separated these measures found no significant differences in glutamate levels in participants with depression [67].

Preliminary research is also investigating the response of inflammatory proteins to psychological therapy. In one study, poor response to treatment was associated with higher

baseline levels of TNF-α, IL-6, and soluble intracellular adhesion molecule-1 and with higher post-therapeutic levels of CRP, thymus and activation-regulated chemokine, and macrophage chemoattractant protein-4 [68]. At least one review of the literature also reported a general reduction in inflammation after cognitive behavioral therapy for depression [69].

Taken together, inflammatory markers seem to cause bona fide alterations in brain network activity that may, in turn, cause depressive symptoms. Thus, the evidence suggests that inflammation contributes to depressive pathology in at least some cases and that determining potential mediators of the stress response may inform the development of therapeutic interventions.

4. Potential Mediators Between Depression and Inflammation

4.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis

HPA axis hyperactivity is one of the most consistent findings in studies exploring the underlying pathophysiology of depression. In healthy states, the HPA axis is activated by acute stress, stimulating the release of corticotropin-releasing hormone (CRH) and vasopressin (AVP) from the hypothalamus. This, in turn, stimulates the release of adrenocorticotrophic hormone (ACTH) and glucocorticoids (primarily cortisol in humans and corticosterone in rodents). After an acute stressor, these glucocorticoids interact with their widely expressed receptors (either mineralocorticoid or glucocorticoid receptors), some of which interact with the hypothalamus to form a negative feedback loop to shut off HPA axis activity. Chronic stress disrupts this feedback loop, causing a downregulation of glucocorticoid receptors that impairs the ability to shut off the HPA axis, leading to dysfunctional hyperactivity [70].

Many individuals with depression exhibit HPA axis dysfunction, such as continuously elevated levels of cortisol and CRH [71]. This hypersecretion can cause hypercortisolism and, as a result, decreased dopaminergic reward-system responsivity [72]. In females, increased hair cortisol concentrations were associated with poor performance on measures of cognition and memory, an association that appeared to be mediated by CRP levels [73]. Early-life adversity has also been shown to increase vulnerability to acute social stress, an effect mediated by HPA-axis and immune activation [74], and was also found to impact later diurnal HPA axis functioning in adulthood [75].

One of the most compelling theories regarding the clinical relevance of inflammation in depression is that inflammation may differentiate depressive subtypes and mediate specific symptoms. For example, a recent study found that biomarkers of HPA axis activity and subsequent inflammation (such as cortisol and CRP) were more strongly associated with the presence of somatic symptoms than cognitive-affective symptoms [76]. For instance, a recent review found that cancer patients—who are significantly more likely to have depressive symptoms and a worsened symptom profile—may exhibit increased depressive-like behaviors due to hyperactivity of the HPA axis caused by cancer and anti-cancer treatments [77]. In a CORT-injected mouse model, the antidepressant-like effects of catalpol, an iridoid glucoside, also appeared to be mediated through the HPA axis, suppressing levels of CORT, ACTH, and CRH [78].

4.2 The Kynurenine Pathway

One hypothesis of inflammation-mediated depressive pathogenesis is that stress and inflammatory cytokines promote kynurenine pathway signaling [79]. Tryptophan, a precursor for

serotonin synthesis, is competitively consumed by the kynurenine pathway. One of the rate-limiting enzymes of this pathway, indoleamine-2,3-dioxygenase (IDO), is expressed mainly in immune and neuronal cells and induced by cytokines, cortisol, and LPS, generally indicating a pro-inflammatory state [80]. Tryptophan-2,3-dioxygenase (TDO), the other main enzyme in the kynurenine pathway that catalyzes tryptophan catabolism, is also induced under pro-inflammatory states [81]. Thus, increased cytokine and cortisol levels may reduce serotonin levels via tryptophan depletion, a process that has been experimentally shown to induce depressive symptoms in vulnerable persons [82], though these findings have not always been consistent [83]. Tryptophan-kynurenine metabolism may also provide a link between the gut-brain axis that connects inflammatory bowel disease and depression, two disorders that are strongly associated with one another [84]. Acute and chronic stress also impact the rate-limiting enzymes involved in the tryptophan/kynurenine balance (see Figure 1). For example, IFN-gamma and Il-1β are potent inducers of IDO and TDO, which are highly impacted by immune activation in the brain. In addition, stress-induced corticosterone release and the consequent cascading activation of hepatic TDO to tryptophan metabolism ultimately lead to the production of kynurenine, which provokes a depression-related behavioral phenotype [85]. Both IDO and TDO may therefore represent promising targets for the treatment of depression associated with stress-related disorders marked by kynurenine pathway activation (see Figure 1).

