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Convergent mechanisms underlying rapid antidepressant action

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Abstract

Traditional pharmacological treatments for depression have a delayed therapeutic onset, ranging from several weeks to months, and there is a high percentage of individuals who never respond to treatment. In contrast, ketamine produces rapid-onset antidepressant, anti-suicidal and anti-anhedonic actions following a single administration to depressed patients. Proposed mechanisms of ketamine's antidepressant action include *N*-methyl-*D*-aspartate receptor (NMDAR) modulation, GABAergic interneuron disinhibition, and direct actions of its hydroxynorketamine (HNK) metabolites. Downstream actions include activation of mechanistic target of rapamycin (mTOR), deactivation of glycogen synthase kinase-3 and eukaryotic elongation factor 2 (eEF2), enhanced brain-derived neurotrophic factor (BDNF) signaling, and activation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs). These putative mechanisms of ketamine action are not mutually exclusive and may complement each other to induce potentiation of excitatory synapses in affective-regulating brain circuits, which results in amelioration of depression symptoms. We review these proposed mechanisms of ketamine action in the context of how such mechanisms are informing the development of novel putative rapid-acting antidepressant

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Compliance with Ethical Standards

Conflicts of Interest

T.D.G. has received consulting fees from Janssen Pharmaceuticals, and research funding from Janssen Pharmaceuticals and Roche Pharmaceuticals during the preceding three years. Ronald S. Duman has received consulting fees from Janssen Pharmaceuticals and Taisho, and research funding from Janssen Pharmaceuticals and Taisho, Allergan, Naurex, Navitor, and Relmada during the preceding 3 years. C.A.Z. is listed as a coinventor on a patent for the use of ketamine in major depression and suicidal ideation. P.Z., C.A.Z. and T.D.G. are listed as co-authors in 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. S.M.T. is listed as a co-inventor on a patent application for the use of negative allosteric modulators of $GABA_A$ receptors containing alpha 5 subunits as fast-acting antidepressants.

drugs. Such drugs that have undergoing pre-clinical, and in some cases clinical, testing include the muscarinic acetylcholine receptor antagonist scopolamine, GluN2B-NMDAR antagonists (i.e., CP-101,606, MK-0657), (*2R,6R*)-HNK, NMDAR glycine site modulators (i.e., 4-chlorokynurenine - pro-drug of the $glycine_B$ NMDAR antagonist 7-chlorokynurenic acid), NMDAR agonists (i.e. GLYX-13 (rapastinel)), metabotropic glutamate receptor 2/3 ($mGluR_{2/3}$) antagonists, $GABA_A$ receptor modulators, and drugs acting on various serotonin receptor subtypes. These ongoing studies suggest that the future acute treatment of depression will typically occur within hours, rather than months, of treatment initiation.

1. Introduction

Major depressive disorder is a mental illness afflicting approximately 16 percent of the world population, characterized by depressed mood, lack of engagement in pleasurable activities, disturbances in activity levels, loss of concentration, and suicidal ideation [1]. Currently-available interventions including monoamine-based pharmacotherapies and psycho-behavioral therapies require several weeks to months for beneficial effects to occur [2] and there is a high percent of depressed patients undergoing standard treatment who remain treatment resistant [3]. In addition to treatment resistance associated with the use of the currently available antidepressants, these treatments are often accompanied by undesirable side effects [4–6]. Therefore, there is an urgent need for better antidepressant medications, with a faster onset of action, which will be also effective in patients that do not respond to classical antidepressants.

1.1. Towards the development of rapid-acting antidepressants

In contrast to the delayed therapeutic effects of monoamine-based antidepressants, there is evidence for designing therapeutics with rapid-acting antidepressant actions. For instance, electroconvulsive therapy (ECT) often exerts a more rapid antidepressant action in major depression when compared to monoamine-acting antidepressants [7], with remission rates typically ranging from 50–75% [8–10]. For severe major depression cases and suicidal patients, ECT can induce relatively rapid relief of symptoms [11], however any acute effects are transient [e.g. 12]. An average of six ECT applications over two weeks induces a sustained reduction in depressed mood symptom severity [13, 14].

Acute sleep deprivation is a well-documented highly effective fast-onset (within 24–48 h) antidepressant, which rapidly relieves depressed mood [15]. This initial improvement rapidly reverses following subsequent sleep cycles [15, 16], however, the exact mechanisms underlying this rapid and transient effect of sleep deprivation are currently unknown. These established non-pharmacological interventions comprise a proof of principle for the more rapid relief of depressive symptoms and suggest the feasibility of designing rapid-acting antidepressant medications [17].

