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Mechanisms of Ketamine Action as an Antidepressant

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Abstract

Clinical studies have demonstrated that a single sub-anesthetic dose of the dissociative anesthetic ketamine induces rapid and sustained antidepressant actions in treatment-resistant patients. Although this finding has been met with enthusiasm, ketamine's widespread use is limited by its abuse potential and dissociative properties. Recent preclinical research has focused on unraveling the molecular mechanisms underlying the unique antidepressant actions of ketamine in an effort to develop novel pharmacotherapies, which will mimic ketamine's antidepressant actions but lack its undesirable effects. Here, we review hypotheses for the mechanism of action of ketamine as an antidepressant, including direct synaptic or extra-synaptic (GluN2B-selective) NMDAR inhibition, selective inhibition of NMDARs localized on GABAergic interneurons, and the role of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) activation. We also discuss links between ketamine's antidepressant actions and downstream mechanisms regulating synaptic plasticity, including brain-derived neurotrophic factor (BDNF), eukaryotic elongation factor 2 (eEF2), mechanistic target of rapamycin (mTOR), and glycogen synthase kinase-3 (GSK-3). Mechanisms that do not involve direct inhibition of the NMDAR, including a role for ketamine's (*R*)-ketamine enantiomer and hydroxynorketamine (HNK) metabolites, specifically (*2R,6R*)-HNK, are also discussed. Proposed mechanisms of ketamine's action are not mutually exclusive and may act in a complementary fashion to exert the acute changes in synaptic plasticity, leading to sustained strengthening of excitatory synapses, which are necessary for antidepressant behavioral actions. Understanding the molecular mechanisms underpinning ketamine's antidepressant actions will be invaluable for the identification of targets, which will drive the development of novel, effective, next-generation pharmacotherapies for the treatment of depression.

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Conflicts of interest

P.Z. and T.D.G. are listed as co-authors in a patent applications related to the pharmacology and use of (*2S,6S*)- and (*2R,6R*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation and post-traumatic stress disorders.

Introduction

Major depressive disorder (MDD) is a devastating mental disorder affecting approximately 16 percent of the world population, causing serious health and socio-economic consequences [1]. Although interventions such as pharmacotherapies and cognitive behavioral psychotherapies are available, a high proportion of patients remain treatment-resistant [2]. Moreover, even when effective, existing monoaminergic-based pharmacotherapies often take several weeks or months to exert their full therapeutic effects [3]. Placebo-controlled trials have provided strong evidence for the rapid-acting (within hours) and sustained (lasting up to 7 days) antidepressant effects of a single administration of a sub-anesthetic dose of the non-competitive *N*-methyl-*D*-aspartate receptor (NMDAR) antagonist ketamine in treatment-resistant depressed patients [4–8]. Moreover, antidepressant effects of ketamine have been demonstrated in many antidepressant-relevant tests in experimental animals (e.g. [9, 10–14]); also see [15]. However, ketamine's routine clinical use for the treatment of depression is restricted due to its dissociative effects, changes in sensory perception, intravenous route of administration, as well as its abuse liability [16]. These limitations have led investigators to explore the exact mechanisms of action underlying ketamine's antidepressant clinical responses in an effort to understand its primary targets that will lead to the development of novel treatment interventions for depression. These treatments are intended to mimic the unique antidepressant actions of ketamine but lack its undesirable side effects.

The first clinical trial reporting antidepressant actions of ketamine was published in 2000, where ketamine was administered intravenously (40-min infusion) at the sub-anesthetic dose of 0.5 mg/kg [4]. This contrasts with the typical dose of ketamine used in anesthesia of up to 2 mg/kg [17]. A robust antidepressant effect of ketamine was achieved within four hours post-infusion compared with depressed subjects who received placebo [4]. A subsequent double-blind randomized clinical trial demonstrated the efficacy of ketamine in treatment-resistant major depressed patients, who failed at least two conventional antidepressant treatments [5]. The antidepressant effects of ketamine manifested within 2 hours post-infusion and 35% of patients maintained response for at least 7 days [5]. Following these initial reports, several other clinical trials demonstrated rapid antidepressant actions of ketamine in treatment-refractory patients (e.g. [8, 18]). Importantly, in an effort to address the functional un-blinding of treatment status (ketamine *versus* placebo) due to the acute dissociative effects of ketamine, Murrough *et al.*, (2013) using a psychoactive placebo, midazolam, demonstrated a 64% response rate for the patients administered ketamine compared to 28% for those who received midazolam [19]. In addition to the therapeutic effects of ketamine in major depressed patients, ketamine exerts antidepressant actions in patients suffering with bipolar depression, with a similar response rate [20, 21].

The actions of ketamine to induce rapid antidepressant effects are in sharp contrast with the delayed effect onset of currently approved antidepressant treatments, which is particularly important in cases of patients with suicidal ideation, where a lag in the onset of antidepressant action has been associated with increased risk for suicidal behavior [22]. Ketamine has been also shown to induce a rapid amelioration of suicidal ideation in major depressed patients [23, 24] and to rapidly reduce anhedonia [25–27].

Here, we review hypotheses for the mechanism of action of ketamine as a rapid-acting antidepressant drug, including direct NMDAR inhibition (extra-synaptic NMDAR inhibition; inhibition of spontaneous NMDAR-mediated neurotransmission; inhibition of NMDAR-dependent burst firing of lateral habenula neurons), inhibition of GABAergic interneuron NMDARs (resultant pyramidal neuron disinhibition), and the role of the ketamine metabolite (*2R,6R*)-HNK. These pre-clinically demonstrated mechanisms of ketamine action are not mutually exclusive and may act in concert to exert the antidepressant actions of the drug.