Kynurenine pathway products are biologically active. Kynurenic acid (KA) is considered both neuroprotective [86] and a potential therapeutic target for drug development in mood disorders. Another product, quinolinic acid (QA), is an endogenous neurotoxin that generates free radicals [87] and causes excitotoxicity by inducing the release and inhibiting the reuptake of glutamate [88]. One major component of the kynurenine pathway is its ability to affect the

glutamatergic system, where it both directly and indirectly influences ionotropic and metabotropic glutamate receptors and vesicular glutamate transport [89]. These effects are hypothesized to act as a main link between chronic stress, depression, and inflammation [90]. For instance, QA directly activates N-methyl-D-aspartate receptors (NMDARs), increases synaptosomal glutamate release, and inhibits glutamate uptake, making it uniquely placed to mediate interactions between ketamine and inflammation [91]. KA and QA are metabolized from kynurenine by astrocytes and microglia, respectively, and evidence suggests that individuals with MDD have reduced astrocyte density [92] and function [93] along with increased microglial activation and number [94].

Supporting the clinical relevance of this pathway, studies have reported higher ratios of kynurenine to tryptophan levels [95,96], lower levels of KA [97], and lower KA:QA ratios [98] at baseline in MDD participants. In addition, QA elevations were found in the CSF of recent suicide attempters [99], and more QA-positive cells were found in the brain of suicide decedents [100]. Finally, altered peripheral ratios of KA:QA levels were shown to correlate with increased anhedonia in MDD participants [101] as well as with both depression and fatigue in cancer patients [102]. Taken together, this evidence suggests that the kynurenine pathway may play a key role in mediating the links between inflammation and depression.

5. Ketamine and Inflammation

The NMDAR antagonist ketamine is uniquely effective for treating TRD, with a response rate ranging from 25% to 85% at 24 hours post-infusion [103]. It has also been shown to effectively reduce suicidal ideation and anhedonia [15,16], as well as fatigue and amotivation symptoms [104,105]. Recent clinical and preclinical evidence indicates that, at antidepressant

doses, ketamine may exert these unique therapeutic effects in part by modulating inflammation [19,95]. It is important to note that most of the studies described below reflect acute, not chronic, ketamine administration, which could affect the interpretation of results.

5.1 Preclinical Evidence of Ketamine's Anti-inflammatory Effects

Substantial preclinical evidence suggests that ketamine reduces inflammation by regulating the immune system. *In vitro* ketamine application to rodent glial cells [106] and macrophages [107] attenuated markers and mediators of LPS-induced inflammatory responses, such as TNF-α, IL1-β, high mobility group box 1 (HMGB1), nitric oxide (NO), inducible nitric oxide synthase (iNOS), and prostaglandin E-2.

In animal models, administration of intraperitoneal ketamine had a prophylactic effect against both LPS- and chronic stress-induced depressive behaviors [108-110]. Ketamine's neuroprotective effects appear to be, at least in part, regulated through the NLRP3 inflammasome pathway [111]. Concurrent with the aforementioned behavioral changes, ketamine also attenuated plasma cytokine elevations [112] and cytokine expression in rodent tissue samples from the PFC, hippocampus, cerebellum, and spinal cord [110,113].

