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Crosstalk Between Inflammation and Glutamate System in Depression: Signaling Pathway and Molecular Biomarkers for Ketamine's Antidepressant Effect

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Abstract

Depression is a worldwide illness with a significant impact on both family and society. Conventional antidepressants are ineffective for more than 30% of patients. In such patients, who have what is called treatment-resistant depression (TRD), inflammatory biomarkers are expressed excessively in both the central nervous system (CNS) and the peripheral blood. Ketamine, a glutamate receptor antagonist, exerts a rapid and sustained therapeutic effect in patients with TRD. Thus, the investigation of the relations between inflammation and glutamate underlying depression has drawn great attention. Inflammation influences glutamate release, transmission, and metabolism, resulting in accumulated extracellular glutamate in the CNS. Downstream of the glutamate receptors, the mammalian target of rapamycin (mTOR) signaling pathway plays a key role in mediating ketamine's antidepressant effect by improving neurogenesis and plasticity. Based on the mechanism and clinical evidence of the inflammatory contribution to the pathogenesis of depression, extensive research has been devoted to inflammatory biomarkers of the clinical response of depression to ketamine. The inconsistent findings from the biomarker investigations are at least partially attributable to the heterogeneity of depression, limited sample size, and complex gene–environment interactions. Deep exploration of the clinical observations and the underlying mechanism of ketamine's antidepressant response can provide new insights into the selection of specific groups of depressed patients for ketamine treatment and to aid in monitoring the therapeutic effect during antidepressant medication. Further, targeting persistent inflammation in patients with TRD and the key molecules mediating ketamine's antidepressant effect may encourage the development of novel therapeutic strategies.

Keywords Biomarkers · Depression · Inflammation · Major depressive disorder · Treatment-resistant depression

Introduction

Depression is a widespread psychiatric disorder, creating the third most common global disability burden among non-fatal diseases, and is expected to be the most common cause of disability by 2030 [1]. In the past two decades, great effort has been exerted to develop antidepressant drugs, primarily by targeting the monoaminergic system. However, conventional antidepressant drugs are effective in only about 50% of patients who have major depressive disorder (MDD), and the drugs require weeks to months of use to relieve the syndrome. Such a slow recovery process is a significant risk factor for

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patients with suicidal tendencies [2]. Thus, developing a fast-acting drug with alternative antidepressant mechanisms has drawn great attention.

Ketamine is effective in a great proportion of patients with treatment-resistant depression (TRD) and has the advantage of a rapid onset of action [3–6]. Patients with TRD exhibit higher concentrations of inflammatory markers than those responding to conventional antidepressants [7, 8]. The expression of inflammatory molecules has been associated with antidepressant responsiveness [9–11]. Ketamine is a glutamate antagonist, and inflammatory markers in the peripheral blood are linked to the glutamate concentration in the basal ganglia [12], which has been implicated in the pathophysiology of mood disorders [13]. Therefore, great attention has attended the identification of inflammatory biomarkers for the antidepressant effect of ketamine. For example, the pro-inflammatory cytokines interleukin-6 (IL-6), IL-1β, and tumor necrosis factor (TNF)-α have been investigated as predictive biomarkers for ketamine's antidepressant efficacy in patients with TRD [14–16]. Given the clinical significance of ketamine's antidepressant effect in patients with elevated inflammation, as well as its potential adverse effects, identification of biomarkers and understanding of the mechanism underlying the antidepressant action of ketamine are of great importance. This review describes the interplay between inflammation and glutamate signaling in depression and the therapeutic effect of ketamine using evidence from clinical studies and animal experiments, depression signaling pathways, and molecular biomarker development.

Depression and Inflammation

The inflammation hypothesis of depression was developed on the basis of the finding that higher concentrations of circulating pro-inflammatory molecules induce and sustain depressive symptoms [17]. The contribution of inflammation to these symptoms has gained support from multiple sources [8, 18, 19]. First, the expression of inflammatory markers such as pro-inflammatory cytokines and their soluble receptors, chemokines, and acute-phase proteins is elevated in the peripheral blood and cerebrospinal fluid (CSF) of patients with MDD [7, 8, 18–20]. In 2009, a meta-analysis reported by Howren et al. [21] revealed the positive correlation between MDD and the expression of C-reactive protein (CRP; $p < 0.001$), IL-6 ($p < 0.001$), IL-1 ($p = 0.03$), and IL-1 receptor antagonist (IL-1RA; $p = 0.02$) in the peripheral blood. Later, another meta-analysis of 24 studies showed a significant association between MDD and the pro-inflammatory cytokines IL-6 ($p < 0.00001$) and TNF-α; $p < 0.00001$) [22]. A recent meta-analysis carried out by Haapakoski et al. [23] confirmed the association between MDD and the expression of IL-6 ($p < 0.0001$), CRP ($p < 0.0001$), and TNF-α ($p = 0.002$), making them the most reliable inflammatory biomarkers in MDD [8]. In addition, depression is a major factor in suicide. Increased pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, were detected in the postmortem brains of teenage suicide victims compared with normal subjects [24]. In the postmortem brains of depressed suicide victims, the cardinal innate immune receptors Toll-like receptor 3 (TLR3) and TLR4 also are overexpressed [25]. Second, the high comorbidity between depression and inflammation-related diseases, such as acquired immunodeficiency syndrome (AIDS), cardiac disease, inflammatory bowel disease, and cancer, have been revealed by independent studies [26, 27]; and people with conditions linked to inflammation, such as childhood trauma, obesity, and inflammatory disease, show less responsiveness to antidepressants [9, 28–30]. A recent meta-analysis of high-quality in vivo studies revealed that the baseline composite measure of peripheral inflammation is significantly higher in non-responders to antidepressant treatment ($p = 0.009$) [30]. Also, the amount of TNF-α is significantly reduced in responders to antidepressant treatment ($p = 0.008$) but not in non-responders ($p = 0.9$) [30].