More recently, it has been found that ketamine, an anesthetic drug that was first commercially available for human use in 1970 [18, 19], exerts robust, rapid (within 2 h following administration) and sustained (7 days on average) antidepressant actions in major depressed patients, following a single administration -typically intravenous- at a sub-

anesthetic dose [20–24]. Meta-analyses have confirmed and further supported the significance of both ketamine's antidepressant [25–28] and anti-suicidal [29] actions compared to placebo controls. This finding revolutionized and established the concept of rapid-acting antidepressant medications. Nevertheless, ketamine's widespread clinical use for the treatment of major depression is restricted to certain subgroups (e.g., treatment-resistant depression, suicidal ideation) and it requires close monitoring when it is administered, due to its side effects, including dissociation, psychotomimetic properties and abuse potential [30, 31], indicating that alternative medications that share ketamine's robust antidepressant actions, but lack its side effect, are an urgent need.

Following these promising findings with ketamine and based on the hypothesized mechanism of action of this prototype rapid-acting antidepressant drug, pre-clinical and clinical studies have assessed alternative putative rapid-acting antidepressant drugs including subunit-specific *N*-methyl-*D*-aspartate receptor (NMDAR) antagonists, the muscarinic acetylcholine receptor (mAChR) antagonist scopolamine, group II metabotropic glutamate receptor ($mGluR_{2/3}$) antagonists, $glycine_B$-NMDAR modulators, $GABA_A$ receptor modulators (positive and negative allosteric modulators) and serotonin 2C ($5\text{-}HT_{2C}$) receptor antagonists (see Table 1). These compounds/drugs have shown efficacy in several animal tests predictive of rapid-acting antidepressant actions (see Section 1.2).

1.2. Animal tests predictive of rapid-acting antidepressant efficacy

Tests in mice and rats predictive of antidepressant activity of different drugs have been widely used for mechanism of action studies and drug development purposes [32]. A valid model of antidepressant efficacy is expected to have predictive sensitivity in regards to the time course of antidepressant actions in humans. Classical, monoamine-based antidepressants require long-term (weeks if not months) administration to exert their effects in depressed patients [2], thus these drugs should have a similar slow-onset time frame of action in animal tests with predictive validity [32]. Such validated tests (as reviewed by Ramaker and Dulawa [32]) include the forced-swim test assessed at 24 h following drug administration (i.e., 24-h forced-swim test), rather than the typical 1-h or 30-min time point, novelty-suppressed feeding, novelty-induced hypophagia, reversal of learned helplessness, tests of stress-induced social avoidance and anhedonia (i.e, chronic corticosterone administration, chronic mild stress and chronic social defeat stress), as well as reversal of the hyperlocomotor effects following olfactory bulbectomy (Table 1). We note that the only drug repeatedly demonstrated to have rapid antidepressant efficacy in human clinical trials is ketamine, along with the non-pharmacological options ECT and sleep deprivation. Other putative rapid-acting antidepressant agents that were identified in preclinical models have not yet been demonstrated to produce a rapid clinical effect (within 72 h of administration), thus their rapid-onset antidepressant efficacy has yet to be validated in humans. For a description of animal tests predictive of rapid antidepressant efficacy see Table 1.

2. Ketamine: the prototype rapid-acting antidepressant

Among other actions, ketamine is a non-competitive NMDAR antagonist at the phencyclidine (PCP) binding site of the receptor [33, 34]. Although it was initially

