REVIEW ARTICLE

Ketamine's mechanism of action with an emphasis on neuroimmune regulation: can the complement system complement ketamine's antidepressant effects?

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Over 300 million people worldwide suffer from major depressive disorder (MDD). Unfortunately, only 30–40% of patients with MDD achieve complete remission after conventional monoamine antidepressant therapy. In recent years, ketamine has revolutionized the treatment of MDD, with its rapid antidepressant effects manifesting within a few hours as opposed to weeks with conventional antidepressants. Many research endeavors have sought to identify ketamine's mechanism of action in mood disorders; while many studies have focused on ketamine's role in glutamatergic modulation, several studies have implicated its role in regulating neuroinflammation. The complement system is an important component of the innate immune response vital for synaptic plasticity. The complement system has been implicated in the pathophysiology of depression, and studies have shown increases in complement component 3 (C3) expression in the prefrontal cortex of suicidal individuals with depression. Given the role of the complement system in depression, ketamine and the complement system's abilities to modulate glutamatergic transmission, and our current understanding of ketamine's anti-inflammatory properties, there is reason to suspect a common link between the complement system and ketamine's mechanism of action. This review will summarize ketamine's anti- inflammatory roles in the periphery and central nervous system, with an emphasis on complement system regulation.

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INTRODUCTION

Over 300 million people worldwide suffer from major depressive disorder (MDD), and over 700,000 people die from suicide each year [1]. MDD is the leading cause of disability worldwide [1]. Monoamine dysregulation and changes in neurotrophin levels have been shown to play important roles in the pathophysiology of MDD [2]. MDD pharmacotherapy has focused primarily on serotoninergic, noradrenergic, and dopaminergic activity, as these monoamines, when appropriately regulated, can contribute to improved mood, cognition, sleep, and reward [2]; this rationale is known as the "Monoamine Theory of Depression" [3]. Unfortunately, only 30–40% of patients with MDD achieve remission after conventional monoamine antidepressant therapy [4–6], and in the National Institute of Mental Health (NIMH)-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 33% of approximately 4000 MDD participants who received as many as four varying psychotropic treatment combinations did not respond to standard treatment [7]. The failure to respond to two antidepressants of adequate dose and duration defines treatment-resistant depression (TRD) [8].

In recent years, racemic (*R,S*)-ketamine (hereafter referred to as ketamine) and (*S*)-ketamine (esketamine) have revolutionized the treatment of MDD. Ketamine's rapid antidepressant effects manifest within a few hours, as opposed to weeks with conventional antidepressants, and approximately half of individuals with TRD respond to a single ketamine infusion compared to the less than 15% who respond to conventional antidepressants [9]. Though ketamine has been shown to be efficacious in treating TRD [10], acute suicidality [11], and post-traumatic stress disorder (PTSD) [12], its mechanism of action remains unclear.

This review article summarizes the relationship between MDD and the immunoregulatory mechanism of ketamine's antidepressant effects with a focus on the potential role of the complement system in mediating these effects. We conducted a narrative review of available literature up to September 2023 using PubMed and Web of Science. The search terms were as follows: "major depressive disorder," "depression," "cytokine," "complement system", "complement component", "inflammation," "immune," "microglia", "macrophages", "ketamine," "esketamine," "NMDAR," "glutamate receptor," and "glutamate." We included both animal and human studies.

IMMUNOMODULATORY EFFECTS OF KETAMINE IN MOOD DISORDERS

Considerable research has sought to identify ketamine's mechanism of action in mood disorders. The available literature suggests a

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number of pathways that may mediate ketamine's antidepressant effects, including the N-methyl-D-aspartate (NMDA) receptor [13], the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [14], mechanistic target of rapamycin (mTOR) [15], and the opioid pathway [16]. In addition, a convergence of multiple mechanistic pathways may contribute to ketamine's therapeutic effects [17, 18]. Furthermore, studies have proposed an important link between ketamine's mechanism of action in the setting of immune system dysfunction [15]. Given that inflammation is known to play a major role in the pathophysiology of depression, it is important to further investigate alternative neuroimmune pathways in which ketamine may exert its therapeutic effects. Of note, various classic antidepressants have also been shown to regulate immune processes, and these pharmacological agents and their individual mechanisms of action have been widely discussed elsewhere [19–23].