NMDAR inhibition-mediated mechanisms

NMDARs are glutamatergic, ligand-gated, ion channel receptors which exist as heterotetramers. Seven different NMDAR subunits have been identified to date: GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B [28]. NMDARs typically contain two GluN1 subunits and either two GluN2 subunits or a mixture of GluN2/GluN3 subunits [28, 29]. NMDAR activation requires concurrent binding of L-glutamate and glycine/D-serine at the GluN2 and GluN1 subunits respectively, as well as voltage-dependent repulsion of magnesium (Mg^{2+}) block at the ion channel pore via membrane depolarization, resulting in calcium influx [28]. Trullas and Skolnick, 1990, were the first to show that the NMDAR non-competitive channel blocker MK-801 and the competitive NMDAR inhibitor AP-7 decrease immobility time in the forced-swim test in mice, a measure of antidepressant efficacy [30]. It was also reported that chronic, but not acute, administration of 17 different classical antidepressants in mice decreases radioligand binding to NMDARs, indicative of adaptive changes to the receptor [31, 32]. Therefore, Skolnick et al. (1996) [33] hypothesized that direct NMDAR inhibition might represent a target for faster-acting antidepressant actions.

Inhibition of NMDARs expressed on GABAergic interneurons (Disinhibition hypothesis)

Although ketamine is expected to block excitatory glutamatergic neurotransmission via NMDAR inhibition, it was shown to increase overall activity in the prefrontal cortex in healthy volunteers [34], which was hypothesized to be due a preferential inhibition of NMDARs expressed on GABAergic interneurons [35–37]. This preferential action of ketamine at inhibitory interneurons is supported by early findings showing that the NMDAR antagonist MK-801 initially inhibits firing of fast-spiking interneurons and subsequently increases firing of pyramidal neurons in freely-moving rats [36]. This is postulated to be due to the higher frequency of interneuron firing compared with the pyramidal neurons [38], which allows for increased depolarization-dependent relief of Mg^{2+} block, thus permitting ketamine access to bind at the NMDAR channel pore selectively on interneurons [39]. In addition, ketamine is reported to have higher affinity for GluN2D NMDAR subunits [40, 41], which are highly expressed in forebrain inhibitory interneurons [42, 43]. Inhibition of NMDARs specifically on GABAergic interneurons is predicted to induce a decrease in overall inhibition, leading to pyramidal cell disinhibition and an enhancement of excitatory glutamatergic neurotransmission in the medial prefrontal cortex (mPFC), and potentially other mood-relevant cortico-limbic brain regions [35] (see Figure 1). In rats, ketamine administration at sub-anesthetic doses results in a significant increase in extracellular glutamate levels [35] and an increase in glutamate cycling [44] in the prefrontal cortex. Further

supporting this hypothesis, administration of partial inverse agonists at the benzodiazepine binding site of alpha5-containing $GABA_A$ receptors, which are selectively expressed in the forebrain, including prefrontal cortex and hippocampus, promote coherent network activity via disinhibition of excitatory neurotransmission [45] and exert rapid antidepressant actions in several animal tests [46–48]. Notably, ketamine [13], similar to negative allosteric modulators of alpha5-containing $GABA_A$ receptors [47], enhance gamma band electroencephalography power, which is hypothesized to be directly related to cortical disinhibition [49–52], further supporting the role of cortical disinhibition in the rapid antidepressant actions of these drugs.

However, there is also evidence arguing against a primary role of suppression of the inhibitory GABAergic interneuron activity in ketamine's action as an antidepressant. In particular, ketamine administration to mice with a global reduction of $GABA_A$ receptor function, reversed behavioral despair and novelty-induced hyper-anxiety and selectively potentiated GABAergic synaptic inhibition within the mPFC [53]. Similarly, potentiation of GABAergic inhibitory input to pyramidal cells via a disinhibition of somatostatin-positive GABAergic interneurons induced sustained antidepressant-like effects in mice [54]. Enhancement of inhibition with pharmacological activation of $GABA_A$ or $GABA_B$ receptors also resulted in an antidepressant effect in rats [55, 56]. Moreover, pharmacological-induced disinhibition of synaptic neurotransmission via administration of the ionotropic $GABA_A$ receptor antagonist picrotoxin did not reduce behavioral despair in mice [10]. In addition, mice lacking NMDAR (GluN1) in parvalbumin-expressing interneurons, designed to mimic disinhibition of pyramidal cell activity, retained ketamine-induced antidepressant activity [57].

Inhibition of spontaneous NMDAR-mediated transmission

Spontaneous synaptic vesicular glutamate release "at rest", occurring via a spontaneous fusion of presynaptic vesicles of the pre-synaptic terminal [58, 59], results in miniature excitatory postsynaptic currents (mEPSCs) that have a role in regulating synaptic strength and protein synthesis [60–62]. In particular, mEPSCs tonically suppress protein synthesis [62], whereas folimycin-induced selective depletion of spontaneously releasable vesicular pools induces synaptic potentiation in rat hippocampal slices [63]. Ketamine and other NMDAR antagonists, including AP-5 and MK-801, were shown to block NMDAR-mediated neurotransmission at rest (NMDAR-mEPSCs), thus inducing a de-suppression of protein synthesis leading to synaptic potentiation in the CA1 region of the hippocampus and behavioral antidepressant actions [10, 63] (see Figure 1). Importantly, ketamine's inhibition of NMDAR-mEPSCs occurs at physiological levels of Mg^{2+}, an effect that was associated with the rapid antidepressant behavioral actions of ketamine [64]. In contrast, memantine, a non-competitive NMDAR channel blocker, failed to exert antidepressant actions in animal tests [64] and in humans [65–67], and which was suggested to be because memantine does not block NMDAR-mEPSCs under physiological Mg^{2+} levels [64]. Spontaneous NMDAR-mediated neurotransmission is hypothesized to contribute to ketamine's antidepressant actions by enhancing synaptic neurotransmission through a protein synthesis-dependent mechanism involving eukaryotic elongation factor 2 kinase (eEF2K) and BDNF (see Figure 1), as described later [10].