developed as an anesthetic drug [18], to be used as an alternative to PCP, it was subsequently reported to exert robust antidepressant actions in depressed patients by Krystal and colleagues [20], who found that a single 40-min intravenous infusion of a sub-anesthetic dose of ketamine (0.5 mg/kg), which produced transient dissociative effects, resulted in significant improvement in depression symptoms within hours after administration of the drug (see Table 2). A robust antidepressant effect of ketamine occurred within 4 h post-administration [20], a time point well after the dissociative effects were no longer present. Following this finding, other clinical studies have replicated and further extended the findings of ketamine efficacy into patients with treatment-resistant depression, using the same dose and intravenous route of administration [e.g. 21, 24, 35]. Following this finding, other clinical studies have replicated and further extended the findings of ketamine efficacy in patients with treatment-resistant depression, using the same dose and route of administration [e.g. 21, 24, 35]. Importantly, there is also significant separation between ketamine's antidepressant response (64% of patients achieved a ≥ 50% reduction in Montgomery-Asberg Depression Scale [MADRS] scores) and placebo (28% of patients) when a psychoactive drug, i.e., midazolam, was used as an active placebo to counteract the functional un-blinding role of the dissociative side effects of ketamine [36]. In addition to its effects to relieve mood in major unipolar depressed patients, ketamine also exerts robust antidepressant effects in treatment-resistant bipolar depression, with a comparable response rate [37, 38] (Table 2). Such antidepressant effects may last 1–2 weeks [e.g. 21, 24, 35]. Nevertheless, individuals who positively respond to ketamine usually relapse. However, there is considerable variability in time of relapse among the patients receiving a single infusion of ketamine [e.g. 21, 24, 35], possibly influenced by the an individual's underlying genetics, as well as environmental influences, previous prescription history, and other factors. Relapse to depression following ketamine treatment might be related to the reversal of the synaptic effects of ketamine [39]; also see Sections 4 and 5. In addition to its antidepressant actions, a single infusion of ketamine induces anti-anhedonic effects [40] and reduces suicidal ideation [29] in depressed patients with an effect commencing within a few hours of administration and lasting for up to 1 week, similar to its antidepressant time course. Importantly, the anti-suicidal actions of ketamine are partially independent of its antidepressant effects [29, 41], although further studies are required to confirm this conclusion. The clinical findings regarding ketamine's antidepressant actions are also supported by animal tests that predict rapid-onset antidepressant action, including the 24-h forced-swim test [42–44], learned helplessness [42, 43, 45–51], novelty-suppressed feeding [49, 52–55], and novelty-induced hypophagia [56, 57]. Ketamine also reverses anhedonia and other maladaptive behaviors following chronic mild stress [43, 55] and chronic social defeat stress [45, 58–61]; also see Table 1. Only few animal studies have been published to date assessing the effects of ketamine on endophenotypes of suicidal behavior (as discussed in [62]).

Ketamine is manufactured as a racemic mixture containing equal portions of its two enantiomers, the (*S*)- and (*R*)-ketamine. In a randomized, double-blind placebo-controlled trial, intravenous infusion of the (*S*)-ketamine enantiomer (40-min infusion, 0.2 and 0.4 mg/kg) exerted antidepressant responses one day post-administration, which was sustained for three days, and in some patients lasted for up to two weeks following a single infusion

[35]. In addition, a randomized controlled clinical trial indicated dose-dependent antidepressant actions of intranasally-administered (*S*)-ketamine (administration regimen: 28–84 mg, twice a week for a total of 2 weeks) in treatment-resistant depressed patients under oral classical antidepressant treatment [63]. Pre-clinical rodent studies have also indicated rapid-acting antidepressant behavioral actions of (*S*)-ketamine following chronic social defeat stress, where the drug reduced behavioral despair (i.e. it decreased immobility time), and reversed anhedonia (i.e. it restored sucrose preference) induced by chronic stress [64]. Moreover, (*S*)-ketamine decreased escape failures in the learned helplessness paradigm [45] and reduced high behavioral despair in the forced-swim test following repeated corticosterone administration [65] in rodents. These behavioral actions of (*S*)-ketamine in rodent tests require higher doses compared to the (*R*)-ketamine enantiomer [45, 64, 65], indicating that (*R*)-ketamine is a more potent antidepressant compared to the (*S*)-ketamine enantiomer, at least in rodents [66]. The (*S*)-ketamine enantiomer is currently in Phase III clinical trials for the treatment of treatment-resistant depression and suicidal ideation after receiving the FDA Fast Track Designation (Clinical Trial ID: NCT02417064). (*R*)-ketamine has yet to be tested in clinical trials for the treatment of major depression.

Although ketamine's antidepressant actions are unique and it is the prototype rapid-acting antidepressant with multiple clinical trials supporting its robust effects in major depressed patients, its widespread use for the treatment of major depression is limited due to its significant adverse effects, as discussed earlier; also see [30, 67–70]. Therefore, other potent and effective antidepressant alternatives to ketamine that lack its undesirable side effects have become a focus in the search for rapid-acting treatments for major depression.

3. Scopolamine as a rapid-acting antidepressant

Scopolamine is a non-selective mAChR antagonist, although it was reported to have some more selective antagonist activity on mAChR subtypes 1 and 2 (M1 and M2 respectively) [71]. The first preclinical evidence indicating antidepressant action of this drug came from Browne in 1979, where administration of scopolamine reduced behavioral despair of rodents in the acute forced-swim test [72]; a finding that was replicated in subsequent rodent studies also using the acute forced-swim test model [73]. However, this test does not predict fast-onset antidepressant actions (Table 1). Although studies assessing the effects of anticholinergic agents, such as biperiden, were performed in the early 1980s [74], the first human trial (not placebo-controlled) assessing the effects of scopolamine in major depressed patients came from Gillin *et al.* in 1991 [75]. Administration of scopolamine for two consecutive nights induced a small, but significant, antidepressant effect 24 h following the second intramuscular injection [75].