Psychoneuroimmunology is the study of psychological, neuronal, and immune function interactions [24]. Great research strides have been made to further understand the interrelationship between neuronal and immune pathophysiology in neuropsychiatric disorders, bringing us one step closer to identifying novel therapeutic drug targets. "The Macrophage Theory of Depression" hypothesizes that psychological stress, in combination with genetic and environmental factors, leads to the upregulation of inflammatory cytokines, hypothalamic-pituitary-adrenal (HPA) axis abnormalities, and serotonergic dysregulation, ultimately increasing depressive symptoms [25, 26]. In recent years, there have been many advances towards identifying inflammatory biomarkers that can serve as predictors of treatment response, treatment resistance, and predisposition to certain neuropsychiatric disorders and secondary comorbidities, allowing for more efficacious patient-directed therapy. Although its role is not completely understood, it appears that this area of research can help shine light on the various etiologies of mental illness. The following section will summarize ketamine's established anti-inflammatory roles in the periphery and central nervous system, while also providing additional insight into several neuroimmune components that may serve as predictive biomarkers in the field of neuropsychiatry (Table 1). We will conclude with a discussion of the potential role of an alternative neuroimmune pathway – the complement system – on ketamine's therapeutic effects.

Microglia and astrocytes

Microglia and astrocytes are primary CNS immune cells involved in the regulation of neuroinflammation [27, 28]. Studies have shown decreased astrocytic markers – such as glutamate transporter-1 (GLT-1) and glial fibrillary acidic protein (GFAP) – in humans with MDD [29]. Acute administration of ketamine has been shown to normalize decreased levels of GLT-1 and GFAP in mouse models of depression; these findings are hypothesized to be due to the neuronal changes that accompany ketamine-NMDA receptor inhibition [30]. Under pathological inflammatory conditions, microglia have also been implicated in the pathophysiology of depression [31]. For example, lipopolysaccharide (LPS)-induced

Table 1. Ketamine's Effect on Immune System Regulation.

Study Target	Significance	Ketamine's Regulatory Effect
Microglia and Astrocytes	Primary central nervous system cells involved in the regulation of inflammatory responses	Increased astrocyte activation in mouse models [129] Blocked autophagy flux of microglia caused by lipopolysaccharide (LPS) [35]
Infiltrating Immune Cells	Cells involved in cell adherence and migration in the setting of foreign insult	Reduced expression of leukocyte adhesion molecules in rat venules [41] Reduced migration and cell adherence of neutrophils through human umbilical endothelial cell monolayers [42] Increased monocyte activation state in depressed patients [68] Reduced circulating levels of classical pro-inflammatory monocytes in mice [68]
Cytokines	Signaling molecules involved in the upregulation of inflammatory reactions	Downregulated interleukin (IL)-1beta, tumor necrosis factor (TNF)-alpha, and IL-6 levels in the hippocampus of rodents [48] Inhibited early post-operative IL-6 inflammatory levels [49] Preserved post-operative IL-2 levels [50, 51] Attenuated LPS-induced increases in TNF-α, IL6, and IL-8 levels in human whole blood [52] Decreased TNF-α levels in patients with treatment-resistant depression (TRD) [54] Increased IL-6 plasma levels in depressed patients with no association with clinical response [55]
C-Reactive Protein (CRP)	An acute phase protein that serves as a marker of systemic inflammation	Association between CRP and increased glutamate levels in the left basal ganglia [63] No significant change in serum CRP levels between baseline and after ketamine infusion in participants with TRD [54]
Macrophages	Specialized cells of the innate immune system involved in the initiation of inflammatory responses and the removal of foreign substances via phagocytosis	Inhibited LPS-induced TNF-α, IL-1beta, and IL-6 mRNA levels in macrophages [65] Downregulated granulocyte-macrophage colony-stimulating factor (GM-CSF) in major depressive disorder (MDD) patients [67]
T-Cells	Immune regulatory cells that serve as a major component of the adaptive immune system	Suppressed Th17 cell differentiation and proliferation in mouse models of experimental encephalitis [74] Inhibited LPS-stimulated increases of both CD11b and CD16 expression in human neutrophils [77] Inhibited upregulation of CD18 and CD62L cells in activated human neutrophils [76]