Another line of evidence for the inflammatory contribution to depressive symptoms came from the administration of relevant stimuli. Administration of IFN-α or endotoxin triggers depression in humans [31–35], whereas blockage of pro-inflammatory cytokines relieves depressive symptoms [11, 36–38]. For example, immunotherapy with IFN-α induced depressive symptoms in patients with malignant melanoma, as measured by Hamilton Depression Rating Scale (HAM-D) scores, and the effect was significantly reduced in comparison with the placebo group by antidepressant drug administration [31]. In another randomized placebo-controlled study, lipopolysaccharide (LPS) triggered a depressed mood, as measured by an abbreviated version of the Profile of Mood States, as well as significant IL-6 and TNF-α expression in the peripheral blood [34]. On the other hand, infliximab, a TNF-α antagonist, particularly benefited TRD patients with high inflammation [7]. Besides, in cancer patients receiving docetaxel, which induces fatigue (one of the most prevalent MDD symptoms), the TNF-α decoy receptor etanercept significantly reduced fatigue and increased tolerance for higher-dose docetaxel treatment [38].

Inflammatory molecules have been investigated extensively as biomarker candidates to predict the response to conventional antidepressants [39, 40]. The baseline concentrations of pro-inflammatory cytokines, such as IL-6, TNF-α, macrophage-inhibiting factor (MIF), and IL-1β, were significantly higher in antidepressant non-responders than in responders in various studies. These cytokines thus may be therapeutic targets and predictors of the response to conventional antidepressants [41, 42]. Moreover, the changes in pro-inflammatory cytokines during antidepressant administration correlate with the treatment response. Among depressed

patients, the serum concentrations of IL-6 and TNF-α were significantly lower in responders to antidepressant drugs, whereas the changes in these two cytokines were either not significant or were in the opposite direction in non-responders [9, 42]. In addition, a significant association has been detected between genetic polymorphisms in inflammatory molecules, such as IL-6, IL-1β, and TNF-α, and the pathogenesis of MDD as well as the responsiveness to antidepressant treatment [43–46]. Together, these findings suggest that inflammatory molecules are good candidates for both predictors and indicators of the therapeutic effects of antidepressant drugs, improving the "personalized medicine" approach.

Interplay of Inflammation and Glutamate in Depression

The glutamatergic system in the limbic area plays a key role in mood disorders, including MDD, through alterations of neurogenesis and neuroplasticity [13]. Glutamate release/transmission dysregulation is one of the major contributors to depression and is involved in the mechanism of antidepressant action [13]. The glutamate contribution to MDD is supported by the therapeutic effect of ketamine, a glutamate receptor *N*-methyl-D-aspartate (NMDA) antagonist, in depressed patients [4, 47, 48]. Multiple randomized placebo-controlled trials proved that a sub-anesthetic dose of ketamine (5 mg/kg over 40 min) provides a significant antidepressant effect in patients with MDD [5, 49]. Rapid reduction of suicidal tendencies also has been observed after a single infusion of ketamine [50]. In animal studies, administration of ketamine immediately before LPS delivery completely blocked the endotoxin-induced suppression of sucrose preference, a typical depressive-like behavior in mice [51, 52]. On the other hand, inflammatory cytokines can alter glutamate metabolism, and the response to ketamine is associated with the degree of inflammatory cytokine expression in the peripheral blood, indicating a convergent contribution of inflammation and glutamate to depressive symptoms [53, 54].

Inflammation affects glutamate release and transmission as well as metabolism and leads to an excessive extracellular concentration in the CNS [53, 54]. Pro-inflammatory cytokines and free radicals reduce the expression of glutamate transporters on glial cells, reducing glutamate uptake [55]. Also, the inflammatory context enhances glutamate expression and release from astrocytes [56]. The elevated glutamate concentration in the extrasynaptic space then preferentially binds to NMDA receptors, leads to suppression of synthesis and release of brain-derived neurotrophic factor (BDNF), which is a crucial mediator of neuroplasticity [7, 57]. Synaptic and extrasynaptic NMDA receptors have different effects on neuroplasticity and neurogenesis. Activation of synaptic NMDA receptors leads to neuroprotection, whereas stimulation of extrasynaptic NMDA receptors results in neuronal dysfunction, which may contribute to depression [57, 58]. Although ketamine is an NMDA receptor antagonist, not all NMDAR antagonists can trigger the same sustained antidepressant action [3, 59]. As assessed by a mouse forced swim test, alternative NMDAR antagonists MK-801 and Ro25-6981 provided only a short-term antidepressant effect, which was markedly blocked by pre-treatment with 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo (F)-quinoxaline (NBQX), an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antagonist [8]. Zanos et al. demonstrated that the therapeutic effect of ketamine depends on its metabolite hydroxynorketamine (HNK) [59]. In mice, the HNK-induced antidepressant actions were independent of the blockage of NMDA receptors, whereas they were associated with sustained activation of AMPA receptors [59]. On the other hand, pro-inflammatory cytokines, such as TNF-α and IL-6, can activate indoleamine-2,3-dioxygenase (IDO), which degrades the precursors of monoamine neurotransmitters and ultimately causes build-up of a greater concentration of quinolinic acid (QUIN), a powerful NMDA receptor agonist [60, 61] (Fig. 1). Interestingly, the NMDA receptor antagonist ketamine significantly altered LPS-induced depressive behaviors in mice, which also are mediated by IDO, without affecting inflammatory cytokine expression [51, 52]. The immunemodulatory effect of ketamine has been investigated by several independent studies [62, 63]. When given at induction of anesthesia, ketamine (0.25 mg/kg) significantly reduced peripheral IL-6 after cardiopulmonary bypass (CPB) [64]. In a rat model, ketamine administration decreased the expression of both IL-6 and IL-1β in the prefrontal cortex and hippocampus compared with the saline-treated group ($p < 0.05$), a change associated with reduction of depressive behavior [65]. Given the correlation between inflammatory markers and glutamate concentration in the CNS [12] as well as the responsiveness to conventional antidepressants [9, 42], inflammatory markers may guide the selection of those depressed patients who will benefit from ketamine.