Following these positive results, Furey and Drevets conducted a double-blind, placebo-controlled trial in patients with depression, published in 2006 [76]. This study showed that 15-min intravenous infusions of scopolamine separated by 3–4 days between each administration session resulted in significant decreases in depression scores after 3 sessions (thus 3 scopolamine infusions in total), compared to placebo; significant clinical responses were observed in the evaluation after the first scopolamine infusion, 3 to 4 days after the first treatment. This effect of scopolamine was replicated in a second double-blind placebo-

controlled trial conducted by the same investigators using the same study design [77]. The antidepressant effects of scopolamine were reported to appear following just a single 15-min intravenous infusion in a subsequent placebo-controlled clinical trial, with a greater effect in women than men [78] (see Table 2). It is worth noting that other anticholinergic drugs, including the M1 muscarinic antagonist biperiden, showed inconsistent results for the treatment of major depression in human trials, indicating that scopolamine's effects might be mAChR subunit-specific, or via another target [79, 80]. We note that in contrast to ketamine and ECT, there have been no studies published to date testing scopolamine in treatment-resistant depression.

In rodents, scopolamine administration resulted in rapid antidepressant actions in the 24-h forced-swim test [81, 82], learned helplessness [83, 84], novelty-suppressed feeding paradigm [81, 82] and attenuated chronic stress-induced deficits in sucrose preference [81] (see Table 1). These antidepressant effects in animal models were shown to be mediated by the effects of scopolamine to block the M1 subtype of mAChRs [81, 85], however, some evidence for M2 mAChR blockade as the mediator of these effects of scopolamine in animal models also exists [86].

4. Mechanisms underlying fast/rapid onset antidepressants actions

Consensus neurobiological mechanisms underlying the ability of ketamine and other drugs to exert rapid antidepressant actions are complex and have not been fully elucidated. The sustained effects of these drugs appear at time points well beyond when the drugs are eliminated from the brain [87], indicating that they act rapidly to induce long-lasting synaptic plasticity changes that maintain persistent antidepressant actions (see Figure 1). Here, we review proposed mechanisms of ketamine antidepressant action in the context of describing shared, convergent, and also distinct mechanisms with putative novel rapid-acting antidepressants.

4.1. *N*-methyl-*D*-aspartate receptor (NMDAR) modulation

4.1.1. NMDAR inhibition—NMDARs are glutamatergic ion channel receptors, co-activated by glutamate and glycine, and are composed of four different subunits that may be derived from seven different subunit genes: GluN1, GluN2A-D, and GluN3A-B [88]. The first study to report that NMDAR blockers decrease behavioral despair in mice was conducted by Trullas and Skolnick in 1990, who showed that the non-competitive NMDAR channel blocker MK-801 (dizocilpine) and a competitive NMDAR inhibitor, AP-7, decrease immobility time in the forced-swim test acutely following administration [89]. At the time, chronic, but not acute, administration of different antidepressant treatments, including tricyclic antidepressants, monoamine oxidase inhibitors and "atypical agents" had been shown to alter radioligand binding to NMDARs [90, 91]. These findings led to the hypothesis that NMDAR inhibition could be a key target for designing rapid-acting antidepressants. Indeed, it has long been thought that ketamine exerts its rapid antidepressant behavioral actions through its effects on blocking the NMDAR [92].

Evidence from pre-clinical work supports the hypothesis that NMDAR inhibition might induce rapid-onset antidepressant behavioral actions. In particular, a single administration of

the GluN2B acting NMDAR antagonist Ro 25–6981 decreases behavioral despair in the 24-hr forced-swim test [42, 47, 93, 94], novelty-suppressed feeding test [42, 47, 55], novelty-induced hypophagia [56] and reverses anhedonia following chronic mild stress [55]. Similarly, ifenprodil, another GluN2B-NMDAR antagonist, reverses chronic unpredictable stress-induced sucrose preference deficits and behavioral despair in rodents following a single administration [95]. Recently, it has been shown that ketamine might induce its acute (1-h) antidepressant actions via blockade of NMDAR-dependent burst activity in the lateral habenula neurons [96]; however, it remains to be determined whether this action of ketamine is responsible for the long-lasting antidepressant actions of the drug.