microglial activation can result in the overactivation of inflammatory mediators and release of neurotoxins [32], which may result in neuronal damage and progression of neuropsychiatric disease [33]. Evidence also suggests that ketamine plays an inhibitory role in LPS-induced microglial activation [34]. Ketamine was also found to improve LPS-induced depressive-like behaviors and regulate microglial autophagy flux through the high-mobility group box 1 (HMGB1) and receptor for advanced glycation end products (RAGE) pathway in mice [35]. However, another study found that ketamine reversed behavioral effects in mice without mediating or reversing LPS-induced cytokine expression in the brain [36]. Rodent studies have highlighted different mechanisms underlying the therapeutic effects of ketamine enantiomers. For instance, an RNA-sequencing analysis of prefrontal cortex (PFC) samples from mice treated with either (*R*)-ketamine or (*S*)-ketamine showed that transforming growth factor (TGF)-β, an anti-inflammatory molecule known to inhibit excessive microglial activation, might be involved in the differential antidepressant effects of the two enantiomers [37]. Specifically, (*R*)-ketamine, but not (*S*)-ketamine, significantly attenuated social defeat stress-induced reduction in the expression of Tgfb1 and its receptors (Tgfbr1 and Tgfbr2) in the mouse PFC and hippocampus [37]. In addition, microglial depletion using PLX3397 significantly blocked the antidepressant effects of (*R*)-ketamine in social defeat stress susceptible mice [37]. These results demand further investigation into the role of microglial mechanisms mediating ketamine's enantiomer-specific antidepressant effects.

Infiltrating immune cells

Growing evidence suggests the role of immune cells infiltrating the CNS in the pathophysiology of depression. Increases in monocyte and neutrophil levels in the serum [38, 39], and an increase in neuroinflammation as visualized using positron emission tomography (PET) imaging [40], have been reported in individuals with depression. Schmidt and colleagues [41] examined the effects of ketamine on endotoxin-induced leukocyte adherence in rat mesenteric venules and found reduced expression of adhesion molecules in ketamine-treated rats, implicating ketamine's attenuating role in cell adherence and migration in the setting of endotoxin exposure. Furthermore, in LPS-stimulated leukocytes, ketamine significantly reduced the migration and cell adherence of human neutrophils through human umbilical endothelial cell monolayers by nearly half [42]. Evidence also suggests that monocyte activation and monocyte brain infiltration may contribute to the pathophysiology of depression [43]. However, the effects of ketamine on infiltrating cells in individuals with depression requires additional investigation.

Cytokines

Inflammatory cytokines are known to be involved in the pathophysiology of depression [44]. In a meta-analysis that evaluated cytokine concentrations in patients with major depression, depressed patients exhibited significantly higher serum tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 levels compared to non-depressed participants [45]. Yang and colleagues [46] suggested that serum IL-6 may serve as a predictive biomarker of therapeutic response to ketamine in TRD. Moreover, a recent study corroborated the association between elevated IL-6 levels and TRD, finding that low pretreatment levels of fibroblast growth factor 2 were associated with therapeutic response to ketamine [47]. Chronic stress exposure has been shown to upregulate levels of IL-1beta, TNF-α, and IL-6 in the hippocampus of rodents; these levels normalized after ketamine administration [48]. Additionally, a meta-analysis revealed that pre-surgical ketamine administration inhibited early post-operative IL-6 inflammatory response [49], while other studies found that ketamine preserved post-operative IL-2 levels responsible for cellular and humoral immune response [50, 51].

In terms of immunomodulatory effects, ketamine has also been shown to attenuate LPS- induced increases in TNF-α, IL-6, and IL-8 levels in human whole blood [52] and to attenuate increased levels of TNF-α, IL-6, and IL-10 following an Escherichia coli endotoxin challenge in rat models [53]. Decreased TNF-α levels have also been observed after a single ketamine infusion in patients with TRD; these TNF-α levels also correlated with antidepressant efficacy [54]. In contrast, Yang and colleagues [46] found no alterations in serum TNF-α levels post-ketamine administration but did find decreased serum IL-1beta and IL-6 levels. In contrast, increased IL-6 levels were found in the plasma of depressed patients post-ketamine infusion, with no association with clinical response [55]. Cytokines such as IL-1β, IL-6, and TNF-α are known to upregulate the enzyme indoleamine 2,3-dioxygenase (IDO), which converts tryptophan (TRP) into kynurenine (KYN) [56] and further converts KYN into its neurotoxic metabolite, quinolinic acid (QUIN) [57]. Ketamine treatment has been shown to reduce QUIN levels in both clinical and preclinical studies [58]. Ketamine has also been found to regulate levels of adipokines – cytokines released by adipose cells – in individuals with MDD and bipolar disorder experiencing a major depressive episode [59]. It should be noted that although several of the above studies suggested that ketamine may have anti-inflammatory properties, a recent meta-analysis found no statistically significant association between baseline or longitudinal levels of pro-inflammatory markers and response to ketamine [60].