Signaling Pathways Underlying Ketamine's Inflammation-Related Antidepressant Effect

The stress-caused synaptic atrophy in the limbic system, including the hippocampus and prefrontal cortex (PFC), has been implicated in the pathogenesis of depression [66, 67]. During inflammation, the overexpressed cytokines interfere with the synthesis, release, and transmission of glutamate as well as with the kynurenine pathway, resulting in a higher concentration of extracellular glutamate in the limbic system [12, 53, 68]. Both NMDARs and AMPARs are glutamate receptors expressed on the post-synaptic membrane and are involved in the pathogenesis of depression as well as in

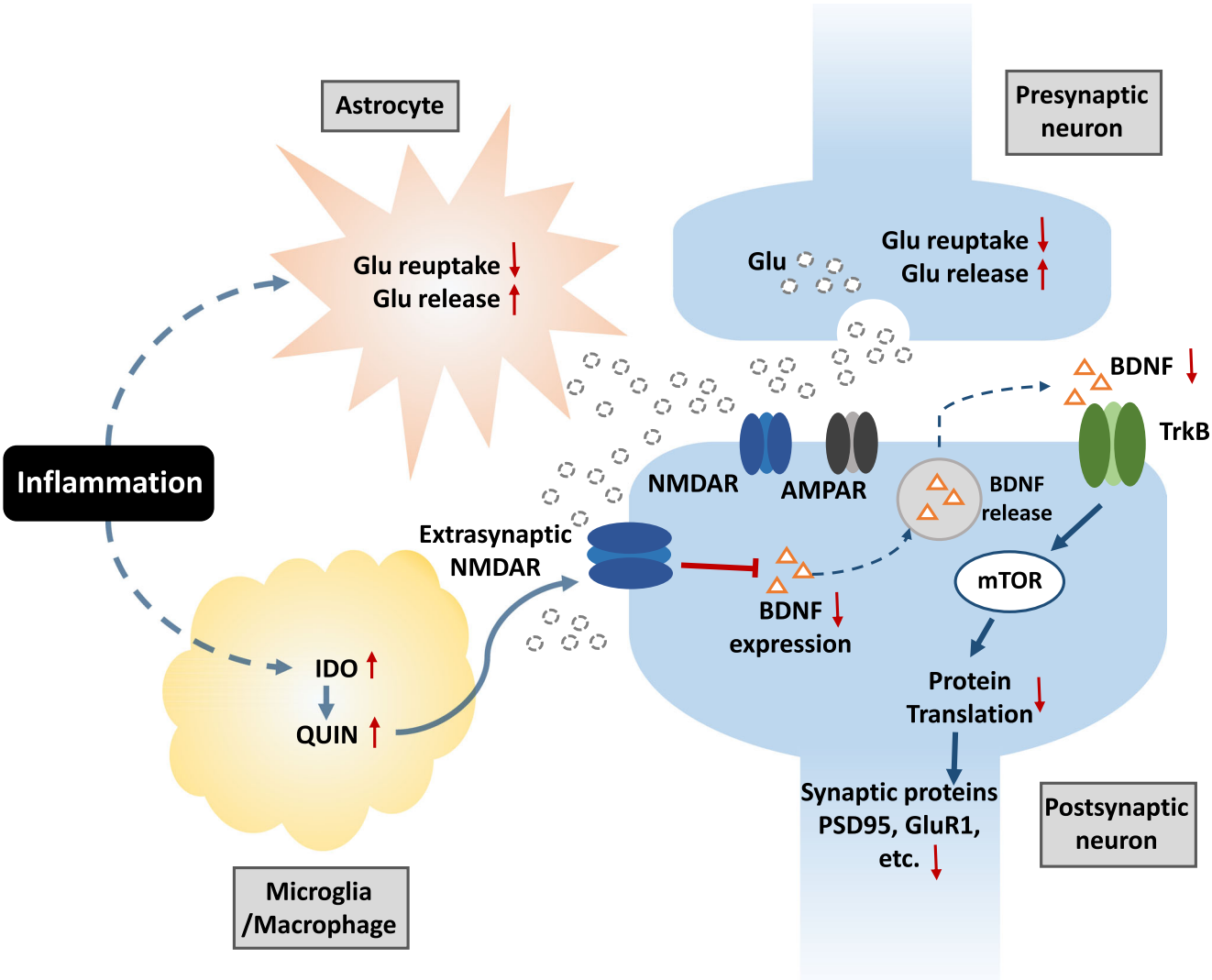

Fig. 1 Inflammatory regulation of the glutamatergic system contributing to depression. Higher concentrations of inflammatory markers, such as IL-6 and TNF-α, result in glutamate accumulation in the CNS by regulating glutamate expression and transmission. Activation of IDO by inflammation leads to upregulation of QUIN. Both QUIN and glutamate are NMDARs agonists. The activation of extrasynaptic NMDARs leads to downregulation of BDNF synthesis as well as of other synaptic proteins and ultimately contributes to synaptic atrophy

antidepressant action [69, 70]. The elevated amount of glutamate is believed to interact primarily with extrasynaptic NMDA receptors and consequently to suppress the mTOR signaling pathway. This process results in decreased neurogenesis and synaptic plasticity, eventually causing depression [71]. Ketamine can block NMDA receptors, and its therapeutic effect is dependent on AMPA receptors [72].

So far, studies on the pathways controlling neurogenesis and synaptic plasticity have focused mainly on learning and memory models. Those studies revealed that long-term memory is dependent on the protein synthesis mediated by mTOR [73–75]. In neurons, the mTOR pathway processes different synaptic signals, such as glutamate and neurotrophins, to regulate protein expression during neurogenesis [76]. In a postmortem study, a significant reduction in mTOR signaling was found in patients with MDD compared with controls, further emphasizing the important role of mTOR in depression [77].

There are two types of mTOR-containing complexes: 1 (mTORC1) and 2 (mTORC2). The former can transfer synaptic signals from AMPA and neurotrophin receptors through PI3K/AKT and TSC1/2 to downstream molecules 4E-BPs and S6K1/2, regulating neuronal protein translation, such as production of BDNF, whereas the latter is involved primarily in the regulation of cytoskeletal dynamics [75]. The binding of glutamate to NMDA receptors can suppress the mTOR pathway [78–80]. To be specific, the activation of NMDA leads to de-phosphorylation of PKB, and the inhibition of PKB/AKT and ERK increases the activity of TSC1/2, which suppresses the mTOR signaling pathway [78, 79]. The NMDA receptors also can activate glycogen synthase kinase 3 (GSK-3), another inhibitor of the mTOR pathway [80] (Fig. 2). BDNF, a major