Moreover, inhibiting the NMDAR at the co-agonist glycine$_B$ binding site also exerts antidepressant actions in rodent tests predictive of rapid antidepressant activity. In particular, Zhu *et al.* (2013) [97] demonstrated that peripheral administration of 7-chlorokynurenic acid, a glycine$_B$ antagonist, exerted rapid antidepressant actions in the novelty-suppressed feeding and the learned helplessness paradigms following a single injection. Chronic stress-induced anhedonia was also reversed by administration of 7-chlorokynurenic acid, as it reversed decreased sucrose preference [97, 98]. Similar to these findings, 4-chlorokynurenine, a brain-penetrant pro-drug of 7-chlorokynurenic acid, induced fast-onset antidepressant behavioral actions in several animal tests including the 24-h forced-swim test, learned helplessness and novelty-suppressed feeding paradigms [46]. Neither 7-chlorokynurenic acid nor 4-chlorokynurenine administration were associated with ketamine-like psychostimulant effects, sensory dissociation, or abuse liability in rodents [46, 97, 98]. 4-chlorokynurenine is currently in a phase II clinical trial for the treatment of major depression (Clinical Trial ID: NCT02484456).

Nevertheless, there are also clinical and pre-clinical findings challenging the hypothesis that NMDAR inhibition is the primary mechanism of ketamine's rapid antidepressant efficacy. For example, (*R*)-ketamine has a ~4-fold lower affinity/potency for blocking the NMDAR compared to (*S*)-ketamine, but is a more potent antidepressant than (*S*)-ketamine in the 24-h forced-swim test, the learned helplessness and novelty-suppressed feeding tests, as well as in reversing anhedonia following chronic social defeats in rodents [45, 64, 65, 99, 100].

In line with this, a recent study demonstrated that ketamine's antidepressant actions are mediated by its (*2R,6R*)-hydroxynorketamine (HNK) metabolite. In particular, when breakdown of ketamine to its (*2S,6S;2R,6R*)-HNK metabolites was inhibited, ketamine did not exert long-lasting antidepressant behavioral effects in mice. There is evidence for enhanced antidepressant behavioral responses of ketamine in female compared to male rodents [45, 52, 101]. Notably, it was recently demonstrated that higher brain levels of the (*2S,6S;2R,6R*)-HNK metabolite of ketamine in female mice might be associated with these enhanced antidepressant behavioral actions of ketamine in female compared to male mice [45]. (*2S,6S;2R,6R*)-HNK is the most prominent HNK metabolite present in the plasma and brain of mice [45, 102] and the plasma of treatment-resistant patients with depression [103] following a single ketamine administration. Similar to the preclinical findings, higher levels of this metabolite have been measured in the plasma of female patients compared with male patients following a single infusion of ketamine, but this difference was not associated with any significantly different antidepressant responses in these patients [103]. (*2R,6R*)-HNK

itself exerts dose-dependent rapid antidepressant actions in mouse tests [45] (see Table 1). In particular, a single intraperitoneal administration of (*2R,6R*)-HNK reduced immobility time in the 24-h forced-swim test, decreased escape failures in the learned helplessness paradigm, reduced anhedonia measures following chronic corticosterone administration, and reversed social interaction deficits induced by chronic social defeat stress [45] (see Table 1). Consequently, (2R,6R)-HNK is sufficient to exert ketamine's rapid antidepressant actions, at least in animal tests.

In line with these findings, Pham *et al.* identified antidepressant-relevant actions of (*2R,6R*)-HNK in the 24-h forced-swim test following peripheral (10 mg/kg, i.p.) administration or direct administration into the medial prefrontal cortex (mPFC; 1 nmol per side) in mice [104]. However, Yang *et al.* (2017) [105] did not observe significant antidepressant behavioral actions using a single dose of (*2R,6R*)-HNK (i.e., 10 mg/kg) following chronic social defeat stress in mice and the same group reported no effects of (*2R,6R*)-HNK in the learned helplessness paradigm in rats [106], highlighting that further studies are required to establish the effective doses of this metabolite in different animal tests predictive of antidepressant efficacy. Importantly, (*2R,6R*)-HNK does not inhibit the NMDAR at antidepressant-relevant concentrations, as was demonstrated by a lack of MK-801 displacement binding studies (Inhibitory constant: Ki > 100 μM; half maximal inhibitory concentration: IC_{50} > 100 μM), lack of functional activity on NMDARs localized in stratum radiatum interneurons in rat hippocampal slices or dissociated primary cell culture [45, 107–109]. However, it does result in modest inhibition of mEPSC-NMDAR responses in mouse hippocampal cell cultures at higher concentrations [i.e., 50 μM; 108].