C-Reactive Protein (CRP)

Several clinical studies have associated circulating CRP levels with increased risk for depression [61]. Interestingly, a recent study found that CRP levels were associated with certain phenotypic manifestations of depression, such as changes in appetite and fatigue, underscoring the importance for further symptomatic assessment, as these symptoms may respond to anti-inflammatory therapy [62]. Haroon and colleagues [63] found a significant association between increased plasma CRP levels and increased levels of glutamate in the left basal ganglia, suggesting that therapeutic strategies that target glutamate, such as ketamine, may be efficacious in the treatment of depressed patients with incidental elevated CRP levels. However, the available literature shows no significant change in serum CRP levels between baseline and after ketamine infusion in individuals with TRD when levels were examined at 40 min, 240 min, Day 3, and Day 7 post-infusion [54].

Macrophages

Macrophages comprise the innate immune system and promote inflammatory responses by performing specific tasks in response to foreign pathogen invasion; these tasks include phagocytosis, chemotaxis, and inflammatory cytokine release [64]. Chang and colleagues (2005) investigated the mechanism of ketamine-induced immunosuppression by evaluating mRNA levels of TNF-α, IL-1beta, and IL-6 in murine macrophages. They found that co-treatment with ketamine and LPS significantly inhibited LPS-induced TNF-α, IL-1beta, and IL-6 mRNA levels in macrophages, concluding that ketamine exerts suppressive effects on macrophage function at the transcriptional level [65]. Increased levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) have also been found to be associated with the pathophysiology of depression [66]. Zhan and colleagues (2020) measured peripheral inflammatory cytokine levels, including GM-CSF, in MDD patients post-administration of six ketamine infusions (0.5 mg/kg) over a 12-day period. They found significant downregulation of GM-CSF concentration post-repetitive ketamine administration that correlated with symptom improvement on Days 13 and 26 compared to baseline [67]. Nowak and colleagues (2019) measured the monocyte and plasma cytokine levels of depressed patients without other comorbidities post-ketamine administration and

found significantly higher pro-inflammatory cytokines that were associated with increased circulatory non-classical monocytes (CD11b+CD16brightCD14neg) and increased classical monocyte activation state (CD40 + CD86 +) [68]. Moreover, in-vitro studies revealed that subanesthetic-dose ketamine programmed human monocytes into M2c-like macrophages by generating CD163, MERTK, CD64, and mTOR-associated gene expression [68]. One limitation of the study was that cytokine and monocyte levels in the participants were not controlled by age, gender, body mass index (BMI), or medication.

T-Cells

Th17 cells are a subset of T-helper cells that aid in inflammatory and autoimmune disease [69]. Th17 cells play critical roles in protection against extracellular pathogens such as Staphylococcus aureus and Klebsiella spp by secreting cytokines IL-17, IL-21, and IL-22 [70]. Th17 cells have been shown to be elevated in patients with MDD [71, 72]. It has been hypothesized that the immune regulatory role of Th17 cells may contribute to ketamine's therapeutic effect [73]. Lee and colleagues. (2017) found that ketamine suppressed Th17 cell differentiation and proliferation in mouse models of experimental encephalitis [74]. Interestingly, improvement of depressive symptoms was found in psoriatic patients with moderate-severe depression status post-treatment with IL-17A antibodies [75], suggesting that Th17 cells may serve as a potential therapeutic target in MDD. A few studies have investigated the effects of ketamine on the immunosuppression of CD11b, CD16, Cd18, and CD62L [76, 77]; these T-cells are involved in cell adhesion, migration, and bacterial phagocytosis. These results are encouraging, as they emphasize ketamine's ability to not only regulate innate immune system components in patients with psychiatric illness, but also in patients who may have psychiatric illness with medical comorbidities.

