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ORIGINAL ARTICLE

# Ketamine as an Antidepressant: Mechanisms, Pharmacokinetics, and Its Role in Stress-Related Depression Models

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## ABSTRACT

**Background:** Depression is a prevalent mental health disorder characterized by persistent sadness, hopelessness, and a diminished ability to experience pleasure. It significantly impacts mental and physical well-being, altering thought processes and behavior. Individuals with depression often struggle with daily activities, including work, sleep, appetite, and overall quality of life. Animal models of chronic stress provide an experimental ground for investigating various neurobehavioral manipulations associated with depression because stress is one of the most important risk factors for the onset of this disease in humans. Prolonged exposure to a stressful environment during the development of a rodent model frequently leads to behavioral despair, withdrawal from social interactions, and anhedonia—symptoms associated with depression. Most importantly, anhedonia seems to be significantly related to the dysregulation of a particular neural pathway controlling reward processing and motivation—the dopamine (DA) system—in both human and animal models. Traditional antidepressants, despite their widespread use, are limited by delayed therapeutic onset and suboptimal efficacy in many patients. In contrast, ketamine—a fast-acting N-methyl-D-aspartate (NMDA) receptor antagonist—has emerged as a promising alternative. Acute administration of ketamine has been shown to rapidly alleviate depressive symptoms in humans and reverse stress-induced behavioral and neurochemical changes in animal models. Notably, many of its effects are mediated through modulation of the DA system. This review aims to provide detailed information on the antidepressant mechanisms of ketamine, emphasizing its impact on depression-related neurobiology, particularly DA dysfunction. It also examines ketamine's effects on depression-relevant endophenotypes, such as anhedonia and behavioral despair, as well as its activity within the ventral tegmental area (VTA) in rodent models of chronic stress. Our goal is to provide a comprehensive overview of ketamine's antidepressant potential, highlighting its effects in both human and animal studies.
**Keywords:** Ketamine; Depression; Stress; Rodents.

## INTRODUCTION

Affecting mostly those in their 20s and beyond, major depressive disorders (MDDs), usually referred to as depression, are said to be the leading cause of disability worldwide and the foremost mental disorder. It entails an enduring state defined by changes in mood characterized by increased negative affect and decreased positive affect. A condition with many faces, depression occupies cognitive, emotional, motivational, and physiological domains, thereby

complicating its functioning in treatment [1, 2].

The recently preferred pharmacological treatments for depression, like selective serotonin reuptake inhibitors (SSRIs), act mainly on monoaminergic systems in the brain. However, they have considerable drawbacks: very low percentages of patients attain full remission within a short time, ranging between 40% and 60%, and these agents usually take weeks to months to show a perceptible therapeutic effect. This slow onset of action is especially disastrous in patients posing high suicidal risks, emphasizing the pressing necessity for faster antidepressant therapies that can squeeze the most with minimal onset time and maximize treatment outcomes [1, 2].

Because of the multifaceted characteristics of MDD pathophysiology, it is difficult to obtain an accurate diagnosis and effective treatment. Indeed, many hypotheses have been offered; however, none of them account adequately for the mechanisms underlying the disorder. Brain remodeling, inflammation, genetic and epigenetic abnormalities, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and psychosocial stressors all appear to be causative agents [3].

New evidence points to astrocytic dysfunction as an important contributing factor in MDD. Experimental and postmortem studies indicated decreased glial cell density within the regions of the brain involved in emotion, including the amygdala, hippocampus, and prefrontal cortex (PFC). Furthermore, decreased expression of astrocytic markers in patients with MDD, such as glial fibrillary acidic protein (GFAP), glutamate transporter-1 (GLT-1), connexins, glutamine synthase (GS), and aquaporin-4 (AQP4), lends additional support to the consideration of astrocytic involvement in the disorder **(Figure 1)** [3].

Aside from being used traditionally for anesthesia, ketamine has now emerged as a rapid-acting antidepressant in treatment-resistant depression. Its action mainly involves NMDA receptor antagonism, which will trigger a sequence of further cellular events towards the bettering of synaptic plasticity and strengthening of neural connections. This is thought to account for the quick effects of this substance in the treatment of depression. Acute ketamine administration has demonstrated efficacy in reversing stress-induced alterations in neural circuits in preclinical models of stress-related depression. Current research indicates that ketamine enhances both the structural and functional integrity of synapses in brain regions adversely impacted by chronic stress. These neurobiological effects contribute to the alleviation of depressive symptoms, underscoring ketamine's potential as a rapid-acting antidepressant. In addition, it is known that ketamine modifies systemic and neuroinflammatory conditions, thus contributing to its antidepressant action [4].