Direct inhibition of extra-synaptic NMDARs

Both immunohistochemical and electrophysiological studies have confirmed the existence of extra-synaptic NMDARs, which are not located in the post-synaptic density [68], and are primarily comprised of GluN2B-containing heterotetramers [28, 29]. The extra-synaptic GluN2B-containing NMDARs, and in particular those that are localized on dendrites adjacent to glial cells, are not activated by the typical transient synaptic glutamate release, but are chronically activated by low-levels of ambient glutamate within the extracellular space [69, 70]. These tonic ambient glutamate levels are directly regulated by the glutamate transporter EAAT2 (GLT-1), which is expressed on glial cells (see Figure 1) [69, 70]. Ketamine is hypothesized to specifically inhibit extra-synaptic GluN2B-NMDARs, thus preventing ambient glutamate-induced tonic activation of these receptors, an effect that is expected to induce an excitation of pyramidal neurons [71]. Under basal conditions, activation of cortical extra-synaptic GluN2B-selective NMDARs acts through the mTOR signaling pathway to suppress protein synthesis, which maintains synaptic homeostasis [71–74]; therefore, blockade of extra-synaptic GluN2B-containing NMDARs would de-suppress protein synthesis and induce antidepressant actions via an mTOR-dependent mechanism (see Figure 1), as described later.

In support of a role of GluN2B-NMDARs in ketamine's antidepressant actions is the findings that ketamine administration does not further decrease behavioral despair in mice lacking GluN2B-specific NMDARs localized to pyramidal neurons [71], suggesting that ketamine might act via inhibition of GluN2B-specific NMDARs on pyramidal neurons to exert its antidepressant effects. However, developmental homeostatic effects in genetically modified mice cannot be ruled out. In fact, mice lacking GluN2B-specific NMDARs localized to pyramidal neurons are characterized by low baseline levels of behavioral despair [71], possibly precluding any further effects of ketamine on this outcome. Furthermore, it is unclear how ketamine, with no selectivity for GluN2B subunit inhibition, specifically acts at this site to induce its antidepressant actions. In fact, it has been reported that at physiological magnesium concentrations ketamine has greater selectivity for inhibiting GluN2C- and GluN2D-containing NMDARs compared with GluN2B- and GluN2A-containing receptors [40, 41].

Independent of the mechanism of ketamine action, GluN2B selective antagonists exert rapid antidepressant actions in rodent models [9, 75–78]. Moreover, deletion of GluN2B-containing NMDARs from pyramidal cortical neurons in the brain of mice induced an enhancement of protein synthesis and increased the number of excitatory inputs measured in the prefrontal cortex, concomitant with decreased behavioral despair in the forced-swim test and tail-suspension test, and reduced corticosterone-induced behavioral deficits [71]. The value of targeting GluN2B selectively is further supported by the finding that GluN2B-selective NMDAR blockers may exert antidepressant actions in humans; however, these antidepressant effects do not appear as rapidly as the effects of ketamine. In particular, intravenous administration of the GluN2B-NMDAR antagonist CP-101,606 (traxoprodil) did not induce a rapid antidepressant response at the first time point measured (2 days following treatment), but induced a significant antidepressant action 5 and 8 days following a single administration [79]. Although this study provided evidence for a beneficial action of this drug,

it had a small sample size (n=15 subjects/group). CP-101,606 is not currently in development for the treatment of depression and there have been no further studies confirming this initial finding. Moreover, there is a controversy regarding whether the effects of this compound are solely due to block of GluN2B-NMDARs, since it also possesses high affinity at sigma-1 receptors [80, 81], which have been suggested as a target for antidepressant actions [82–84]. Another GluN2B-preferring NMDAR antagonist, MK-0657 (CERC-301), induced modest improvement in mood scores in depressed patients (Hamilton Depression Rating Scale, but not the Montgomery-Åsberg Depression Rating Scale), 5 days, but not 1–4 days, following a single infusion [85]. A larger phase II clinical trial failed to identify significant antidepressant actions of MK-0657 (as reported in [86]).

Inhibition of NMDAR-dependent bursting activity of lateral habenula neurons

The lateral habenula (LHb) is a highly conserved region of the epithalamus that acts as an intermediary between the forebrain, and midbrain monoaminergic systems [87, 88]. Glutamatergic LHb neurons are transiently activated by aversive stimuli including acute stressors [89, 90] and exert a feedforward inhibitory influence on the activity of midbrain dopamine neurons by virtue of their connections with GABAergic cells in the rostromedial tegmental area [91–93]. Activation of LHb neurons is also associated with depression-related phenotypes in animal models [94–96] and in patients with MDD [88, 97]. It has been recently demonstrated that LHb neurons show enhanced burst activity in rats characterized by congenital helpless behavior [98]. The same authors showed that direct application of ketamine to LHb slice preparations decreases abnormally high NMDAR-dependent burst firing [98]. Importantly, *in vivo*, ketamine-induced reduction in bursting activity was associated with an acute antidepressant effect in congenially helpless rats measured in the forced-swim and sucrose preference tests [98]. Although these findings are exciting and promising, the role of the LHb in regulating the antidepressant actions of ketamine was only assessed acutely (i.e, 1 h following drug infusion) and thus it is critical to investigate whether reducing NMDAR-dependent burst firing in the LHb can elicit long-lasting (e.g., 24 hours post-treatment) antidepressant behavioral actions, similar to the effects of ketamine when administered peripherally to rodents. Moreover, future studies should aim to determine whether different classes of putative rapid acting antidepressants also act via this mechanism and to determine whether these effects converge with the other known antidepressant-relevant actions of ketamine.

NMDAR inhibition-independent mechanisms

Following the finding that ketamine exerts rapid and sustained antidepressant actions in treatment-resistant depressed patients [4, 5], several human trials have been initiated to investigate the antidepressant potential of alternative NMDAR antagonists that, similar to ketamine, inhibit the NMDAR in a voltage-dependent manner. However, clinical trials indicate that these alternative NMDAR antagonists, lack the rapid, robust and/or long-lasting antidepressant actions of ketamine in humans [99]. In particular, memantine, repeatedly failed to exert antidepressant actions in major depressed patients [65–67]. In addition, a single intravenous administration of AZD6765 (i.e., lanicemine), a low-trapping non-selective NMADR channel blocker, exerted transient (~110 min) antidepressant responses in major

depressed patients, which were not maintained [100]. Although a follow-up study, where patients received 3 intravenous infusions of AZD6765 per week (total of 3 weeks), reported significant improvement in depressed mood and symptom remission at the end of treatment [101], this is in contrast with the sustained antidepressant actions of ketamine following a single infusion. Additionally, a four-country, 49 site placebo-controlled study comparing AZD6765 to placebo as an adjunctive treatment for depression in 302 patients, failed to show separation from placebo [102]. This literature leads to the conclusion that while alternative NMDAR channel-blocking antagonists may exert clinical antidepressant actions, such actions are not of the same time frame or magnitude as those exerted by ketamine. Similar to these human data, animal studies show that the NMDAR channel-blocking antagonist MK-801 does not exert sustained antidepressant actions, though it does have acute actions in some studies [9, 10, 13, 103].