It is important to note that most of the initial studies using ketamine as an anti-inflammatory drug were conducted in the field of anesthesiology. In major surgery or sepsis, ketamine was used to modulate proinflammatory cytokines that are known to cause undesirable effects, such as shock, hypotension, and multiple organ failure [78]. The mixed evidence regarding ketamine's anti-inflammatory properties as a potential mechanism for its antidepressant effects requires additional investigation into the role of novel immunoregulatory mechanisms underlying the ketamine response.

THE COMPLEMENT SYSTEM AS A POTENTIAL MECHANISM UNDERLYING KETAMINE'S ANTIDEPRESSANT EFFECTS

While a number of recent articles have reviewed the role of various immune pathways in treatment response to ketamine [73, 79–83], no literature review has been conducted exploring the potential association between ketamine and an essential player of innate immunity – the complement system. The complement system plays an important role in innate immune response and serves as a vital component in synaptic plasticity [84]. The complement system consists of more than 30 proteins that act via receptors to regulate the growth, maturation, and responsiveness of cell populations [85]. Complement activation results in the production of both complement and various immune molecules that participate in many inflammatory reactions.

The complement pathway can be divided into three major pathways: the classical pathway, the lectin pathway, and the alternate pathway, all of which converge on the cleavage of C3, the major complement component. The classical pathway begins when the recognition molecule C1q binds to immune complexes (ab-ag complexes). C1q-initiated activation of the associated serine proteases C1r and C1s results in the cleavage of C2 and C4, which generates the C3 convertase C3b2b. C3 cleavage activates downstream complement signaling components [86]. The lectin pathway is analogous to the classical pathway, except that the initiating step is the binding of mannose-binding lectin (MBL) to mannose residues on microbial surfaces. The activation of MBL-associated serine proteases (MBL serine protease 1 (MASP1) and MASP2) results in the cleavage of C4 into the C4 convertase, C4b2b. The alternative pathway acts as an amplification loop of C3b. All complement pathways cleave C3 into activated components C3a and C3b. C3a then uses its seven-transmembrane domain receptor, C3aR, to regulate inflammatory signaling [87, 88].

Glucocorticoids, known to play a major role in stress-induced changes in neuroplasticity, have been shown to modulate complement components in human monocytes, with dexamethasone increasing synthesis of C1 inhibitor, factor B, and C2, but decreasing synthesis of C3 [89]. TNF-α has been shown to upregulate C3 activation during the acute stress response in hepatocytes [90]. Shavva et al. [91] found that nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase kinase 1/2 (MEK1/2) indirectly upregulated C3 expression via TNF-α-induced C3 activation in human hepatoma cells; additionally, hepatic nuclear factor 4-alpha (HNF4-alpha) was found to act individually and in combination with TNF-α to upregulate C3 transcription.

In the brain, C3 is expressed primarily by astrocytes, and C3 receptors are present on microglia. In postnatal neuronal development, complement system components have been shown to contribute to neurogenesis and early neuronal functions in mice, such as progenitor cell migration and differentiation [92], in addition to unwanted synapse elimination [86]. Furthermore, Lian and colleagues (2015) found that in neurodegenerative conditions, NF-κB promotes neuronal-glial interaction by mediating C3 expression in astrocytes, which may suggest an extended functional role of C3 in postnatal neuronal development to the adult brain [93]. In summary, complement system components can express themselves through a variety of physiological and pathological stress conditions, resulting in neuroimmune modulation implicated in many neuropsychiatric disorders, such as MDD [94]. Moving forward, we will discuss some potential ways in which the complement system's neuroimmune stress response may contribute to ketamine's mechanism of action in depression.

THE COMPLEMENT SYSTEM AND MOOD DISORDERS

To date, few studies have investigated the role of the complement cascade in neuropsychiatric disorders. Studies have found increased concentrations of serum complement components C3a and C5a in bipolar disorder [95], elevated serum C1q levels in MDD [96], and higher basal plasma levels of C3 (and its breakdown products) and C4 in a cohort of depressed patients [97]. One study was able to differentiate between atypical and melancholic MDD subtypes with corresponding levels of complement C3 [98]. More recently, a significant increase in C3 expression was reported in the PFC of suicidal individuals with depression [87]. In contrast, a recent study by Pillai and colleagues [99] revealed marginally lower complement C3 levels in the cerebrospinal fluid of cognitively intact elderly individuals with MDD; these findings may be explained by an age-dependent mechanistic variant, or by a downregulation of C3 expression via negative feedback from potentially elevated downstream complement components. The complement system can become activated under various stress conditions that may be associated with several pathophysiological processes of depression [100]. Furthermore, in rodent studies, inhibition of complement signaling has been shown to attenuate chronic stress-induced depressive-like behavior in mice [87]. Although there is some evidence to suggest ketamine's role in various immune system pathways, as discussed above, there are currently no known studies evaluating the interaction between

rapid-acting antidepressants and the complement system, underscoring the need for further investigation.