In this review, we aimed to thoroughly analyze the mechanisms of action, pharmacokinetics, and antidepressant effects of ketamine in both human and animal models subjected to chronic or repetitive stress. In particular, we spotlight how ketamine works on the neurobehavioral and neurochemical deficits associated with depression, which emphasize stress-induced dysfunctions in the mesolimbic dopamine system, synaptic plasticity, and brain-derived neurotrophic factor (BDNF) signaling. This research article's aim is to highlight ketamine's potential not only as an effective treatment for treatment-resistant depression but also as a preventive intervention against stress-induced neurobiological and behavioral adaptations.

The well-established rapid antidepressant actions of ketamine are known to have serious gaps in the understanding of mechanism-related processes and long-term effects, especially concerning stress-related forms of depression. This research gap includes a relatively inadequate knowledge of the underlying molecular and cellular pathways via which ketamine exerts its effects on the mesolimbic dopamine system, BDNF signaling, and synaptic plasticity, as well as the potential contributions of the secondary metabolite, (2R,6R)-hydroxynorketamine (HNK), to antidepressant action with fewer side effects. Most of these are preclinical findings broken down into several components, but their actual clinical relevance, especially concerning stress resilience and long-term effectiveness, remains very difficult to ascertain. That being said, ketamine does seem to have some ability to prevent stress-induced changes, but long-term safety and mechanisms for that preventative effect require extensive exploration and study.

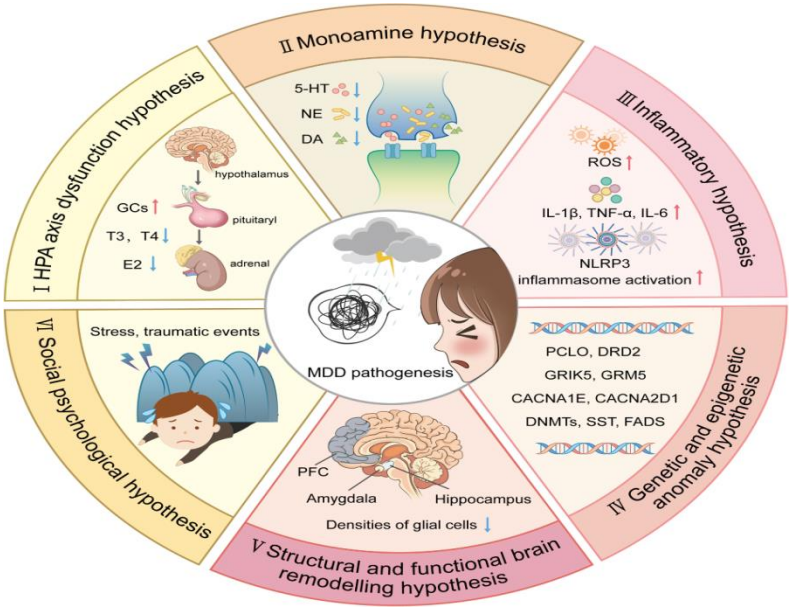


**Figure 1:** shows depression pathogenesis hypotheses.

(

I) HPA axis dysfunction hypothesis: high levels of glucocorticoids (GCs) play a core role in the pathogenesis of MDD, and thyroid hormone (TH) and estrogen are also involved in functions of the HPA axis; (II) the monoamine hypothesis: the functional deficiency of serotonin (5-HT), dopamine (DA) and norepinephrine (NE) are the main pathogenesis of MDD; (III) the inflammatory hypothesis: the neuro-inflammation induced by reactive oxygen species (ROS), inflammatory cytokines and inflammasomes activation is suggested to promote the occurrence of MDD; (IV) the genetic and epigenetic anomaly hypothesis: some genes are susceptible in the patients with MDD, including presynaptic vesicle trafficking (PCLO), D2 subtype of the dopamine receptor (DRD2), glutamate ionotropic receptor kainate type subunit 5 (GRIK5), metabotropic glutamate receptor 5 (GRM5), calcium voltage-gated channel subunit alpha1 E (CACNA1E), calcium voltage-gated channel auxiliary subunit alpha2 delta1(CACNA2D1), DNA methyltransferases (DNMTs), transcription levels of somatostatin (SST), fatty acid desaturase (FADS); (V) the structural and functional brain remodeling hypothesis: the postmortem results of patients with MDD are mostly associated with the reduced densities of glial cells in the prefrontal cortex (PFC), hippocampus, and amygdala; (VI) the social psychological hypothesis: the traumatic or stressful life events are the high risks of the occurrence of MDD

## Hypothesis of MDD

### A. Genetic Hypothesis of MDD

MDD involves a web of interactions between genetics and environmental factors,

with estimates of heritability ranging from 30% to 50% [4]. Genome-wide association studies (GWAS) identified a gene locus more than 100 with MDD involvement, among them genes associated with presynaptic vesicle trafficking (PCLO), dopaminergic signaling (GRIK5, GRM5), and neuronal calcium signaling (CACNA1E, CACNA2D1). There is also evidence that copy number variants (CNVs) located in regions like 1q21.1 and 15q11-13 have been implicated [4].