Interestingly, ketamine appears to act directly on immune cells. For instance, *S*-ketamine—the *S*-enantiomer of racemic ketamine—decreased micoglial activity levels in the CNS after chronic stress exposure [110]. An immunohistochemistry study performed on rodent hippocampus samples found that ketamine reversed stress-induced activation of microglia caused by chronic restraint by downregulating Toll Like Receptor (TLR)/p38 pathway activation and P2X7 receptors [113]. In chronically stressed mice, pharmacological inhibition of TGF-β1-signalling in microglia eliminated ketamine's antidepressant effects [114]. In addition, ketamine

and its antidepressant metabolites altered the localization of signal transducer and activation of transcription 3 (STAT3) in human microglial cells to regulate the "response to interferon I" inflammatory pathway [115].

More recently, acute intraperitoneal ketamine administration in mice was shown to skew the distribution of macrophage populations away from pro-inflammatory and cytokine-inducing M1 phenotypes towards tissue-supporting M2 phenotypes [116]. This finding was also observed *in vitro* in human monocyte cultures, where the effect could be abolished by inhibiting mammalian target of rapamycin (mTOR), a key protein implicated in ketamine's antidepressant effects [117]. PBMC samples collected from healthy volunteers and participants with MDD after a suicide attempt or with active suicidal ideation found that macrophages in MDD participants also skewed towards the inflammatory M1 phenotype [116].

Ketamine may also indirectly affect inflammation by mediating HPA axis function. In chronically stressed mice, acute ketamine administration restored hippocampal glucocorticoid receptor expression, counteracting the negative feedback associated with HPA over-activation [118]. In mice injected with LPS, ketamine significantly reduced corticosterone and ACTH production six hours later [119]. Similarly, both single and repeated seven-day ketamine administration reduced corticosterone and ACTH levels in mice that had undergone 40 days of chronic mild stress [120].

Ketamine and kynurenine appear to converge during stress conditions in order to affect brain and behavior. One study found that while ketamine did not affect QA production after LPS administration, it mediated the effects of QA by blocking NMDARs, where QA generally binds to contribute to inflammation [91,109]. In a chronic unpredictable mild stress model, ketamine decreased the KYN:tryptophan ratio in addition to other measures of inflammation [121].

5.2 Clinical Evidence of Ketamine's Anti-inflammatory Effects

Multiple inflammatory markers have been linked to ketamine's clinical therapeutic efficacy. In a recent randomized, controlled trial, subanesthetic-dose ketamine (0.5mg/kg) acutely decreased TNF-α levels in TRD patients, and these decreases correlated with reductions in Montgomery-Åsberg Depression Rating Scale (MADRS) scores [18]. A smaller study of individuals with TRD similarly found that higher baseline levels of IL-6 were associated with antidepressant response to ketamine [122]. In an open-label trial, ketamine robustly reduced peripheral levels of multiple cytokines elevated at baseline in TRD participants, but these levels returned to baseline within 24 hours and did not correlate with antidepressant response [123]. In addition, a recent study in remitted depressed participants found significant decreases and time x treatment interactions for multiple cytokines [124]. However, other studies obtained mixed results. For example, a post-hoc analysis of three ketamine randomized, controlled trials of participants with TRD and treatment-resistant bipolar depression found that ketamine decreased levels of soluble tumor necrosis factor receptor 1 (sTNFR1) but increased peripheral levels of IL-6 and TNF-α [125]. Interestingly, a recent open-label ketamine trial found that IL-8 did not predict antidepressant response to ketamine, but that there was a trend towards prediction in females, suggesting a potential sex-specific effect [126].

The effects of ketamine on the HPA system are less clear. One case study found that cortisol levels—as measured by the dexamethasone suppression test—normalized in a TRD participant who received three standard ketamine infusions; cortisol levels rose to baseline a week later as depressive symptoms returned [127]. In contrast, a randomized, controlled trial of 12 healthy volunteers who received two back-to-back ketamine infusions (0.29mg/kg for 1 hour,

then 0.57mg/kg for 1 hour) reported doubled plasma cortisol levels 200 minutes later [128]. Furthermore, another randomized, placebo-controlled trial of healthy volunteers found that the post-ketamine increase in cortisol was specific to ketamine, as the NMDA antagonist memantine caused no such effect [129]. For now, the dearth of properly-powered studies examining potential HPA biomarkers post-ketamine treatment in TRD participants makes it difficult to draw firm conclusions.