Human clinical findings also challenge the NMDAR inhibition hypothesis. Several other NMDAR antagonists lack the rapid, robust or sustained antidepressant action of ketamine in humans [25]; also see Table 2. For instance, memantine, an NMDAR channel antagonist, which acts at the same site as ketamine, failed to show significant antidepressant actions in individuals with major depressive disorder in multiple studies [110–112]. Moreover, a single administration of AZD6765, a low-trapping NMDAR channel blocker (i.e., fast off-rate when glutamate is no longer bound to the NMDAR) also acting at the same site as ketamine, exerted modest but transient (~110 min) antidepressant effects in major depressed patients, although this effect was not sustained [113]. However, in a subsequent study, a single infusion of AZD6765 failed to induce a significant change in MADRS scores compared to placebo at 24 h post-administration [114]. Within the same paper it was reported that patients receiving of AZD6765 (three intravenous infusions per week) for a total period of 3 weeks displayed an improvement in depressed mood and symptom remission during the trial [114]. Finally, a follow up larger, four-country, forty-nine site placebo-controlled human trial comparing AZD6765 to placebo as an adjunctive treatment for depression in a total of 302 patients, failed to show a difference between AZD6765 and placebo [115]. Thus, this drug is no longer under development for the treatment of major depression.

It has also been hypothesized that GluN2B-selective NMDAR inhibition would exert rapid antidepressant actions. Intravenous administration of one such compound, CP-101,606 (traxoprodil), did not result in a rapid beneficial effect (first assessed at 2 days post-treatment), however, it did induce a significant antidepressant response 5 and 8 days

following a single infusion [116]. This was a small study (n=15 subjects/group); there have been no further studies and this drug is not currently in development for depression treatment. There is evidence that this drug may also possess moderate to high affinity at sigma-1 receptors [117, 118], which has been suggested as a target for antidepressant action [119–121]. Therefore, it is difficult to conclude that the delayed antidepressant efficacy of CP-101,606 is solely due to block of GluN2B-containing NMDARs. Another GluN2B-selective NMDAR antagonist, MK-0657 (CERC-301), resulted in modest improvement in the Hamilton Depression Rating Scale (HDRS), but not the MADRS, rating scale 5 days following a single oral administration [122], however, a larger phase II follow-up study with MK-0657 failed [as reported in 123].

4.1.2. NMDAR activation—Another finding that appears to contrast with the NMDAR inhibition hypothesis underlying rapid antidepressant efficacy is the observation that positive modulation of the NMDAR also exerts rapid antidepressant actions. However, as discussed later in this review, rapid-acting antidepressants converge to enhance excitatory neurotransmission, and subsequently activate AMPA and NMDAR receptors [124, 125]. GLYX-13 is a synthetic peptide described as a functional partial agonist of the NMDAR [57, 126]. In humans, a single intravenous infusion of GLYX-13 decreased depression symptoms within 2 h of administration and this effect persisted for ~7 days in a double-blind, randomized clinical trial [127] (see Table 2). Moreover, a single administration of GLYX-13 induces rapid and sustained antidepressant actions in several animal tests, including the 24-h forced-swim test [57, 128], learned helplessness [57], novelty-suppressed feeding [128], novelty-induced hypophagia [57], and female urine sniffing test [128]. Moreover, it reversed anhedonia and other maladaptive behaviors following chronic mild stress [57] and chronic social defeat stress [58] (see Table 1).

The antidepressant actions of GLYX-13 through its agonist activity at the NMDAR are in line with earlier evidence for antidepressant actions of other NMDAR glycine$_B$-site agonists. Specifically, sarcosine, which is a co-agonist at the glycine$_B$ binding site of the NMDAR [129], improved mood scores following 6-week administration in patients [130]. Similarly, the NMDAR glycine site partial agonist D-cycloserine also produced some antidepressant effects in human clinical trials [131, 132] and in the short-term, 60-min forced-swim test in mice [133]. However, it should be noted that the high dose of D-cycloserine used in the study conducted by Heresco-Levy et al. [131] (i.e., 1 g/day) could have instead induced NMDAR inhibition [134], therefore further research is warranted to clarify whether D-cycloserine at the doses tested acted as an NMDAR partial agonist or antagonist. Finally, 1-aminocyclopropanecarboxylic acid (ACPC), a high affinity glycine$_B$ partial agonist, produces antidepressant actions for up to 6 h in the forced-swim test in mice [135].