Stress-related interactions between an individual's genes and environment assume an important role in MDD. Studies suggest that the activity of the prefrontal DUSP6 gene is decreased in women resulting in increased ERK signaling with greater excitability of neurons, making them more vulnerable to stress. [4].

### B. Neurotransmitter Hypothesis in MDD

The monoamine hypothesis of major depressive disorder suggests that dysfunction in genes encoding key neurotransmitters—serotonin (5-HT), dopamine (DA), and norepinephrine (NE)—plays a central role in the pathophysiology of the disorder. Selective serotonin reuptake inhibitors exert their antidepressant effects primarily by increasing synaptic serotonin levels through inhibition of the serotonin transporter (SERT), thereby enhancing serotonergic neurotransmission. This increase in extracellular serotonin is reported to influence astrocytic function, potentially through interactions with serotonin receptors such as 5-HT1 and 5-HT2, which are known to modulate neuronal-glial signaling and synaptic plasticity [5, 6].

Brilliant prospects for the designation of astrocyte 5-HT2B receptors as pharmacological targets have been created. For example, fluoxetine affects signaling pathways such as PI3K/AKT and MAPK/ERK due to the 5-HT2B receptor activation, which further influences mood-regulatory proteins including SERT and cPLA2. Therefore, the importance of astrocytic-associated downstream pathways in the action of antidepressants is emphasized [7].

Norepinephrine (NE) is one of the prime elements in the regulation of neurophysiological processes, such as mood and stress. NE reuptake inhibitors (NRIs) like atomoxetine and serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine (DXT) and venlafaxine, bring about effective relieving of MDD symptoms by inhibiting the reuptake of NE and serotonin in the depressed patient, thereby enhancing their levels and modulating astrocytic and neuronal functions. Chronic DXT treatment augments astrocytic gap junctions through connexin 43 (Cx43) expression and reverses, partially, depressive behavior inflicted by stress. Desvenlafaxine (DVS) has been shown to ameliorate oligodendrocyte dysfunction in chronic stress models, indicating its therapeutic potential [8].

Dopamine (DA) dysregulation, commonly observed in depression, is exacerbated by chronic stress, reducing DA levels in regions like the striatum and hippocampus. Astrocyte-neuron interactions regulate DA homeostasis, and astrocytic dysfunction can lead to DA imbalances, disrupting neuronal activity. Dopamine targeting antidepressants, such as sulpiride, function by modulating dopaminergic transmission, which plays a key role in mood regulation and cognitive function. Sulpiride, a selective dopamine D2 receptor antagonist, enhances dopaminergic neurotransmission by blocking presynaptic D2 autoreceptors, leading to increased DA release [9,10].

Stressful life events, such as job loss, divorce, or bereavement, are major triggers for MDD. Chronic stress disrupts neuronal

structure and function, primarily by over-activating the HPA axis, elevating glucocorticoid levels, and impairing synaptic plasticity. Chronic stress affects astrocytes function by reducing astrocytic glutamate reuptake leading to excessive extracellular glutamate causig NMDA receptors overactivation leading to neurotoxicity and synaptic dysfunction, as well as reduces astrocytic GABA uptake leading to impaired inhibition and increased neuronal hyperactivity. Glial cells, particularly astrocytes, mediate the neurochemical and structural changes induced by stress, through uptaking excess glutamate from synapses via glutamate transpoters (GLT-1/EAAT2 and GLAST/EAAT1) to prevent excitotoxicity and regulation of inhibitory GABAergic neurotransmission by controlling extracellular GABA levels. Activation of purinergic receptor P2X7R, an ATP-gated ion channel expressed in glial cells, in astrocytes has been identified as a critical mechanism in stress-induced depression. As chronic stress increases extracellular ATP levels which accumulate in the brain due to increased neuronal activity. These high levels of ATP causes activation of P2X7R, leading to prolonged channel opening causing release of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) promoting neuroinflammation, and impairs glutamate uptake causing excitotoxicity as well as reduce GABA release, leading to decreased inhibitory tone [5,10].