Echoing preclinical findings, modulation of the kynurenine pathway may be involved in ketamine's anti-inflammatory effects. A randomized, controlled trial of TRD participants found that those who responded to ketamine had significantly lower plasma kynurenine:tryptophan ratios as well as lower kynurenine levels 230 minutes and 24 hours post-ketamine administration [95]. Furthermore, among participants with TRD and treatment-resistant bipolar depression who received six ketamine infusions over 12 days, those who responded had higher levels of serum KA, both absolute and relative to kynurenine, on Days 1 and 13 [96]. Moreover, at 24 hours, both of these metrics correlated with MADRS score reductions at Days 1, 13, and 26. Finally, a recent randomized, controlled trial of indiviuals with bipolar depression reported that one ketamine infusion increased KA levels one and three days later and decreased IDO levels from 230 minutes post-infusion to three days later [130]. Despite these promising findings, it should be noted that another study found only trend-level decreases in serum kynurenine after repeated ketamine infusions and no change in cortisol-awakening response [97].

There is also indirect evidence of ketamine's anti-inflammatory effects. One post-hoc analysis of four randomized, controlled trials (n=108) found that greater BMI predicted antidepressant response to ketamine in individuals with MDD or bipolar depression [131], which may be linked to the finding that pro-inflammatory agents are often deposited in adipose tissue

[132]. Subsequently, researchers examined adipokine levels and found that ketamine reduced plasma levels of resistin, and that low baseline levels of adiponectin predicted antidepressant response [133]. These findings are congruent with anti-inflammatory effects; resistin is a potent pro-inflammatory agent [134] associated with obesity, while adiponectin is an anti-inflammatory molecule [135]. Another study of medication-free TRD participants found that ketamine decreased the expression of receptor activator of nuclear factor kappa-B ligand (RANKL), a downstream inflammatory mediator [136]. In TRD participants, gene expression signatures related to interferon signaling pathway activation were upregulated in comparison to healthy volunteers, but this did not mediate response to ketamine [137].

Despite these promising findings, it is clear that more research is necessary to clarify ketamine's effects on inflammation in general, and on clinical depression subtypes linked to inflammation in particular. The mixed results suggest that future studies should compare acute versus chronic ketamine administration as well as the short- and long-term effects of ketamine, given that some of the aforementioned studies observed an immediate increase in inflammatory indicators post-ketamine administration that decreased with time. Promising preclincial evidence and strong associations between TRD and inflammation warrant further investigation into the mechanisms by which ketamine may either directly or indirectly mediate inflammatory response.

6. Conclusion

In this era of personalized medicine, the quest to identify subpopulations of individuals with MDD based on pathophysiology, symptom dimensions, and prognostic biomarkers of treatment efficacy holds considerable promise for improving the thus far inadequate therapeutic response associated with many currently available pharmacotherapies. This review presents

evidence that chronic stress-induced, systemic, pro-inflammatory states may constitute a pathogenic factor that may negatively impact treatment-responsiveness in depression. Meanwhile, preliminary but growing evidence suggests that ketamine's unique efficacy in treating these same treatment-refractory symptoms may partly be due to its anti-inflammatory effects, perhaps by directly counteracting the inflammatory consequences of chronic stress; these unique effects are not associated with conventional antidepressants. These effects may occur via some combination of cytokine suppression, alteration of the kynurenine pathway or HPA axis, direct actions on microglia and other monocytes, and additional mechanisms not discussed here.

In this context, the need to verify ketamine's anti-inflammatory properties with rigorous, prospective, clinical research is clear, as is the need to use preclinical models to elucidate the molecular and cellular basis underlying these effects. The effects of sex must also be considered, given the mixed results regarding sex differences in inflammation. This is particularly important because few preclinical or clinical studies have explored the links between TRD, ketamine, and inflammation in a female population. Nevertheless, future research efforts in this area are likely to be complicated by several challenges. First, depressive symptoms that may derive from inflammation and respond to ketamine are neither universal nor specific to any one diagnostic category. Thus, advances in psychiatric nosology are likely needed in order to replicate research with greater inter-study validity. Second, immune system dysregulation has a multitude of other consequences that span multiple systems and that may be further confounded by other factors such as gender and BMI. A more complete understanding of these complex interactions, combined with improved identification of the heterogeneous etiologies of depressive symptoms, are critically needed to move this field forward.