THE COMPLEMENT SYSTEM AND GLUTAMATERGIC MODULATION

The glutamatergic system has long been implicated in the pathophysiology of depression [101], and NMDA receptor modulation has been implicated in synaptogenesis and neuroplasticity [17]. At subanesthetic doses, ketamine's mechanism of action has been associated with ionotropic NMDA receptor antagonism on gamma-aminobutyric acid (GABA)-ergic interneurons, resulting in disinhibition of glutamatergic neurotransmission from pyramidal neurons in the medial prefrontal cortex (mPFC) [102, 103]. Inhibition of NMDA receptor-dependent burst transmission in the lateral habenula – an anti-reward area of the brain found to have mPFC-projecting neurons – resulted in antidepressant-like effects in animals via disinhibition of downstream reward center signaling [104, 105]. Although several studies found glutamatergic involvement in the pathophysiology of depression [106, 107], there is more to be understood about novel pathways that may be involved in mediating this glutamatergic activity.

Some studies have suggested an association between the complement pathway and glutamatergic modulation (Fig. 1). One study revealed C3a to be selectively protective against NMDA excitotoxicity in neuronal-astroglia mixed cultures [108]. Osaka and colleagues [109] reported that C5a protected against glutamate-induced apoptosis in murine cortico-hippocampal neuronal cultures. The same group further corroborated C5a's neuroprotective role against excitotoxicity-induced apoptosis. They found that C5a receptor knockout mice were more vulnerable to excitatory apoptotic injury than wild-type control mice, further implicating C5a's neuroprotective role against glutamate excitotoxicity-induced apoptosis via increased expression and regulation of glutamate receptor subunit 2 (GluR2) [110]. This GluR2 regulation and protection from neurotoxicity ensures proper functionality of AMPA receptors – the mediators of excitatory neurotransmission responsible for synaptic plasticity, neurogenesis, and development of neuronal circuitry. To this end, as glutamatergic modulation serves as a mechanistic commonality between the complement system and ketamine (as discussed above), it would be important to investigate whether complement–NMDA modulation helps mediate ketamine's therapeutic mechanism of action in mood disorders.

COMPLEMENT SYSTEM AND MTOR ACTIVATION

The mTOR signaling pathway is known to be associated with neurogenesis and synaptic plasticity via upregulation of synaptic proteins [15]. Ketamine activates mTORC1 via activation of the brain-derived neurotrophic factor (BDNF) receptor and TrkB, as well as via antagonism of extrasynaptic NMDA receptors. In support, rapamycin-induced mTOR inhibition was found to inhibit ketamine's therapeutic behavioral and molecular effects in animal models, such as upregulating synaptic proteins in the PFC [111, 112]. In contrast to animal models, rapamycin-induced mTOR antagonism in humans has been shown to prolong ketamine's antidepressant effects rather than block them [113]. Recent studies found a link between the complement system and mTOR regulation. For example, in CD4 + T cells, C3a ligand-C3a receptor activation on lysosomes resulted in mTOR activation needed for cell survival [114]. This complement-mTOR activation, in turn, helped modulate multiple stress and metabolic pathways, such as oxidative phosphorylation, cytokine secretion, and inflammasome activation [115]. Kaur and colleagues (2018) investigated how early endosomes – involved in signaling, metabolism, and inflammation [116] – modulate retinal pigment epithelium complement activity in neurodegenerative diseases [117]. In some neurodegenerative disease states, excess ceramide stimulated the expansion of early endosomes in the retinal pigment epithelium. Expanded endosomes then upregulated complement C3 intake, resulting in subsequent cleavage and abnormal mTOR activation as shown in the retinal pigment epithelium of mouse models of early-onset macular degeneration [117]. While these results indicate complement-mTOR regulation during neurodegenerative disease, there is much to be learned about the role of complement-mTOR regulation in neuronal plasticity. Furthermore, because ketamine and the complement system have both been shown to play individual mechanistic roles in mTOR regulation, as discussed above, it would be valuable to understand whether complement-mTOR regulation serves as an important mechanistic pathway in which ketamine exerts its antidepressant effects.