Importantly, and in contrast to the side effects of ketamine, GLYX-13 does not induce sensory dissociation or display abuse liability properties in rodents [57, 136]. Furthermore, GLYX-13 administration prevents ketamine- and phencyclidine-induced memory deficits [137], consistent with its actions as a positive NMDAR modulator. These findings support that NMDAR inhibition is primarily involved in the side effects of ketamine, while activation of the NMDARs either through an enhanced synaptic glutamatergic neurotransmission, such in the case of ketamine, or direct activation of the receptor (i.e.,

GLYX-13) results in the antidepressant actions of these drugs [125]. GLYX-13 is currently in Phase III clinical trials for the treatment of major depression (see Table 2; Clinical Trial ID: NCT02943577).

4.2. Enhancement of synaptic plasticity

4.2.1. Modulation of excitatory synaptic neurotransmission

Inhibition of GABAergic interneuron activity: Hippocampal and cortical circuits comprise both excitatory glutamatergic pyramidal neurons and inhibitory GABAergic interneurons. GABAergic interneurons are critical for the balance between neural excitation and inhibition [138]. There are subgroups of interneurons that can be distinguished based on their dendritic and axonal morphology, electrophysiological properties (fast- or low-spiking), synaptic connections, and the genes expressed on these neurons, including calcium binding proteins (e.g. parvalbumin) and co-transmitters (somatostatin) [139]. Parvalbumin-containing, fast-spiking, interneurons are primarily responsible for controlling the excitability of pyramidal neurons and the synchrony of their firing, via somatic and dendritic synapses [140–142]. High-frequency, gamma power oscillations are hypothesized to be controlled by the activation/inactivation of parvalbumin-containing fast-spiking interneurons in the brain [143, 144]. In contrast to the parvalbumin-containing interneurons, somatostatin-expressing interneurons typically exhibit low-threshold spiking and project to distal dendritic pyramidal cells to control dendritic excitability [145, 146].

Although ketamine and scopolamine are expected to weaken excitatory neurotransmission via blocking NMDARs and mAChRs respectively, both drugs, at low doses, induce a rapid increase in extracellular glutamate levels [85, 147, 148] and an enhancement of glutamate cycling [149] in the mPFC of rodents. One hypothesis that can explain this paradoxical effect is that ketamine and scopolamine exert the effects via receptor subtypes localized on inhibitory GABAergic interneurons, resulting in a reduction in their action potential firing of these neurons. This is predicted to decrease inhibition and increase pyramidal neuron discharge via disinhibition, thus enhancing excitatory glutamatergic neurotransmission [147]. This is also consistent with recent findings indicating that peripheral or intra-mPFC administration of (*2R,6R*)-HNK increases extracellular glutamate levels 24-h post-administration, an effect that was associated with its antidepressant behavioral actions in the 24-h forced-swim test [104]; however, this effect is not due to NMDAR inhibition [45, 107, 108].

NMDAR inhibition would typically lead to decreased neuronal excitability. However, MK-801, which acts on the ketamine/phencyclidine site, was shown to first reduce interneuron firing and subsequently enhance pyramidal neuron firing in awake rats [150]. This finding is proposed to explain how an antagonist of the NMDARs (i.e., ketamine) is able to induce an overall enhancement of excitatory neurotransmission. This effect might be due to the fact that the glutamatergic excitatory synapses on GABAergic interneurons are disproportionally more sensitive to NMDAR blockers than pyramidal neurons [151, 152]. This might be because of their more depolarized resting potential, which results in a disproportionally larger NMDAR-mediated excitation or due to a unique NMDAR subunit composition that renders interneuron NMDARs more sensitive to ketamine [151, 152].

It is well documented that NMDAR antagonism induces an increase in gamma frequency oscillations. Indeed, MK-801 administration enhances cortical gamma EEG power in rats [153, 154], characterized by synchronized high frequency firing as a result of pyramidal neuron disinhibition. Notably, non-selective and GluN2A-NMDAR antagonists, but not GluN2B-, or GluN2C/2D selective subunit inhibitors increase gamma power in rats [155], suggesting NMDAR subunit-specific modulation of cortical EEG activity. However, there is also evidence that GluN2B-NMDAR inhibition increases gamma power specifically during rapid eye movement (REM) sleep state in rats, albeit at a lower magnitude compared with non-selective and GluN2A-NMDAR antagonists [156]. For ketamine, a critical role of GluN2D-NMDARs was reported to underlie the ability of the drug to induce high-frequency gamma oscillations, since this increase was absent in mice lacking the GluN2D gene [157].