### C. Inflammation and Oxidative Stress in MDD

Inflammation in the nervous system and oxidative stress (OS) have become centralized to the pathophysiology of MDD. The elevation in the proinflammatory cytokines TNF-α, IL-1β, and IL-6 indicates the severity of depression. Astrocytes are mediators of neuroinflammation by releasing cytokines, which would also add the connection between glial dysfunction and MDD [11].

Levels of oxidative stress increasingly lead to neuronal damage. Astrocytes can combat oxidative stress by producing a variety of antioxidants such as glutathione and by neutralizing reactive oxygen species (ROS) with several different extracellular enzymes, including—glutathione peroxidase. Lithium salts, which are widely used mood stabilizers, have been shown to decrease ROS production from the site of generation, i.e., mitochondria. This is significant since production of excessive ROS would eventually lead to oxidative stress, causing cell injury associated with several neurological disorders including, but not limited to MDD. Through decreasing mitochondrial-derived ROS production, lithium might actually be able to confer some protection from oxidative stress-mediated injury in astrocytes, the supportive glial cells in the brain which are considered crucial for maintaining neuronal health and function. This protective role of lithium on astrocytes further emphasizes the possibility of lithium as a therapeutic agent in ameliorating astrocytic dysfunctions implicated in MDD [12].

## Structure and Pharmacokinetics of Ketamine

Ketamine, a phencyclidine derivative, is structurally characterized by a cyclohexanone ring attached to a chlorophenyl and an amino group. As a racemic mixture of the enantiomers (R)-ketamine and (S)-ketamine, it is classified as an arylcyclohexylamine. The S-enantiomer is considered more potent in its analgesic and anesthetic effects. Ketamine's high lipophilicity facilitates its rapid crossing of the blood-brain barrier, contributing to its distinct pharmacokinetic and pharmacodynamic properties [13].

Upon administration, ketamine is rapidly absorbed and widely distributed throughout

the body. Its bioavailability varies depending on the route of administration: nearly 100% via intravenous injection but only 20–50% through oral administration due to significant first-pass metabolism. Ketamine is metabolized in the liver by the cytochrome P450 enzyme system, producing an active metabolite, norketamine, which contributes to its pharmacological effects. The elimination half-life of ketamine ranges from two to four hours, influenced by individual metabolic rates and the route of administration [14].

**Mechanism of Action of Ketamine**

Ketamine's diverse receptor activity underpins its unique pharmacological profile. Its primary mechanism is the non-competitive antagonism of NMDA receptors, which inhibits excitatory neurotransmission, producing its characteristic analgesic, dissociative, and anesthetic effects. Additionally, ketamine interacts with opioid receptors, monoaminergic pathways, and voltage-gated calcium channels, enhancing its analgesic and mood-modulating properties. These mechanisms explain its efficacy in conditions such as acute pain, treatment-resistant depression, and status epilepticus [15].

**1. NMDA Receptor Antagonism**

Ketamine can increase the levels of BDNF through NMDA antagonism in the hippocampus through two pathways primarily. The first of these pathways involves the dephosphorylation of eukaryotic elongation factor 2 (eEF2) in case an NMDA receptor-mediated spontaneous miniature excitatory postsynaptic current (NMDA-mEPSCs) is inhibited by ketamine. Thus, this action causes a decrease in eEF2 kinase activity, followed by the reduction of eEF2 phosphorylation and then increasing dephosphorylation. In addition, it essentially acts as an open-channel blocker for NMDA receptors. That means that it binds to the receptor when it is active and open so that it blocks the function of the receptor. This is a primary mechanism for the anesthetic effects of ketamine, as well as the dissociative side effects and abuse potential [15].

**2. Inhibition of GABAergic Interneurons**

Ketamine preferentially inhibits gamma-aminobutyric acid (GABA) interneurons, disinhibiting glutamatergic neurons and subsequent glutamate release, subsequently stimulating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and effecting synaptic plasticity. This mechanism is thought to underlie the rapid antidepressant action of ketamine [19].

**3. AMPA Receptor Activation**

AMPA receptors translated with glutamate thereby facilitate the entry of sodium ($Na^+$) and calcium ($Ca^{2+}$) ions into the postsynaptic neuron. The ionic influx causes depolarization as well as the gradual opening of voltage-dependent calcium channels (VDCCs), further increasing the calcium levels. High intracellular calcium concentrations stimulate the release of BDNF, which is a growth factor that helps neurons grow, survive, and thrive in addition to allowing for plastic changes at the synapse [16].

**4. Modulation of the mTOR Pathway**

The rapid action of ketamine in depression is closely tied to its ability to activate the mammalian target of rapamycin (mTOR) pathway, an important regulator of cell growth and protein translation. Ketamine has a complex effect on glutamate activity in the brain. Initially, it blocks NMDA receptors, which are normally activated by glutamate. These NMDA receptors are found on inhibitory interneurons that regulate the activity of excitatory neurons. By inhibiting these interneurons, ketamine reduces their suppressive effect, leading to

an increase in excitatory neuronal firing [17].