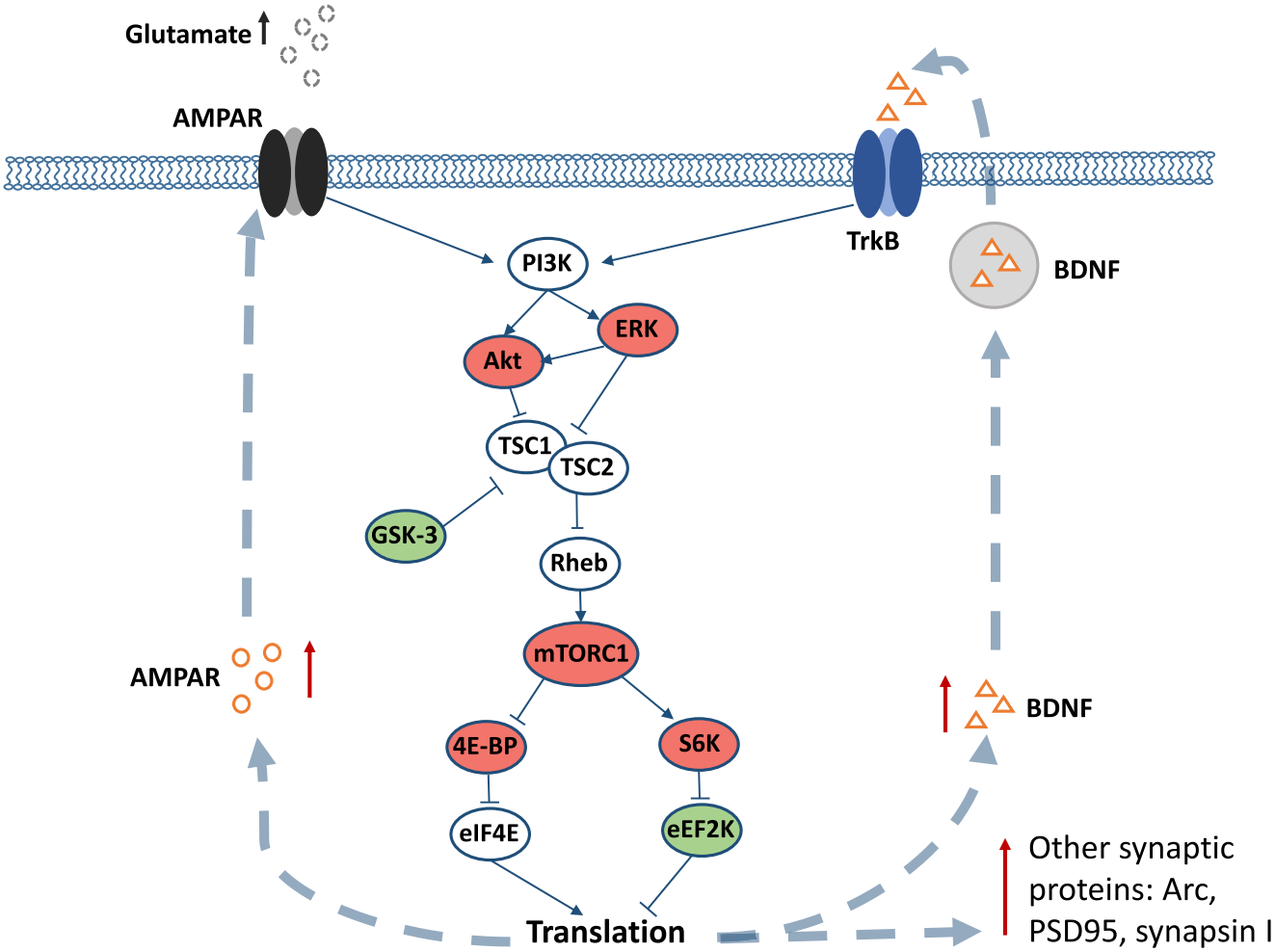

Fig. 2 Activation of mTOR pathway by ketamine. As an NMDAR antagonist, ketamine blocks the extrasynaptic NMDA pathway and forces the binding of glutamate to AMPARs, which rapidly activates the mTOR pathway, leading to greater expression of synaptic proteins as well as BDNF. This creates a positive feedback loop amplifying the antidepressant action of ketamine. In this figure, the molecules reported to be upregulated or activated by ketamine are shown in red, whereas the suppressed molecules are in green

product of the mTOR pathway, is an essential mediator of neural plasticity, given its abundance in plasticity-related brain regions and the significant association between its expression and neuron transmission activities as well as plasticity [81]. The protein's action in the etiology of major depression and in the antidepressant drug response has been well characterized [82–84]. Reduced BNDF expression has been identified in the hippocampus and PFCs of postmortem brains from persons who committed suicide [85], as well as in the brains from animal models of depression [86, 87]. During inflammation, such as in the LPS-induced depressive rat model, BDNF was decreased in the hippocampus in association with anxious and depressive behavior [88], whereas elevated expression of BDNF was detected after antidepressant treatment [89, 90]. Thus, BDNF is suggested to be a bridge between inflammation and neuroplasticity in depression [91].

Ketamine exerts its antidepressant effect by rapid activation of the mTOR pathway, as well as increased BDNF expression and synaptic plasticity in PFCs and the hippocampus [92–96]. Its therapeutic effect is dependent on the activation of AMPA receptors [3, 59]. Treatment with the AMPA receptor antagonist NBQX significantly attenuates ketamine's antidepressant effect in mice, as measured by the forced swim test (FST) [3]. In addition, ketamine can upregulate the expression of AMPA subunits GluA1 and GluA2 in the hippocampus and PFC in rats [59, 97, 98], and AMPARs further activate mTOR signaling. Administration of ketamine to mice significantly induced GSK-3 phosphorylation [94]. This action decreased GSK-3 activity and resulted in a rapid antidepressant-like effect of ketamine in the mouse model of learned helplessness, whereas the mice expressing constitutively active GSK-3 failed to respond to ketamine, suggesting an essential role of GSK-3 phosphorylation in ketamine's antidepressant effect [94]. Administration of a low dose of ketamine (10 mg/kg) into the PFC region of rats induced transit phosphorylation and activation of the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), ribosomal protein S6 kinase B1 (p70S6K), mTOR, ERK1/2, and PKB/Akt, which activate or

reflect the activation of the mTOR pathway [99]. Also, ketamine promotes sustained expression of PSD95 and synapsin 1, which play important roles in mature synapse formation [99]. Ketamine's rapid action is dependent on the inhibition of eEF2K, which phosphorylates eEF2 and consequently induces BDNF translation [100, 101]. In mice, ketamine administration also triggers the expression of BDNF and ARC mRNA, as well as the phosphorylation of TrkB, a BDNF receptor, in the hippocampus [102]. Moreover, as assessed with the FST in mice, the antidepressant effect of ketamine is blocked by infusion of BDNF-neutralizing antibody into the medial prefrontal cortex (mPFC) [103]. Consistently, ketamine's antidepressant action is abrogated in BDNF- and its receptor TrkB-knockout mice, indicating that the sustained antidepressant effect of ketamine is dependent on BDNF [102].