THE COMPLEMENT SYSTEM AND SYNAPTIC PLASTICITY

Synaptic plasticity plays an essential role in most fundamental brain functions, such as the storing and learning of new complex information, in addition to responding and adapting to various stimuli [118]. Reduced dendritic-spine and spine-synapse connectivity in the PFC of post-mortem human brain and in rodent models has been implicated in the pathophysiology of depression and other chronic stress conditions [119–121]. While various novel NMDA antagonists have been associated with the regulation of synaptic plasticity in neuropsychiatric disorders [122], growing evidence also suggests a complement-mediated role in this neurobiological process. During both physiological and pathological states, the complement system helps regulate various neuronal functions such as synaptic pruning [86, 123] and axonal growth [124]. Synaptic pruning is a natural developmental process responsible for neuronal rewiring and elimination of unnecessary excitatory and inhibitory synapses developed during early childhood to make room for the more advanced functional synapses required during adulthood [125]. Although the complement system plays a critical role in neurodevelopment by regulating neurogenesis, neuronal migration, and synaptic elimination, it has been implicated as one of the key mechanisms associated with inflammation-mediated changes in neuronal functions in many neurodegenerative and neuropsychiatric conditions. For example, intensified microglia-induced complement activation has been shown to reduce synaptic count and compromise synaptic wiring in the PFC of individuals with schizophrenia [126, 127]. Furthermore, the synaptic loss seen in Alzheimer's disease has been linked to excessive complement-induced synapse removal in the hippocampus and frontal cortex [128]. This evidence suggests that complement-mediated synaptic regulation may be involved in ketamine's neuroprotective and antidepressant effects in mood disorders.

CONCLUSIONS AND PERSPECTIVES

While the complement system is important for the refinement of synaptic circuits during development, its disruption could lead to impairments in neuroplasticity such as synapse loss in adulthood. This review discussed the important role played by the complement system in the pathophysiology of depression. Given the complement system's role in modulating a number of pathways implicated in ketamine's antidepressant properties, there is reason to suspect a common link between the complement system and ketamine's mechanism of action. The complement system may be able to *complement* ketamine's antidepressant effects via glutamatergic modulation, neuronal function regulation, and mTOR activation (Fig. 1). Due to the heterogeneity in the factors and pathways associated with treatment response to ketamine, future studies should seek to use machine-learning approaches, which