As a result, there is a surge in glutamate release in the synaptic space. This excess glutamate then activates AMPA receptors, another type of glutamate receptor that plays a crucial role in synaptic plasticity and neural communication. The activation of AMPA receptors contributes to ketamine's rapid antidepressant effects, which are thought to be mediated by increased synaptic strength and neuroplasticity. Although ketamine is an NMDA receptor antagonist, its net effect is an initial increase in glutamate transmission due to the disinhibition of excitatory neurons. However, with prolonged or high-dose use, ketamine can lead to glutamate dysregulation and potential neurotoxic effects. This balance between short-term benefits and long-term risks is a key area of research in ketamine's clinical applications, particularly in psychiatry and anesthesia [17].

This subsequent cascade activates the mTOR pathway and thus promotes the synthesis of proteins necessary for synaptogenesis. Increased synaptogenesis in brain areas like the prefrontal cortex is thought to be a major component of ketamine's fast alleviative action on depressive symptoms [17].

**5. Elevation of BDNF Levels**

Neurotrophic factors, namely BDNF, are essential for neuronal survival, growth, and plasticity. An increase occurs in BDNF levels following ketamine administration, promoting the formation of synaptic connections and strengthening of previously formed ones. This rise in BDNF levels, accompanied by the activation of its receptor Tropomyosin receptor kinase B (TrkB), triggers multiple signaling cascades that account for the formation and strengthening of synaptic connections. This process is crucial for reversing the synaptic deficits often observed in depression. By enhancing synaptic plasticity, ketamine rapidly improves mood and cognitive function, distinguishing it from traditional antidepressants that may take weeks to exhibit similar effects [17]. **(Figure 2)** [18].

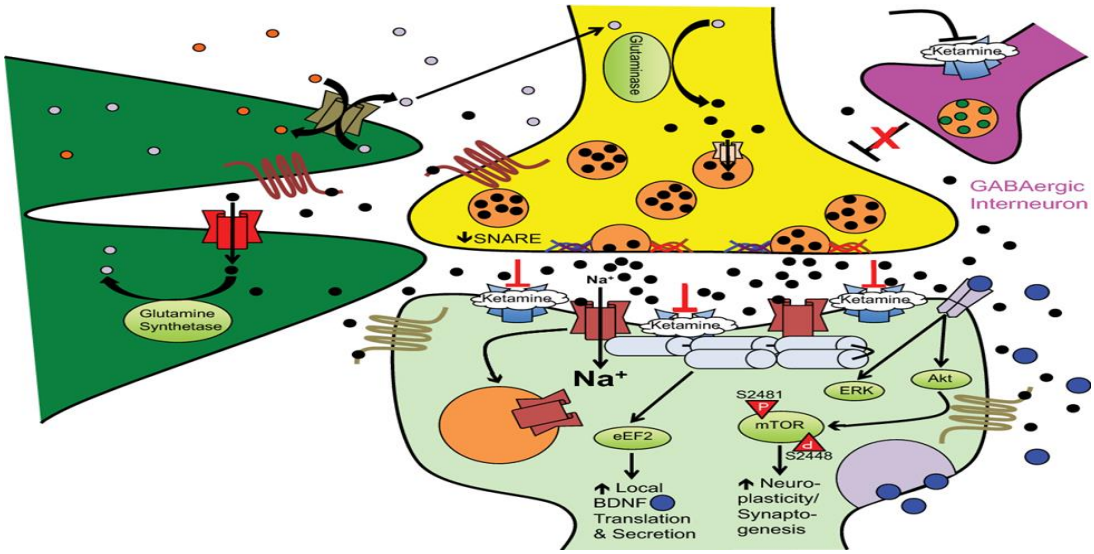


**Figure 2:** Ketamine-induced antidepressant efficacy .

Black circles: glutamate; grey circles: glutamine; blue circles: BDNF; maroon channel: AMPA receptor complex; blue channel: NMDA receptor complex; red channel: glial transporter-1/excitatory amino acid transporter 2 (GLT-1/EAAT2); peach channel: vesicular glutamate transporter; maroon

seven-transmembrane receptor: metabotropic glutamate receptor type 2/3; olive seven-transmembrane receptor: metabotropic glutamate receptor type 1/5; grey dimeric receptor: TrkB receptor. Akt, Ak thymoma/protein kinase B; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; eEF2, eukaryotic elongation factor 2; ERK, extracellular signal-regulated kinase; GABA, γ-aminobutyric acid; mTOR, mammalian target of rapamycin; NMDA, N-methyl-D-aspartate; SNARE, soluble NSF attachment protein receptor (superfamily); TrkB, tropomyosin-related kinase B.