Another finding challenging the NMDAR inhibition hypothesis of ketamine's antidepressant mechanism of action is the fact that partial agonists at the NMDAR glycine$_B$ binding site, including GLYX-13 (i.e., rapastinel) and D-cycloserine manifest antidepressant effects in clinical trials [104, 105] and in animal tests [106–109], without sharing ketamine's NMDAR inhibition-mediated side effects [109]. Furthermore, *in vivo* evidence shows that GLYX-13 is able to reduce ketamine-induced memory deficits in mice [110], which are NMDAR inhibition-mediated.

(R)-ketamine

Ketamine is an enantiomeric mixture of (*R*)-ketamine and (*S*)-ketamine. (*S*)-ketamine has ~4-fold greater affinity/potency at inhibiting the NMDAR compared to its (*R*)-ketamine enantiomer [13, 111–115]. Hashimoto and colleagues were the first to report superior and longer-lasting antidepressant actions of (*R*)-ketamine compared with (*S*)-ketamine in rodent models [116–118]. These findings were subsequently replicated by Zanos *et al.* (2016), who showed that (*S*)-ketamine's antidepressant behavioral actions require higher doses compared to those of (*R*)-ketamine [13]. The superiority of (*R*)-ketamine does not seem to be related to a U-shaped dose response of the drugs, as it has been shown superior to (*S*)-ketamine with up to a 30-fold range of doses in multiple mouse tests of antidepressant efficacy [13, 118]. Importantly, administration of equal, antidepressant-relevant, doses of (*R*)- and (*S*)-ketamine in mice did not yield different levels of these enantiomers in the brain of mice [13], indicating that the antidepressant superiority of (*R*)-ketamine in rodent models is not due to greater brain exposure. These data indicate that it is unlikely that ketamine exerts its full antidepressant actions solely via inhibition of the NMDAR, at least in rodents. Nevertheless, we note that pre-clinical rodent studies have also indicated rapid-acting antidepressant behavioral actions of (*S*)-ketamine in mice [13, 116–118]. In addition, in patients with depression, intravenous, 40-min infusion of (*S*)-ketamine (0.2 and 0.4 mg/kg) has been reported to exert antidepressant responses within 2 hours following administration, an effect that was sustained for at least 3 days, with some patients reporting beneficial effects for up to a period of two weeks following a single administration [18]. In addition, intranasal administration of 28–84 mg (*S*)-ketamine twice a week for a total period of two weeks induced antidepressant actions in treatment-resistant depressed patients as an adjunct treatment [119]. To date, there is no human clinical trial directly comparing the antidepressant

efficacy of (*S*)- and (*R*)-ketamine enantiomers, or assessing antidepressant actions of (*R*)-ketamine in depressed patients.

(2S,6S;2R,6R)-hydroxynorketamine (HNK) metabolite

Following ketamine administration, (*2S,6S;2R,6R*)-HNK is the major HNK metabolite found in the plasma and brain of mice [13], as well as the plasma of humans [120]. While maximal concentrations of (*2S,6S;2R,6R*)-HNK in the plasma of patients receiving ketamine are lower than ketamine levels (0.16 *vs* 0.78 μM, respectively), total exposure of (*2S,6S;2R,6R*)-HNK is higher than that of the parent drug (5.72 *vs* 4.36 μM) [120]. In addition, (*2S,6S;2R,6R*)-HNK exposure is ~1.8-fold higher in humans compared to mice ([121] and unpublished analyses) when given at antidepressant doses. These data indicate that there may be sufficient total exposure of (*2S,6S;2R,6R*)-HNK to exert biologically meaningful effects, but also suggest the possibility that other ketamine metabolites may be additive in humans to exert the full antidepressant actions of ketamine.

Early pharmacodynamic studies assessing the anesthetic properties of ketamine and its principle metabolite norketamine, and (*2S,6S;2R,6R*)-HNK demonstrated that ketamine and norketamine manifested anesthetic effects and induced hyper-locomotor activity during the post-anesthetic recovery period in rats, whereas (*2S,6S;2R,6R*)-HNK had no effect on these outcomes [122]; for review see [123]. (*2S,6S;2R,6R*)-HNK was thus described as an “inactive” metabolite in regards to anesthetic action.

There is evidence that metabolism of ketamine to (*2S,6S;2R,6R*)-HNK is necessary for its antidepressant action in rodent tests [13]. This was shown by chemically altering ketamine via deuteration at the C6 position, which did not change its binding affinity for the NMDAR, but dramatically decreased its *in vivo* metabolism to (*2S,6S;2R,6R*)-HNK. This manipulation prevented ketamine’s antidepressant actions in mice [13], indicating that metabolism of ketamine to (*2S,6S;2R,6R*)-HNK is required for ketamine’s antidepressant responses. In addition, greater antidepressant behavioral responses of a single administration of ketamine have been observed in female compared to male rats and mice [13, 124, 125]. In mice, this behavioral effect was associated with higher brain levels of (*2S,6S;2R,6R*)-HNK, but not ketamine or norketamine levels [13], further supporting a role of this metabolite in the antidepressant actions of ketamine.