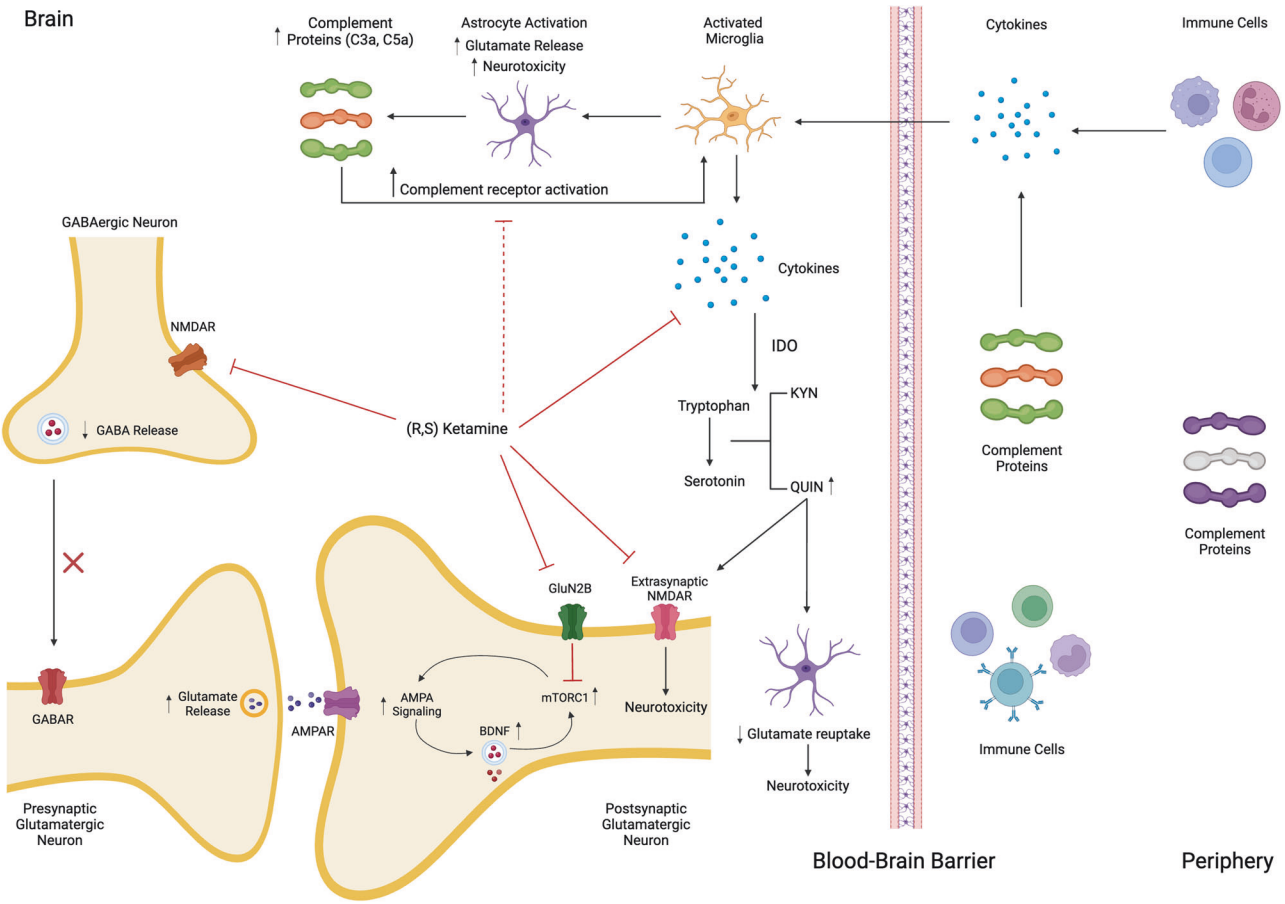

Fig. 1 Proposed immunoregulatory mechanisms of ketamine's antidepressant actions. In the periphery, a number of immune markers including pro-inflammatory cytokines, immune cells, and complement proteins have been associated with major depressive disorder (MDD). In the brain, cytokines entering from the periphery through the blood-brain-barrier activate various neuroimmune cells in the brain, such as microglia. Activated microglia result in the upregulation of cytokines as well as activation of astrocytes, leading to increased production of complement proteins. Complement proteins, in turn, result in increased microglial activation by interacting with receptors such as complement 3a receptor (C3aR), which is present on microglia. Elevated cytokine levels activate the kynurenine pathway by increasing IDO expression, resulting in an imbalance in the production of neuroactive kynurenine metabolites. Increased levels of the neurotoxic metabolite QUIN can inhibit glutamate reuptake from astrocytes and act as an NMDAR agonist, leading to glutamate neurotoxicity. Ketamine can reduce neuroinflammation via cytokine inhibition, prevent QUIN from binding to NMDARs, and/or may regulate microglial activation via complement inhibition. GABAR γ-aminobutyric acid receptor, AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, mTORC1 mammalian target of rapamycin complex 1, BDNF brain-derived neurotrophic factor; NMDAR N-methyl-D-aspartate receptor, IDO Indoleamine 2,3-dioxygenase, KYN Kynurenine, QUIN Quinolinic acid. Created with BioRender.com.

may provide a unique and effective method for understanding the network of molecular pathways. Such studies will enable additional insights into specific biomolecular drug targets that may aid in the treatment of depression.

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AUTHOR CONTRIBUTIONS

BQ prepared the initial manuscript draft. AP and CAZ edited the manuscript. All authors had an opportunity to review and provide input on the final manuscript.

COMPETING INTERESTS

AP received research funding support from Acadia Pharmaceuticals. Dr. Zarate is a full-time U.S government employee. He 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 disorder. 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. Dr. Quintanilla has no conflict of interest to disclose, financial or otherwise.

ADDITIONAL INFORMATION

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