**6. Anti-Inflammatory Effects**

Emerging evidence suggests that ketamine possesses anti-inflammatory properties. It modulates the immune response by reducing the production of pro-inflammatory cytokines, which have been implicated in the pathophysiology of depression. By decreasing inflammation, ketamine may alleviate depressive symptoms linked to immune system dysregulation [20].

**7. Opioid Receptor Interaction**

Ketamine interacts with opioid receptors, particularly the mu and kappa subtypes. While this interaction contributes to its analgesic properties, its role in ketamine's antidepressant effects is still under investigation. For instance, research from Stanford University demonstrated that the antidepressant effects of ketamine require activation of opioid receptors. In this study, participants with treatment-resistant depression received ketamine infusions after being pre-treated with either naltrexone (an opioid receptor antagonist) or a placebo. The findings revealed that naltrexone pre-treatment significantly diminished ketamine's antidepressant effects, suggesting that opioid receptor activation plays a crucial role in mediating these effects. Some studies suggest that opioid receptor modulation may enhance mood, but the exact contribution to antidepressant outcomes remains to be fully elucidated [21].

Ketamine’s rapid onset of antidepressant effects represents a significant advantage over traditional treatments, particularly for individuals with treatment-resistant depression—defined as insufficient response to at least two antidepressants at therapeutic doses and durations. Clinical trials have consistently shown that a single low-dose intravenous ketamine infusion (0.5 mg/kg) produces rapid and lasting antidepressant effects, with symptom relief observed within two hours and persisting for up to seven days [16].

Animal models of chronic stress, which mimic the physiological and behavioral changes observed in human depression, have demonstrated similar antidepressant effects of ketamine. These models highlight ketamine’s ability to reverse stress-induced alterations in the brain’s reward system, including the dopaminergic pathways [16].

**Impact on the Mesolimbic Dopamine System**

The mesolimbic pathway, encompassing regions such as the VTA, nucleus accumbens (NAc), and prefrontal cortex (PFC), plays a pivotal role in regulating mood and motivation. Dysfunction within this system is often associated with depressive symptoms, including anhedonia the diminished ability to experience pleasure [23].

The exact mechanisms by which ketamine influences the mesolimbic dopamine pathway are complex and multifaceted. One proposed mechanism involves ketamine's antagonism of NMDA receptors on GABAergic interneurons in the VTA. This action leads to disinhibition of dopaminergic neurons, resulting in increased dopamine release in downstream targets like the NAc and PFC, improving motivation and reward processing. Additionally, ketamine may induce synaptic plasticity changes within the mesolimbic system by activating AMPA receptors in the NAc causing increase in BDNF release, enhancing the responsiveness of these regions to rewarding

stimuli and contributing to its antidepressant properties [24].

Furthermore, ketamine's effects on the mesolimbic dopamine system may involve modulation of other neurotransmitter systems and intracellular signaling pathways. For instance, ketamine has been shown to influence the release of glutamate, which can interact with dopamine pathways to regulate mood and reward processing. Additionally, ketamine increases serotonin release in the PFC and hippocampus. 5-HT1B receptor activation in the NAc enhances dopamine signaling, contributing to ketamine's antidepressant effects. These interactions highlight the intricate network of neurochemical processes underlying ketamine's antidepressant effects and underscore the need for further research to fully elucidate these mechanisms [25].

Acute ketamine administration increases dopamine release and activity in the prefrontal cortex, nucleus accumbens, and striatum, alleviating depressive symptoms in animal models. This effect is accompanied by a 62–180% increase in dopamine cell firing in chronically stressed rats [23].

Animal models of depression, which often involve chronic stress, exhibit impaired mesolimbic dopamine signaling and associated behavioral deficits, such as anhedonia and behavioral despair. Common assessments of anhedonia include sucrose preference tests, where reduced consumption of a sweetened solution indicates diminished reward sensitivity. Behavioral despair is often evaluated using the forced swim or tail suspension tests, where reduced struggle behaviors reflect depressive-like states. These models provide insights into ketamine's ability to restore mesocorticolimbic dopamine function and alleviate depressive behaviors [24].