Regardless, further systematic research into the connections between inflammation, treatment-resistant symptom severity, and response to ketamine is warranted. Ideally, such investigations should measure central levels of inflammatory markers and products of related pathways such as the HPA and kynurenine pathways and correlate these with suicidal ideation, anhedonia, and other hallmark symptoms of TRD.

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Declaration of Interest

Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (*R,S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety,

anhedonia, suicidal ideation, and post-traumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose, financial or otherwise.

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Figure Legends

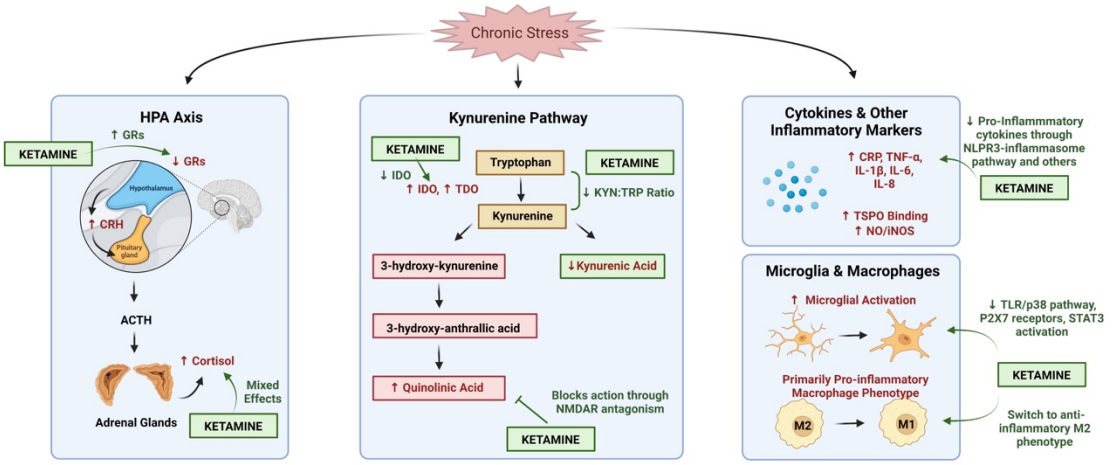

Figure 1. The hypothesized impact of ketamine on stress and inflammatory pathways. Chronic stress leads to over-activation of the hypothalamic-pituitary-adrenal (HPA) axis, which increases levels of corticotropin releasing hormone (CRH) and cortisol while decreasing expression of glucocorticoid receptors (GRs). This decrease in GR expression prevents the shut-off of the HPA axis, leading to prolonged activation that can have negative consequences. Ketamine, an N-methyl-D-aspartate receptor (NMDAR) antagonist, appears to mediate this stress response by increasing the number of GRs. Studies examining ketamine's effect on cortisol levels have yielded mixed results. Under chronic stress conditions, the kynurenine pathway, another potential mediator between stress and inflammation, demonstrates increased levels of indoleamine-2,3-dioxygenase (IDO), tryptophan-2,3-dioxygenase (TDO), and quinolinic acid, as well as decreased levels of kynurenic acid. Ketamine decreases IDO levels and the ratio of kynurenine:tryptophan through indirect mechanisms while blocking the action of quinolinic acid through direct NMDAR antagonism. Ketamine also decreases pro-inflammatory cytokine levels (increased by chronic stress) through the NLPR3-inflammasome pathway, decreasing microglial activation via TLR/p38 signaling, P2X7 receptors, and signal transducer and activator of

transcription 3 (STAT3) activation, as well as switching macrophages to the anti-inflammatory M2 phenotype. Created using Biorender.

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