Both the (*2S,6S*)- and/or (*2R,6R*)-HNK enantiomers are sufficient on their own to exert dose-dependent antidepressant actions in several rodent tests including the 1-hour [13] and 24-hour [13, 126] forced-swim test, learned helplessness paradigm [13], as well as reversal of social interaction deficits following chronic social defeat, and anhedonia deficits following chronic corticosterone administration [13]. In accordance with the findings that (*R*)-ketamine is a more potent antidepressant compared to the (*S*)-ketamine [13, 116, 117, 127], the (*2R,6R*)-HNK metabolite, which is solely produced via the metabolism of (*R*)-ketamine, exerts more potent and longer-lasting antidepressant actions compared with the (*2S,6S*)-HNK enantiomer, which is produced via the metabolism of (*S*)-ketamine. Nevertheless, Yang *et al.* (2017) [128] failed to identify antidepressant-relevant actions of a single dose of (*2R,6R*)-HNK (10 mg/kg) following chronic social defeat stress in mice, indicating that further studies are required to establish the effective doses of this metabolite in different animal tests predictive

of antidepressant efficacy. Indeed, a dose of 20 mg/kg was capable of reversing anhedonia following chronic social defeat stress in mice [13].

Important for the mechanism of action of (*2R,6R*)-HNK as an antidepressant (and thus ketamine's action) is the fact that at relevant concentrations (i.e., 10 mg/kg or brain C_{max} = ~10 μmol/kg in mice), (*2R,6R*)-HNK does not appear to inhibit the NMDAR. [^{3}H]-MK-801 binding displacement studies showed that the affinity of (*2R,6R*)-HNK to displace MK-801 from the NMDAR is >100 μM, and that of (*2S,6S*)-HNK is 7–20 μM [111, 112]. In addition, at 10 μM concentration, (*2R,6R*)-HNK does not functionally inhibit the NMDARs localized at stratum radiatum interneurons in hippocampal slices, compared to ~50% inhibition by ketamine at this concentration [13]. Suzuki et al. (2017) [129] recently confirmed that (*2R,6R*)-HNK does not functionally inhibit NMDAR-mEPSCs at 10 μM [129]. These authors also reported that at a higher concentration (50 μM), (*2R,6R*)-HNK induces a modest (~40%) inhibition of NMDAR-mEPSCs [129], which could result in off-target effects of this metabolite at high doses. However, (*2R,6R*)-HNK did not induce any NMDAR inhibition-mediated side effects in mice in the open-field test (locomotor activity; doses up to 125 mg/kg), the rota-rod test (motor incoordination; doses up to 125 mg/kg) and the pre-pulse inhibition test (sensory dissociation; doses up to 375 mg/kg) [13, 130], in contrast to the antidepressant dose of 10 mg/kg.

Downstream mechanisms involved in ketamine's antidepressant actions

α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR)

α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs) are ionotropic transmembrane glutamatergic receptors and the principal receptors responsible for the transduction of fast synaptic neurotransmission in the brain, and are targets for multiple signaling pathways that regulate synaptic plasticity [131]. The disinhibition hypothesis of ketamine action proposes that an increase in synaptic glutamatergic neurotransmission causes an acute activation of the post-synaptic AMPARs [132]. We note that ketamine-induced enhancement of synaptic excitatory neurotransmission would be predicted to not only activate post-synaptic AMPARs, but also NMDARs. Although synaptic NMDAR activation has not yet been reported/studied to underlie ketamine's antidepressant actions, it is likely to contribute to the antidepressant effects of the drug. Indeed, activation of both AMPARs and NMDARs is required for synaptic potentiation and synaptic plasticity [133], which both are thought to be involved in the antidepressant actions of ketamine [134].

Quantitative EEG measurements in humans [101], as well as rats e.g. [135] and mice [e.g. 13] revealed ketamine-induced increases in gamma-band power, which, in addition to a putative measure of cortical disinhibition, also indicates activation of fast ionotropic excitatory receptors, including AMPARs [136–138]. Pre-treatment with a subthreshold dose of an AMPAR agonist (C×546) enhanced the antidepressant effects of ketamine in the forced-swim test in rats [139], indicating that AMPAR activation might be involved in ketamine's antidepressant effects. Indeed, pre-treatment with the AMPAR antagonist NBQX prevents the antidepressant-like actions of ketamine in the forced-swim test [9, 13, 117, 139, 140], tail-suspension test [117, 141], novelty-suppressed feeding test [142], learned helplessness test [141] and stress-induced sucrose preference deficits [117, 143]. Importantly, NBQX does not prevent the

antidepressant actions of monoamine-acting antidepressant drugs [9, 144], highlighting AMPAR activation as a unique mechanism underlying ketamine's antidepressant actions. Notably, as AMPAR activation typically leads to membrane depolarization and voltage-dependent release of NMDAR Mg^{2+} blockade [28], inhibition of AMPARs could also be mechanistically linked to preventing NMDAR activation, thus inactivation of both AMPARs and NMDARs could be responsible for the lack of ketamine's antidepressant actions following administration of NBQX.

Ketamine administration also results in an upregulation of the membrane AMPAR subunits, GluA1 and GluA2, in the hippocampus three hours post-injection [63]. AMPAR containing GluA1 and/or GluA2 subunit upregulation was also observed in mPFC [75] and hippocampal [13] synaptoneurosome fractions at 24 hours post-injection, indicating a rapid-triggered and sustained recruitment of AMPAR in the synapse, consistent with synaptic strengthening. In fact, low doses of ketamine were shown to induce an enhancement of AMPAR-mediated synaptic transmission in the mPFC [145] and hippocampus [146] of rats, as measured by AMPAR currents in pyramidal neurons and extracellular *in vivo* electrophysiological recordings in CA3 pyramidal neurons respectively. Additionally, application of ketamine to hippocampal slices (non-stimulated [10, 63] and stimulated [147]) enhanced AMPAR-mediated synaptic potentiation in the CA1 region. The AMPAR subunit GluA2 was shown to be required for ketamine's induction of synaptic potentiation, since ketamine did not induce AMPAR-mediated synaptic potentiation of Schaffer collateral-CA1 synapses in hippocampal slices of mice lacking the *GluA2* gene [63]. In addition, GluA2 knockout mice did not manifest ketamine-induced antidepressant responses [63]. Similar to ketamine, other NMDAR antagonists, including MK-801 [63] and AP-5 [148] mimicked ketamine's effect in inducing AMPAR-mediated synaptic potentiation. This finding was hypothesized to indicate that ketamine, via blocking the NMDAR at rest, drives synaptic potentiation, leading to synaptic plasticity changes that might be relevant to the antidepressant actions of NMDAR antagonists [10]. However, MK-801 failed to induce long-lasting antidepressant actions in several animal tests [9, 10, 13, 103].