**The efficacy of ketamine in Rodent models of Chronic Unpredictable Mild Stress (CUMS):**

Development of animal models for mental disorders intends to replicate symptoms and behavioral patterns of human beings. Such models should comply with validity principles: (a) to cause the same underlying mechanisms or risk factors for the disorder; (b) to reflect other major anatomical, biochemical, or behavioral features of the disorder; and (c) to predict their responses to treatment in humans. One widely used method is the chronic stress or repeated stress model in rodents that replicate the consequences of stress exposure, a significant risk factor for human depression. The depressive symptoms in these animal models emerge through a broad range of behavioral and physiological abnormalities that produce cellular and molecular alterations in stress-sensitive areas of the brain [26].

The model of chronic mild stress (CMS) is most commonly used to study changes in behavior and neurobiology associated with stress and depression. It involves delivering a series of mild unpredicted stresses (social separation, food and water deprivation, and cage change) to rodents for 4 to 6 weeks. This paradigm results in anhedonia, which manifests behaviorally as decreased reward responses, reflecting altered dopamine functioning. Behavioral signs of anhedonia in CMS-exposed rodents include reduced sucrose intake and preference, decreased sexual activity, and increased intracranial self-stimulation thresholds in the VTA [27]. CMS triggers behavioral despair, which has been defined as passive coping. In-vivo electrophysiological work has demonstrated that CMS decreases activity of dopaminergic neurons in the VTA, particularly for the region receiving input from the ventromedial striatum-an area important for processing reward. The underlying mechanisms rely on activation of the basolateral amygdala-ventral pallidal pathway. Similar decreases in firing rate of

dopaminergic neurons have also been recorded in CMS-treated mice, thus indicating a remarkably conserved dopamine dysfunction across species [28].

Chronic stress disrupts the mesolimbic dopamine pathway resulting in reduced dopaminergic signaling and neuronal degeneration in the hippocampus and medial prefrontal cortex. This process is driven by stress-induced glucocorticoid signaling and corticosterone overproduction. By improving the dopaminergic system, Ketamine has been able to reverse these effects in addition to the restoration of synaptic integrity [16].

Preclinical studies suggest low-dose ketamine injection (10 mg/kg) restores synaptic signaling proteins like GluR1 and PSD-95 in stressed rats' medial prefrontal cortex. The mTOR pathway has been shown to be highly involved in ketamine's effects on synaptic and behavioral properties. The importance of mTOR signaling in mediating ketamine's antidepressant action is shown by findings that when mTOR signaling is blocked, ketamine no longer induces these effects in animal models [19].

Furthermore, ketamine's antidepressant effects are linked to sustained dendritic spine growth in the medial prefrontal cortex, as demonstrated through two-photon imaging in stress-exposed mice. These structural changes correlate with increased BDNF production and release, emphasizing the role of neuroplasticity in ketamine's long-term efficacy [20,21].

Another key mechanism involves glycogen synthase kinase-3 (GSK3), a serine-threonine kinase implicated in MDD. Ketamine's rapid antidepressant effects require GSK3 inhibition in the hippocampus and prefrontal cortex. Preclinical studies have demonstrated that GSK3-deficient mice fail to respond to ketamine, further validating the enzyme's role as a therapeutic target. Interestingly, lithium—an established mood stabilizer—shares similar GSK3-inhibitory effects, suggesting overlapping mechanisms between the two drugs [22:25].

Acute ketamine administration (10–15 mg/kg, intraperitoneally) reverses depressive-like behaviors in CMS-exposed rats, restoring sucrose consumption and reducing immobility in the forced swim test (FST). Ketamine also increases the activity of VTA DA neurons, with effects lasting between two- and seven-days post-administration. These findings suggest that ketamine alleviates anhedonia and despair in CMS models by modulating the dopamine system [29].

**The antidepressant effect of ketamine metabolites**

Despite ketamine's therapeutic potential, its psychotomimetic effects (e.g., dissociation and transient psychosis), particularly at high doses, limit its widespread use in humans. Consequently, research has focused on identifying alternative agents with improved safety profiles. Among these, the ketamine metabolite (2R,6R)-hydroxynorketamine (HNK) has garnered significant interest. Unlike ketamine, (2R,6R)-HNK produces antidepressant-like effects in rodents without causing adverse effects such as ataxia, sensory detachment, or abuse liability. Additionally, HNK metabolites, including (2S,6R)-HNK and (2R,6S)-HNK, have been detected in human plasma following ketamine infusion, further supporting their clinical relevance [30].

While promising, preclinical findings on (2R,6R)-HNK require validation in human clinical trials to assess its safety and efficacy as a potential antidepressant or preventative therapy. Parallel research on alternative compounds, such as 5-HT4 receptor agonists, has demonstrated stress-protective effects in rodent models, highlighting the potential for developing safer, targeted interventions for depression [31].