Taking these findings together, we can conclude that ketamine exerts its antidepressant effect by blocking NMDARs and activating AMPARs, actions which trigger the mTOR signaling pathway and thus induce expression of multiple synaptic proteins as well as BDNF. Synaptic proteins contribute directly to the neuro-formation process, while the secreted BDNF interacts with its receptor TrkB, inducing further activation of the mTOR pathway and AMPA receptor expression. This process creates a positive feedback loop that amplifies the antidepressant signal. The effect of fast activation of the mTOR pathway includes increasing synaptic protein expression and spine number in the PFC region, resulting in upregulation of 5-HT neurotransmission, which contributes to the rapid and sustained antidepressant effect of ketamine [2]. Further studies on the mechanism underlying ketamine's selective activation of AMPA receptors and rapid stimulation of mTOR signaling will provide valuable targets for the development of novel antidepressant drugs.

Molecular Biomarkers for Depression and Treatment Response to Ketamine

During the last decade, numerous studies have been carried out to discover genetic markers for depression and antidepressant responses. Various polymorphisms associated with depression and the treatment response have been identified in inflammatory genes [104]. Among these molecules, IL-1β, IL-6, TNF-α, and C-reactive protein (CRP) have been well-replicated and are the mostly relevant (Table 1). Increased concentrations of those molecules in the peripheral blood of MDD patients have been confirmed by meta-analysis [21, 23, 122]. Importantly, multiple SNPs on those genes were reported to be associated with both depression and treatment response [43]. As an important mediator between inflammation and neuroplasticity, BDNF also has been investigated extensively as a potential biomarker for depression and antidepressant effect. In this section, we focus on the expression changes in these molecular markers during depression and ketamine treatment, as well as the associated polymorphisms reported in at least three independent studies.

IL-6 Interleukin-6 is one of the best-documented pro-inflammatory markers involved in depression. Using meta-analysis, an elevated peripheral IL-6 concentration has been demonstrated in patients with MDD [21, 23, 122]. The protein also is suggested to be a predictor of the antidepressant effect of ketamine [14]. In an animal study, ketamine administration reduced IL-6 in rat PFC and hippocampus [65]. A clinical study involving 16 patients with MDD and 24 matched healthy controls indicated that the baseline serum concentration of IL-6 is significantly higher in ketamine responders (dose 0.5 mg/kg) than in controls and non-responders, whereas no significant difference was detected between the control and non-responder groups. Moreover, the serum concentration of IL-6 decreased significantly at 230 min to 3 days after ketamine injection in the responder group ($p < 0.001$), but not in non-responders [14]. In a recent study involving 33 patients with TRD and 26 healthy controls [15], serum IL-6 expression was significantly higher in the patients ($p = 0.004$). After 4 h of treatment with ketamine (0.5 mg/kg), IL-6 had decreased significantly from the baseline in the patients ($p < 0.05$), and this change diminished by 24 h. However, no association between IL-6 changes and the ketamine response was observed at any time. Also, no significant difference was detected in IL-6 between ketamine responders and non-responders [15]. In another study of 80 patients with treatment-resistant MDD or bipolar depression (BD) [16], IL-6 expression was transiently increased 4 h after ketamine infusion ($p < 0.001$), which was in the opposite direction from the studies reported by Yang et al. [14] and Kiraly et al. [15]. No significant correlation was detected between the changes in IL-6 at 4 h and depression severity [16]. It appears that ketamine can alter IL-6 expression rapidly, but further study is needed to characterize the influence of the baseline IL-6 concentration on ketamine's antidepressant effect as well as the association between IL-6 expression and depression measurements during ketamine medication (Table 2).

The rs1800795 (G-174C) SNP in IL-6 has been associated with depression symptoms in multiple independent studies [106, 110–113, 115]. During IFN-α and ribavirin treatment for chronic hepatitis C virus infection, individuals with the rs1800795 GG genotype, which is linked to high IL-6 expression, exhibit more severe depressive symptoms [110]. This finding was confirmed by an independent report in which individuals with the CC genotype showed less depression and anxiety after IFN-α induction [111]. After controlling for gene × gene interaction with DRD2 rs224592, Roetker et al. [113] discerned that women with homozygous genotypes in rs1800795 (CC or GG) have a higher depression risk than heterozygous individuals. During chronic interpersonal stress,

Table 1 Most highly investigated inflammatory genetic markers associated with depression