In line with an AMPAR activation-dependent mechanism of ketamine's antidepressant action, (*2R,6R*)-HNK induces an increase in AMPAR-mediated excitatory post-synaptic potentials recorded from the CA1 region of hippocampal slices following stimulation of Schaffer collateral axons, suggesting an enhancement of excitatory synaptic transmission [13] (see Figure 1). This effect appears independent of any possible NMDAR inhibition by (*2R, 6R*)-HNK, since the NMDAR antagonist AP-5 was present in the vehicle wash solution [13]. In support of this, (*2R,6R*)-HNK, at the same concentration which did not alter NMDAR EPSCs (i.e., 10 μM), increases the frequency of AMPAR-mediated excitatory post-synaptic currents recorded from CA1 stratum radiatum interneurons, which receives glutamatergic inputs from the Schaffer collaterals [13]. Similar to ketamine, (*2R,6R*)-HNK treatment in mice induces an acute and transient increase in high frequency gamma power [13]. Importantly, administration of the AMPAR antagonist NBQX prior to (*2R,6R*)-HNK abolished the gamma power oscillation increases, as well as the acute and sustained antidepressant effects of this metabolite in mice, indicating that acute AMPAR activation is required for gamma power increase and its rapid and sustained antidepressant actions [13]. In addition, (*2R,6R*)-HNK administration in mice, while not altering the levels of GluA1 or GluA2 AMPAR

subunits 1 hour post-injection in hippocampal synaptoneurosomes, increases these AMPAR subunits 24 hours post-injection [13], indicating that maintenance of the antidepressant actions of this metabolite requires sustained activation of the AMPARs. Consistent with a mechanistic model where the sustained activity of synaptic AMPARs is required for the long-lasting antidepressant actions of (*2R,6R*)-HNK, it was shown that similar to ketamine [140] blockade of the AMPAR (with NBQX) 23.5 hours after (*2R,6R*)-HNK administration abolished its antidepressant actions at 24 hours post-injection [13].

Brain-derived neurotrophic factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a growth factor that regulates neurite outgrowth, functional neuronal connections, synapse formation and synaptic plasticity in the central nervous system [149–152]. With regards to depression, systemic or intra-hippocampal administration of BDNF exerts antidepressant-like effects [153–155], and over-expression of BDNF in the hippocampus leads to resilience to chronic stress [156]. Activation of the high-affinity BDNF receptor, tropomyosin receptor kinase B (TrkB), was shown to be necessary for these antidepressant-related behavioral actions [157, 158]. Moreover, classical antidepressants induce BDNF-related changes following several weeks of administration [159]. In contrast, ketamine administration rapidly (within 30 min of administration) increases the phosphorylation (activation) of hippocampal TrkB [10] and induces a rapid increase in total BDNF protein levels [10, 160]. In addition, ketamine and (*2R,6R*)-HNK administration increases synaptoneurosomal BDNF protein levels 24 hours post-injection in the hippocampus of mice [13].

BNDF signaling was shown to be necessary for ketamine's antidepressant actions. In particular, ketamine failed to exert antidepressant actions in mice with *Bdnf* gene knockdown specifically in the forebrain [10] and intra-mPFC infusion of a BDNF-neutralizing antibody prevented ketamine's antidepressant behavioral responses [161], showing that BDNF release is essential for the actions of ketamine. In support of this, mice expressing the human $BDNF^{Val66met}$ (rs6265) single nucleotide polymorphism (SNP) – especially Met/Met carriers –, which induces deficits in BDNF processing and activity-dependent secretion [162], do not manifest ketamine-induced antidepressant effects [163]. Similar to these findings in mice, Laje *et al.*, (2012) [164] demonstrated that major depressed patients carrying the Met rs6265 allele did not respond to ketamine, further suggesting that increase in BDNF synthesis is required for the antidepressant actions of ketamine.

Eukaryotic elongation factor 2 kinase (eEF2K)

Eukaryotic elongation factor 2 kinase (eEF2K, also known as calmodulin-dependent protein kinase III), belongs to the atypical alpha-kinase family, and its activity is dependent on calcium and calmodulin cellular levels. Its primary downstream substrate (eEF2) is associated with the regulation of protein synthesis and synaptic plasticity [165]. Under physiological conditions, NMDAR-dependent activation of eEF2K results in inactivation (phosphorylation) of eEF2 leading to the blockade of the elongation phase of protein synthesis and thus inhibition of protein translation [166, 167]. Administration of eEF2K inhibitors reduced behavioral despair in the forced-swim test 30 min post-injection in mice [10]. Autry *et al.*, (2011) proposed that a single sub-anesthetic dose of ketamine, via inhibition

of spontaneous synaptic NMDAR-mediated glutamatergic neurotransmission, decreases activation of eEF2K [10] resulting in eEF2 de-phosphorylation and a subsequent disinhibition of protein translation *in vitro* [10, 62]. *In vivo* eEF2 dephosphorylation was shown to de-suppress BDNF protein translation, which was hypothesized to mediate the long-term effects of ketamine via the induction of synaptic plasticity [10]. Mice lacking the *eEF2K* gene do not manifest ketamine-induced increases in hippocampal BDNF protein expression and lack ketamine antidepressant-like responses in the 30-min forced-swim test [63].

(*2R,6R*)-HNK administration also induced a decrease in hippocampal eEF2 phosphorylation 1 and 24 hours post-treatment, concomitant with increased BDNF levels at 24 hours [13], suggesting that protein synthesis through the eEF2 kinase/BDNF translation pathway might be involved in the antidepressant actions of this metabolite. This finding is of particular importance, since the concentrations achieved in the brain following peripheral administration of this metabolite are not associated with NMDAR inhibition [129, 130], thus synaptic plasticity changes and downstream signaling alterations occur independent of NMDAR inhibition. Indeed, several NMDAR inhibition-independent mechanisms have been proposed, which may explain eEF2 dephosphorylation caused by (*2R,6R*)-HNK administration [168–170]. These findings might suggest that ketamine acts to inhibit eEF2K activity via an NMDAR inhibition-independent mechanism, which converges with the mechanism of antidepressant action of its HNK metabolite as well.