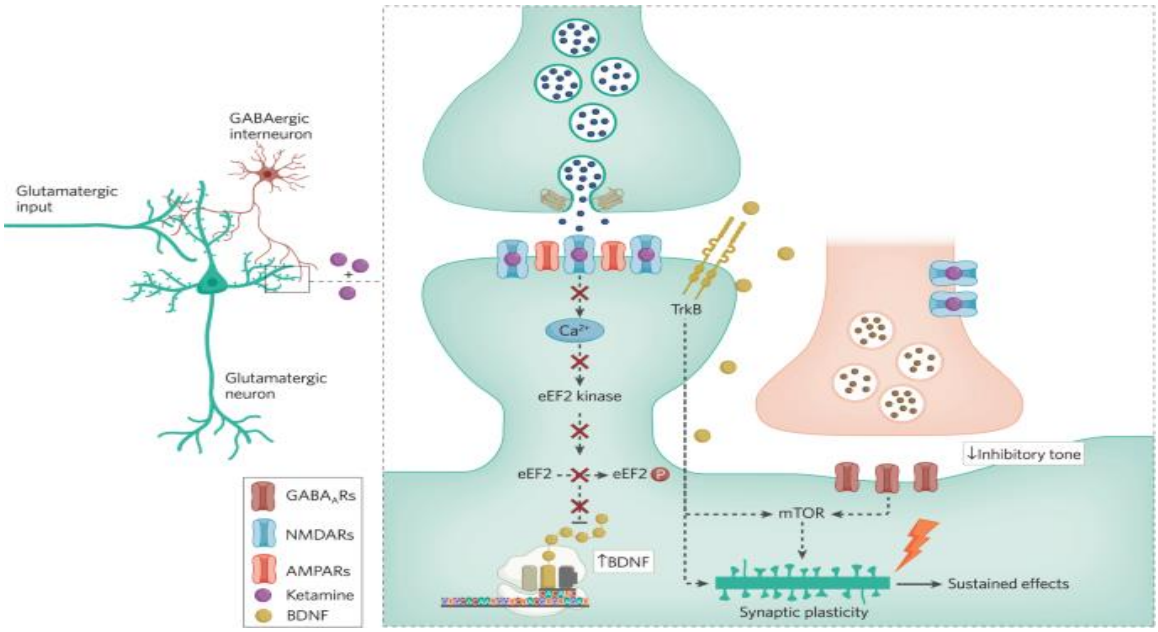


**Figure 3:** Mechanism of antidepressant effect of ketamine

**Ketamine for the Prevention of Stress-Induced Depression**

Recent research has explored ketamine's potential neurobehavioral protective effects against stress, focusing on its ability to enhance resilience and resistance to future stressors. Repeated intraperitoneal administration of ketamine (20 mg/kg, twice daily for 15 days) produced stress-resistant phenotypes in rats, observable up to two months after the final dose [32].

Adolescent (postnatal days 35–49) and adult (postnatal days 75–89) rats treated with ketamine exhibited anxiolytic effects, as evidenced by increased time spent in the open arm of the elevated plus maze (EPM), reduced immobility in the FST, and enhanced active coping behaviors. Importantly, these effects were consistent across age groups, suggesting no critical developmental period for ketamine's preventative effects. Moreover, ketamine-induced behavioral changes were not attributed to baseline locomotor activity, as no alterations were observed two months post-treatment. These results demonstrate that repeated ketamine exposure promotes long-lasting resistance to depression- and anxiety-like behaviors in rodents [33].

In chronic social defeat stress (CSDS) models, a single dose of ketamine (30 mg/kg, i.p.) administered one week prior to two weeks of CSDS reduced stress-induced immobility in the FST and alleviated social avoidance. However, ketamine's protective effects were specific to depressive phenotypes, as no significant impact on anxiety-like behaviors was observed in the EPM. Prophylactic ketamine treatment also increased ΔFosB expression in the ventral CA3 region of the hippocampus, a transcription factor involved in synaptic plasticity and stress resilience [34].

**Conclusions:** Ketamine, a fast-acting NMDA receptor antagonist, has emerged as an innovative treatment for depression, particularly in cases where conventional therapies have failed. Its ability to provide rapid and sustained antidepressant effects—

often within hours compared to the weeks required for traditional antidepressants—has revolutionized the field. Ketamine achieves its effects by blocking NMDA receptors, activating the mTOR pathway, enhancing synaptic plasticity, and increasing BDNF signaling. Additionally, it modulates the mesolimbic dopamine system, a critical pathway involved in mood regulation. Studies in both animal models and clinical settings have demonstrated that ketamine can reverse stress-induced behavioral and neurochemical deficits and may even offer protective benefits against future stress adaptations.

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**Conflict of interest:** None.

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