Gene	SNP	Alleles (A1/A2) [a]	Phenotype (Measurement)	Sample description	Sample size			*P* value	Reported findings	Ref.
					Cases	Controls	Total			
IL-1β	rs16944	T/G	Depression (age of onset)	Elderly MDD inpatients and normal elderly controls	125	282	407	0.021	Individuals with TT genotype have a significantly later age of depression onset (by 7 years)	[105]
			Depression (HAM-D score)	MDD patients and controls	157	112	388	0.012	The baseline total HAM-D score is different among the three genotypes	[46]
								0.029	The score on "early insomnia" is different among the three genotypic groups	
								< 0.05	Individuals with the TT genotype have a significantly lower baseline total HAM-D score and "early insomnia" score than C allele carriers	
			Depression (Beck Depression Inventory-II [BDI-II] score)	Australian youth subjected to chronic stress	–	–	444	0.022	Rs16944 is associated with depression severity in youth suffering chronic interpersonal stress. Individuals with TT genotype have marginally significant decrease in severe depressive symptoms than TC ($p = 0.060$) and CC ($p = 0.053$) genotypes	[106]
			Depression (Brief Symptom Inventory [BSI])	European volunteers	–	–	1053	0.0043~1.91 × 10^{-6}	T allele is associated with increased anxiety and depression by interacting with childhood adversity	[107]
			Depression (DSM-IV)	Taiwanese MDD patients and healthy controls	189	106	295	> 0.05	No association was detected between rs16944 and MDD	[108]
			Antidepressant response (HAM-D score)	MDD patients	256	–	256	0.02	Rs16944 was significantly associated with non-remission after 6 weeks of antidepressant treatment in the overall sample	[109]
								0.03	Subjects with GG genotype in rs16944 have a higher risk of non-remission than individuals with the AA genotype	
								0.00007~0.026	The number of A alleles is positively associated with responsiveness of the amygdala and ACC to emotional stimuli as revealed by brain imaging	
IL-6	rs1800795	G/C	Depression (BDI-II score)	Australian youth subjected to chronic stress	–	–	444	0.02	Significant association between rs1800795 and depression in youth after chronic interpersonal stress exposure	[106]
								0.02	Individual with GG genotype have fewer depressive symptoms than CC carriers	
			Depression (Beck Depression Inventory and Zung Self-Rating Depression Scale [SDS])	Chronic hepatitis C virus (HCV)-infected patients receiving PEGylated IFN-alpha and ribavirin	–	–	98	0.002	The CC genotype, which is linked to low IL-6 expression, is associated with fewer depressive symptoms	[110]
			Depression and anxiety (Hospital Anxiety and	HCV-infected patients treated with IFN-α and ribavirin	–	–	385	0.005 0.004	Individuals with the CC genotype have smaller changes of the HADS scale rate	[111]

Table 1 (continued)

Gene	SNP	Alleles (A1/A2) [a]	Phenotype (Measurement)	Sample description	Sample size			*P* value	Reported findings	Ref.
					Cases	Controls	Total			
			Depression Scale [HADS])						from baseline in IFN-induced depression ($p = 0.005$) and anxiety (p = 0.004)	
			Depression (Zung Self-Rating Depression Scale [(ZSDS] and Brief Symptom Inventory [BSI])	European volunteers	–	–	1053	$0.015 \sim 2.86 \times 10^{-5}$ $0.021 \sim 7.42 \times 10^{-4}$	The interactions between rs1800795 and RLE have significant influence on depression symptoms, as assessed by BSI and ZSDS The interaction between the Pain Background (PBGR) and rs1800795 is significantly associated with ZSDS	[112]
			Depression (Composite International Diagnostic Interview Short-Form)	Randomly selected high school graduates and siblings.	713	4098	4811	0.006	After controlling for gene–gene interaction with DRD2 rs224592, women with homozygous genotypes in rs1800795 (CC or GG) have a higher depression risk than heterozygous individuals	[113]
			Childhood depression (DSM-IV)	384 families with a child found to have depression before age 15	–	–	460 children and their parents	> 0.05	No significant association was detected between early-onset depression and rs1800795	[114]
			Depression, bipolar (DSM-IV)	Patients with BD or MDD and healthy controls	82	360	442	0.048 > 0.05	BD subjects with CC genotype have an earlier age of onset than G allele carriers No significant association was detected between depression and rs1800795	[115]
TNF-α	rs1800629	G/A	Depression, bipolar (DSM-IV)	Patients with BD or MDD and healthy controls	82	360	442	< 0.001	The percentage of A allele carriers is significantly different among MDD, BD I, BD II, and control groups. Notably, no A allele carrier was found in the BD II group	[115]
			Depression (Geriatric Depression Scale [GDS])	Elderly people with MDD without dementia and age-matched healthy controls	50	240	290	0.007 0.05	The percentage of patients with the GG genotype is significantly higher in those with depression than in controls ($p = 0.007$), as is the frequency of the G allele ($p = 0.05$)	[116]
			CES-D score	Oncology patients and their family caregivers.	167	85	252	0.007	The odds of A allele carriers is significantly lower in the subsyndromal class than in the resilient class after controlling for age, functional status, ethnicity, and adjacent SNP, rs2229094	[117]
			Childhood depression (DSM-IV)	384 families with a child found to have depression before age 15	–	–	460 children and their parents	> 0.05	No association detected between childhood depression and rs1800629	[114]
			Depression (BDI-II score)	Australian youth subjected to chronic stress	–	–	444	> 0.05	rs1800629 does not affect the influence of stress on depression	[106]
CRP	rs1205	C/T	CES-D score	Elderly people with Mini-International Neuropsychiatric Interview as clinical level of depression (DEP) or non-DEP	259	731	990	0.011 0.02	The odds of depression in women with the TT genotype are significantly higher than in people with the CC genotype The number of T alleles in rs1205 is negatively associated with circulating concentration of CRP in women	[118]

Table 1 (continued)

Gene	SNP	Alleles (A1/A2) [a]	Phenotype (Measurement)	Sample description	Sample size			*P* value	Reported findings	Ref.
					Cases	Controls	Total			
			CES-D score	Middle-aged volunteers	–	–	868	0.03	C allele carriers have significantly higher expression of CPR than persons with other genotypes	[119]
								0.004	In individuals with A-G-T (rs1417938—rs1800947—rs1205) haplotype, CRP concentration is positively associated with CES-D scores	
								> 0.05	rs1205 is not associated with depressive symptoms	
			Depression and anxiety (HADS)	Elderly Scottish subjects	–	–	1091	< 0.05	rs1205 is significantly associated with anxiety in women.	[120]
									The associated trait of neuroticism/emotional (in) stability was significant or marginal between rs1205 and the NEO ($p = 0.012$)	
								0.012	The anxiety score NEO is significantly associated with rs1205	
			Depressive symptoms (15-item GDS-15)	Men aged ≥ 70 years	182	3518	3700	< 0.001	The number of T alleles is negatively associated with serum CRP concentration	[121]
								0.022	Men with the TT genotype have significantly higher odds of depression than those with the GG ($p = 0.022$) and GT ($p = 0.022$) genotypes	
								0.022		

[a] *A1* ancestral allele, *A2* derived allele

Table 2 Clinical findings for best-investigated inflammatory biomarkers for the antidepressant action of ketamine