Mechanistic target of rapamycin (mTOR)

Enhanced BDNF translation and/or release, as well as activation of the BDNF receptor target TrkB can further activate downstream pathways important in synaptic plasticity. BDNF-mediated activation of TrkB receptors induces an activation of the phosphatidylinositol 3-kinase (PI3K), which, by changing the inner plasma membrane composition of inositol phospholipids, causes a translocation of Akt (protein kinase B) to the plasma membrane [171]. Alternatively, TrkB activation induces a downstream activation of MEK-MAPK/Erk signaling pathway. These two pathways drive protein translation via the activation of the mechanistic target of rapamycin complex 1 (mTORC1) [172]. Mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that regulates neurogenesis, dendritic spine growth, protein translation initiation, and protein synthesis via a phosphorylation of p70S6 kinase and repression of 4E binding proteins (4EBP [173–175]). mTOR signaling has been implicated in the antidepressant responses of several classical antidepressant drugs [176].

A single antidepressant-dose ketamine administration induced a fast-onset (within 30 min of administration) induction of phospho-mTOR [71, 75, 124, 139, 177–179], phospho-p70S6 kinase and phospho-4EBP1 [75, 177] in the prefrontal cortex and hippocampus of mice and rats, suggesting a mechanism whereby ketamine-induced protein translation occurs in an mTOR activation-dependent manner. These changes are transient and the levels of mTOR-signaling molecules return to baseline levels 2 hrs following ketamine administration [75], indicating that acute activation of mTOR and thus protein translation may induce sustained synaptic plasticity changes responsible for the prolonged effects of ketamine. Additional evidence for the involvement of mTOR signaling in the antidepressant actions of ketamine is the finding

that ketamine administration induced a rapid increase in phospho-Akt and phospho-ERK levels (activation), which are upstream of mTOR signaling activation [75]. Intracerebroventricular administration of both PI3K-Akt and MEK-ERK inhibitors abolished ketamine-induced effects on mTOR pathway phosphoproteins [75]. Although some studies failed to replicate an effect of ketamine administration on mTOR-related signaling [180], this might be due to the different doses of ketamine or the experimental procedures used [181]. Indeed, mTOR activation was shown to be required for ketamine's behavioral antidepressant actions [182]. Specifically, intracerebroventricular pre-treatment with the selective mTOR inhibitor rapamycin blocks ketamine-induced synaptic molecular changes in mice [75], as well as the antidepressant actions of the drug in rats [183] and mice [75]. These findings implicate mTOR as a key downstream point of convergence for explaining ketamine's rapid-acting antidepressant actions. Importantly, and in accordance with mTOR being involved in the antidepressant actions of ketamine, both the antidepressant behavioral effects of ketamine, as well as its actions on the mTORC1 signaling were blocked by pre-treatment with the AMPAR antagonist NBQX [75]. Additionally, (*2S,6S*)-HNK metabolite administration was shown to rapidly induce mTOR phosphorylation in rats [177].

Activation of mTOR signaling is linked to deactivation of the serine/threonine kinase glycogen synthase kinase-3 (GSK-3). In particular, upstream phosphorylation (deactivation) of GSK-3 induces mTOR activation (see Figure 1) [184, 185]. Mice harboring a knock-in mutation at both *GSK-3α* and *GSK-3β* genes, which prevents the phosphorylation-dependent inactivation of the kinase, do not manifest ketamine-induced antidepressant behavioral responses [186]. Administration of combined subthreshold doses of ketamine and lithium (a non-selective GSK-3 inhibitor), or a selective GSK-3 inhibitor, induced an activation of the mTORC1 signaling pathway, phosphorylation of GSK-3, synaptoneurogenesis and enhanced antidepressant actions [187], suggesting that mTORC1 activation and phosphorylation of GSK-3 might be a convergent mechanism involved in ketamine's antidepressant actions. Phosphorylation of GSK-3 might be caused by ketamine-induced activation of the mTOR upstream kinase Akt, which regulates the activity of GSK-3 [188]. This is supported by the finding that PI3K/Akt antagonism prevented ketamine-induced phosphorylation of GSK-3β and mTORC1, and abolished ketamine's antidepressant actions [189].

Conclusions

Most hypotheses regarding ketamine's mechanism of action as an antidepressant have presumed an essential role of inhibition of the NMDAR. These hypotheses include direct effects on spontaneous NMDAR-mediated transmission, preferential inhibition of the NMDAR on GABAergic interneurons, and a role for extra-synaptic (plausibly GluN2B-specific) NMDAR inhibition. However, a growing body of evidence indicates that additional mechanisms are likely involved in mediating the unique properties of ketamine as an antidepressant, which may include ketamine metabolites. Indeed, it was shown that ketamine exerts NMDAR inhibition-independent antidepressant actions, and that these effects require the metabolism of ketamine to the (*2S,6S;2R,6R*)-HNK metabolite [13]. Moreover, the (*2R,6R*)-HNK metabolite is sufficient to induce antidepressant actions, similar to those observed following ketamine administration, in animal tests. This metabolite also exerts

electrophysiological, electroencephalographic and molecular actions that might explain ketamine's unique antidepressant actions [13]. These data highlight the need to consider alternative mechanisms, in addition to NMDAR inhibition, to unravel ketamine's mechanism of action as an antidepressant.