Gene	Sample description	Group	Reported direction	*P* value	Ref
IL-6	16 patients with TRD (12 ketamine responders and 4 non-responders) and 24 matched healthy controls	Ketamine responders vs. non-responders (baseline)	Responders > non-responders	< 0.01	[14]
		Ketamine responders vs. controls (baseline)	Responders > controls	< 0.001	
		Ketamine non-responders vs. controls (baseline)	–	Not significant	
		Responders' baseline vs. 4 h to 3 days of ketamine administration	Baseline > ketamine administration	< 0.001	
		Non-responders' baseline vs. ketamine administration	–	Not significant	
	49 MDD and 31 BD patients	Baseline vs. 4 h of ketamine administration	Baseline < ketamine administration	< 0.001	[16]
	33 patients with TRD and 26 healthy controls	Patients with TRD vs. controls	TRD patients > controls	0.004	[15]
		Baseline vs. 4 h of ketamine administration	Baseline > ketamine administration	< 0.05	
		Responders vs. non-responders	–	Not significant	
IL-1β	16 patients with TRD (12 ketamine responders and 4 non-responders) and 24 matched healthy controls.	Ketamine responders vs. non-responders (baseline)	Responders > non-responders	< 0.05	[14]
		Ketamine responders vs. controls (baseline)	Responders > controls	< 0.001	
		Ketamine non-responders vs. controls (baseline)	Non-responders > controls	< 0.001	
		Responders' baseline vs. 4 h to 1 day of ketamine administration	Baseline > ketamine administration	0.013	
		Non-responders' baseline vs. ketamine administration	–	Not significant	
	33 patients with TRD and 26 healthy controls	Patients with TRD vs. controls	–	Not significant	[15]
TNF-α	16 patients with TRD (12 ketamine responders and 4 non-responders) and 24 matched healthy controls.	Ketamine responders vs. non-responders (baseline)	Responders > non-responders	< 0.05	[14]
		Ketamine responders vs. controls (baseline)	Responders > controls	< 0.001	
		Ketamine non-responders vs. controls (baseline)	Non-responders > controls	< 0.05	
	49 patients with MDD and 31 with BD	Multiple time points comparison from baseline to 3 days.	–	0.007	[16]
	33 patients with TRD and 26 healthy controls	TRD patients vs. controls	–	Not significant	[15]

persons who are CC homozygotes exhibit more severe depressive symptoms than G allele carriers [106]. Nevertheless, in a childhood study focusing on early-onset depression and another study examining 82 patients with MDD or BD, no significant association was detected between depression and rs1800795 [114, 115]. Notably, in a gene–environment interaction study, IL-6 rs1800795 polymorphism interacted with various stress factors contributing to the risk of depression. Consistent with previous findings, individuals with the rs1800795 CC genotype had a higher risk of depression under life stress [112].

IL-1β The relation between the IL-1β protein concentration and depression is controversial [21, 23]. A recent ketamine biomarker investigation found that the serum concentration of IL-1β was significantly higher at baseline in responders than in non-responders and controls, and the decrease in IL-1β after ketamine administration was significant only in responders [14]. However, this finding was not replicated in the study reported by Kiraly et al. [15], although the baseline concentration of IL-1RA, which attenuates the pro-inflammatory effect of IL-1, was significantly lower in ketamine responders than in non-responders ($p = 0.033$).

For IL-1β, the most-investigated genetic target is rs16944 (C-511T). In 2003, Yu et al. [46] first reported that the baseline total HAM-D score in MDD is significantly different among the three genotypic groups ($p = 0.012$), with the patients who have the TT genotype having a lower total HAM-D score than patients with C allele (s). Although a study with Taiwanese samples failed to replicate the association between rs16944 and MDD [108], an association study of this SNP with the age of onset of depression in elderly Chinese adults revealed that T-homozygous individuals had a significantly later age of onset than C-allele carriers ($p = 0.021$) [105]. The IL-1β rs16944 also was found to interact with life stress, contributing to depression. In a Hungarian population with a sample size of 1053, the T allele was associated with increased anxiety and depression only in individuals who experienced childhood adversity, but exerted a weak protective effect against depression in individuals exposed to adult life stressors [107]. A recent study by Tartter et al. likewise found that the C allele in rs16944 is associated with more severe depressive symptoms after chronic interpersonal stress [106]. The effect of the polymorphism rs16944 was investigated in relation to antidepressant responses. The homozygous T carriers among MDD patients were claimed to show a better therapeutic response to fluoxetine [46]. Besides, a significant association was detected between the CC genotype and non-remission after 6 weeks of antidepressant treatment [109].

TNF-α Another important pro-inflammatory cytokine is TNF-α. Its expression is significantly higher in patients with MDD than in controls [21, 23, 122]. In a pre-clinical study on antidepressant-like effects of ketamine assessed with FST, animals not responding to ketamine treatment had a significantly higher concentration of TNF-α than did the control group

[123]. In the clinical study reported by Park et al. [16], ketamine significantly altered TNF-α expression in patients with TRD during 3 days of treatment ($p = 0.007$). The expression of soluble TNF receptor 1 (sTNFR1), which antagonizes circulating TNF-α, was induced by ketamine within 4 h ($p < 0.01$). The baseline concentration of sTNFR1 correlated with Montgomery-Asberg Depression Rating Scale (MADRS) scores ($p = 0.003$) [16]. In a rat model of antidepressant resistance, ketamine administration significantly reduced immobility in the FST ($p < 0.05$) [123]. Moreover, the plasma TNF-α concentration was significantly different among experimental groups ($p = 0.0002$), and ketamine non-responders had lower TNF-α expression than did the control group among antidepressant-resistant animals ($p < 0.05$) [123].

Rs1800629 (G-308A) in TNF-α has been linked to depression. In a study of elderly persons, the percentages of GG genotype and G allele were higher in patients with MDD than in healthy controls, with p values of 0.007 and 0.05, respectively, whereas no AA genotype was identified in the patients [116]. Likewise, the percentage of individuals with the GG genotype was significantly higher in patients with BD II than in controls ($p < 0.001$) [115]. Besides, in a cancer study, A allele carriers presented a lower risk of depressive symptoms, as measured by the Center for Epidemiological Studies Depression (CES-D) score [117]. However, contradictory findings have been reported in a Korean MDD study and a childhood depression-onset study [114, 124]. Interestingly, in a gene–environment interaction study on Australian youth, rs1800629 had a marginally significant influence on depressive symptoms by interacting with non-interpersonal stress ($p = 0.08$) [106].