There is a consensus from most pre-clinical research that AMPAR activity is required for the antidepressant actions of ketamine (see Figure 1). Increased probability of glutamate release, either by interneuron-mediated disinhibition or direct action of (*2R,6R*)-HNK on pyramidal neurons may result in activation of AMPARs, and a subsequent activation of downstream neuroplasticity-related signaling pathways, including those regulated by BDNF and mTORC1, to promote protein synthesis and synaptic plasticity that are involved in ketamine's behavioral antidepressant actions. Alternatively, eEF2 inactivation as a result of NMDAR inhibition at rest, may regulate production of BDNF, resulting in an upregulation of AMPARs. Importantly, we note that all the proposed mechanisms of ketamine's antidepressant actions are not mutually exclusive and may in fact complement each other to result in the unique antidepressant effects of the drug. Indeed, a net result of all these processes is a sustained potentiation of excitatory synapses in cortico-mesolimbic brain circuits involved in the maintenance of mood and stress-reactivity [190]. Additional mechanisms, not discussed in the present review, include ketamine's effects on the monoaminergic systems [191–194], as well as its anti-inflammatory actions, which are postulated to be involved in the mechanisms underlying its antidepressant actions; the reader is directed to reviews by Sleigh et al. (2014) [195] and Loix et al. (2011) [196].

Understanding the mechanisms underpinning ketamine's antidepressant actions not only provides invaluable information on the neurobiology of major depression but it also drives the identification of novel therapeutic targets for the development of the next generation rapid-acting antidepressants, which will be effective and lack undesirable side effects. NMDAR inhibition produces serious side effects, even at low, sub-anesthetic and antidepressant-relevant doses, which makes long-term use of agents fully blocking this receptor impractical for the treatment of depression [197–201]. The NMDAR inhibition-independent hypothesis of the antidepressant actions of ketamine reviewed here provides a framework to guide future studies on the identification of novel targets for the long-term treatment of depression lacking such side effects.

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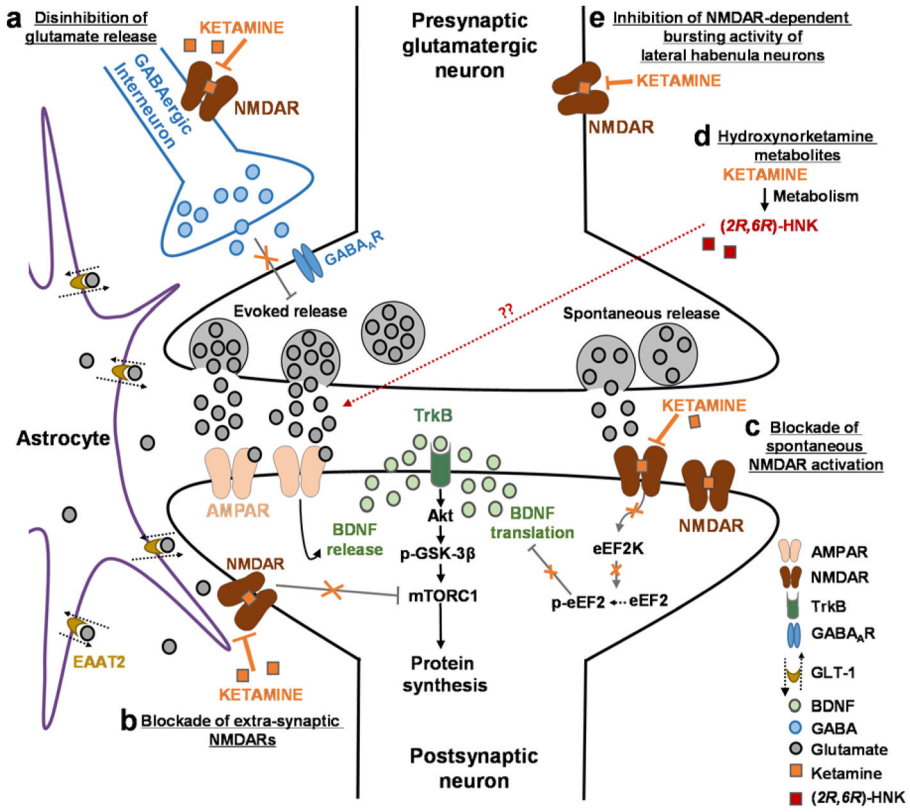

Figure 1. Proposed mechanisms of ketamine action as an antidepressant

(A) Disinhibition hypothesis: Based on the disinhibition hypothesis, ketamine is proposed to selectively block *N*-methyl-*D*-aspartate receptors (NMDARs) expressed on GABAergic inhibitory interneurons, which leads to a disinhibition of pyramidal neurons and enhanced glutamatergic firing. Evoked released glutamate binds to and activates post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) resulting in enhanced brain-derived neurotrophic factor (BDNF) release, activation of the tropomyosin receptor kinase B (TrkB) receptor and subsequently promotion of protein synthesis via the activation of the mechanistic target of rapamycin complex 1 (mTORC1). **(B) Inhibition of extra-synaptic NMDARs:** Ketamine is proposed to selectively block extra-synaptic GluN2B-containing NMDARs, which are tonically activated by low levels of ambient glutamate regulated by the glutamate transporter 1 located on astrocytes. Inhibition of the extra-synaptic GluN2B-NMDARs is hypothesized to de-suppress mTORC1 function, which in turn will induce protein synthesis. **(C) Blockade of spontaneous NMDAR activation:** This hypothesis proposes that ketamine blocks NMDAR-mediated spontaneous neurotransmission, which results in the inhibition of the eukaryotic elongation factor 2 kinase (eEF2K) activity, thus preventing phosphorylation of its eEF2 substrate. This effect subsequently leads to an enhancement of BDNF translation. **(D) Ketamine hydroxynorketamine (HNK) metabolites:** This hypothesis posits that ketamine exerts NMDAR inhibition-independent antidepressant actions via the action of its metabolites, (*2R, 6R*)-HNK and (*2S,6S*)-HNK. Ketamine is metabolized to HNKs following administration, and these HNK metabolites act to promote AMPAR-mediated synaptic potentiation. These

mechanisms of ketamine action are not mutually exclusive and may act complementary in exerting the antidepressant actions of the drug as all hypotheses propose acute changes in synaptic plasticity, leading to sustained strengthening of excitatory synapses, being necessary for antidepressant responses.

Abbreviations: EAAT2, excitatory amino acid transporter 2; GABA, gamma aminobutyric acid; GSK, glycogen synthase kinase