CRP CRP, whose elevated expression has been directly linked to the development of depression [21, 125], is one of the main targets of biomarker studies. In a study involving 60 medically stable patients with TRD, the peripheral CRP concentration of 45% of the individuals exceeded 3 mg/kg [11]. Remarkably, in a pre-clinical study of ketamine's antidepressant effect, a significantly higher concentration of CRP was detected in responders than in the control animals ($p < 0.05$), but not in non-responders [123]. The modulatory effect of ketamine on peripheral CRP expression has been reported in various studies. Low-dose ketamine (0.3 mg/kg) administration lowered the CRP concentration triggered by emergency cesarean section compared with the control group ($p < 0.05$) [126]. The SNP rs1205 was found in significant association with lower serum concentrations of CRP [119, 121]. In a genetic study on CES-D score involving 868 European-American adults, the CRP concentration was positively associated with CES-D scores in individuals with the A-G-T (rs1417938—rs1800947—rs1205) haplotype ($p = 0.004$), but rs1205 was not related to depressive symptoms [119]. Nevertheless, elderly men with the rs1205 AA genotype have shown a higher risk of depression than those with other genotypes [121]. Rs1205 also proved to be associated with anxiety ($p < 0.05$) and neuroticism ($p = 0.012$) in elderly women [120]. In another study of women, individuals with the rs1205 TT genotype had a higher risk of depression with a lower peripheral CRP concentration [118]. One possible explanation is that the change in the CRP concentration is an adaptive response to compensate for external insults [121].

BDNF Deceased serum BDNF has been found in depressed patients [127–129]. In those with BD, a negative correlation between serum BDNF and inflammatory cytokines has been established [130]. Also, in patients with TRD, BDNF expression is negatively correlated with MADRS scores [131]. Antidepressant treatment can significantly upregulate BDNF in the peripheral blood [129]. An animal study demonstrated that ketamine treatment increases BDNF expression in the hippocampus and reduces immobility in the FST [132]. Furthermore, the expression of BDNF is significantly higher in ketamine-responding patients with TRD than in non-responding patients, suggesting peripheral BDNF as a biomarker for ketamine's antidepressant effect [131]. This result has been confirmed by another study focused on the response to ketamine in patients with TRD in which the serum BDNF concentration was significantly increased in ketamine responders after 1 week of treatment [133]. Notably, the genetic variant rs6265 (Val66Met) has been linked to memory and hippocampal function in humans by affecting activity-dependent secretion of BDNF [134]. This variant also has been demonstrated in association with a higher serum BDNF concentration [135], a greater suicide risk [136], and depressive symptoms [137–139]. By using gene–environment interaction analysis, it was found that the interaction between the BDNF rs6265 Met allele and life events could predict MDD [140, 141]. In a genetic study on the antidepressant effect of ketamine involving 62 depressed patients, people carrying the BDNF Val/Val genotype exhibited a better antidepressant response than did Met carriers [142].

Others Other inflammatory proteins have been identified in the exploration of biomarkers relevant to the antidepressant effect of ketamine. For example, IL-1α, IL-13, and IP-10 decreased significantly compared with baseline after 4 h of ketamine administration. Increased IL-7, as well as decreased IL-8 expression, was detected at 24 h after ketamine treatment ($p < 0.0001$). However, none of these changes paralleled the treatment response [15]. Also, the expression of the chemokine MCP-1 was higher in patients with TRD than in controls ($p = 0.02$) [15]. Interestingly, the baseline concentration of fibroblast growth factor 2 (FGF2), which functions in the recruitment of leukocytes to combat inflammation [143], was significantly lower in ketamine responders than in non-responders ($p = 0.0001$). Also, a significant correlation was

defined between MADRS changes and baseline FGF-2 concentration in these patients ($r = -0.565$; $p = 0.0009$) [15]. Besides, adipokines, which exert direct regulatory effects on inflammation, were implicated as predictors of the antidepressant response to ketamine, but the underlying mechanism remains to be explored [144].

The significant association between polymorphisms in inflammatory genes and depression as well as the antidepressant response may indicate a common underlying inflammatory mechanism. However, current knowledge of the genetic contribution to depression development and treatment is limited. Environmental factors, such as stress, have been proposed to contribute to depression through inflammatory mechanisms [145]. Taking both the environmental and genetic elements into account will provide more promising results in determining depression risks. Additional studies with larger samples considering haplotypes and gene × gene and gene × environment interactions clearly are needed. The genetic information on the inflammatory background of depression and antidepressant effects will eventually provide new opportunities for the identification of subtypes of depression and precision medicine.

Summary

An antidepressant drug, ketamine, has the advantages of a rapid and sustained therapeutic effect. The significant relief of depressive symptoms by subanesthetic doses has been demonstrated in both pre-clinical and clinical studies [5, 49, 51]. Its unique antidepressant mechanism has not only extended our knowledge of the involvement of the glutamatergic system in depression but also makes it effective in treating TRD. The elevated inflammatory molecules in patients with TRD make these proteins attractive biomarkers for the identification of subtypes of depression. Great attention is being paid to the exploration of pro-inflammatory cytokines in the prediction of the antidepressant response to ketamine [14–16], but it is still too early to draw definite conclusions about their relations. BDNF is considered a bridging molecule, mediating the inflammatory influence on neuroplasticity and neurogenesis [91]. It also is a crucial contributor to the positive feedback loop amplifying the antidepressant action of ketamine through the mTOR pathway. Therefore, the expression changes and genetic variants in BDNF have drawn great attention in studies of biomarkers for depression development and ketamine's antidepressant actions. However, given the limited sample size and the complexity of the pathogenesis of depression, additional studies are needed to extend our current knowledge of ketamine's antidepressant value at the crossing point of inflammation and depression. Further characterization of the genetic and expression profile differences between ketamine responders and non-responders/controls, as well as the underlying molecular mechanism, will not only shed light on the monitoring of antidepressant processes and precision medication in TRD treatment but also will provide targets for the development of novel therapeutic strategies.

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