The antidepressant actions of scopolamine may also be mediated by its actions at interneurons. Activation of M1-mAChRs expressed on GABAergic interneurons was shown to result in rapid excitation of interneuron activity and thus reinforcing an inhibitory input to the pyramidal neurons [158–160]. M1-mAChR knockdown specifically in somatostatin positive GABAergic interneurons, but not parvalbumin interneurons or pyramidal neurons, prevents the antidepressant behavioral actions of scopolamine [82]. Together, these findings indicate that inhibition M1-mAChR on GABAergic interneurons, resulting in disinhibition of pyramidal neurons and enhancement of glutamatergic transmission may be involved in the rapid antidepressant actions of scopolamine.

In support of the disinhibition hypothesis, administration of negative allosteric modulators of $GABA_A$ receptors (GABA-NAMs), that is compounds acting as partial inverse agonists at the benzodiazepine binding site of the $GABA_A$ receptor, exert rapid antidepressant actions in several animal tests (see Table 1; Fig. 1), presumably through a disinhibition of excitatory glutamatergic neurotransmission [161]. Specifically, administration of GABA-NAMs that are selective for receptors containing alpha5 subunits, such as L-655,781 or MRK-016, reversed social interaction and sucrose preference deficits following several chronic stress paradigms 24 h after administration in rats [162]. The effects of a single injection were long-lasting since decreases in behavioral despair in the forced-swim test and restoration of sucrose preference deficits could be seen up to 7 days post-treatment [163]. In mice, MRK-016 administration rapidly reversed chronic restraint stress-induced decreases in female urine sniffing preference (a measure of hedonic behavior in male mice) and it decreased immobility time in the 24-h forced-swim test [164]. More recently, the alpha5-selective GABA-NAM, RY-080, was shown to reduce behavioral despair in the acute forced-swim paradigm [165]. Importantly, in contrast to ketamine, alpha5-selective GABA-NAMs lack the sensory dissociation and abuse liability at antidepressant-relevant doses in animal models [163, 164] and in humans [166]. Rodent expression of the alpha5 subunit is largely limited to the hippocampus and PFC [167], with humans also showing preferential expression in these regions [168]. Although these findings are promising, the effects of these agents are yet to be assessed in major depressed patients.

In contrast to the evidence supporting a role of inhibition of GABAergic interneuron activity to underlie the rapid antidepressant actions of ketamine and scopolamine, there is also some pre-clinical evidence against this hypothesis. In particular, GABAergic synaptic cortical

disinhibition induced via a global reduction of $GABA_A$ receptor function, increased baseline behavioral despair in the forced-swim test and latency for food consumption in the novelty-suppressed feeding test in mice [169–171], indicative of a depressive-related phenotype. In addition, disinhibition of somatostatin-positive GABAergic interneuron activity in mice, resulting in an enhanced interneuron excitability, and thus inhibition of pyramidal neuron activity induced antidepressant-related behavioral responses in mice (i.e., reduced latency to feed in the novelty-suppressed feeding test and decreased escape failures in the learned helplessness paradigm) [172]; however long-term deletion of $GABA_A$ receptors could result in compensatory changes that might contribute to the observed behavioral effects.

There is evidence of GABAergic neurotransmission deficits in patients suffering with depression. Such depressed subjects have been shown to manifest decreased cerebrospinal fluid GABA levels, reductions in parahippocampal and lateral temporal $GABA_A$ receptor density, as measured by positron emission tomography tracer [11C]-flumazenil [173–175]. Long-term treatment with classical monoamine-based antidepressants restores decreased GABA concentrations in the occipital cortex of depressed patients [176]. Therefore, $GABA_A$ receptor positive allosteric modulators might be able to restore these GABAergic neurotransmission deficits in depressed patients. Clinically, a report combining data from two previously published studies revealed enhanced antidepressant actions of SSRIs when these were administered in conjunction with the positive $GABA_A$ receptor allosteric modulator eszopiclone (Lunesta©), a benzodiazepine site partial agonist, compared to the placebo-SSRI monotherapy groups [177]. However, there was no difference in the remission rates and the response rate advantage of the combined administration of the drugs was lost when insomnia parameters were excluded from the depression score analysis, and there was no evidence for a faster acting antidepressant response of the combined SSRI and eszopiclone group [177]. Positive modulation of $GABA_A$ receptors through an increase of the glycolytic byproduct methylglyoxal [178], delivered via inhibition of the cytosolic enzyme lactoylglutathione lyase (GLO1), induces fast-onset antidepressant actions in animal tests [179]. In particular, a 5-day administration of two GLO1 inhibitors, *S*-bromobenzylglutathione cyclopentyl diester (pBBG) and methyl-gerfelin (MeGFN), reduced behavioral despair in the mouse forced-swim test and tail suspension test and it also blocked maladaptive phenotypes induced by chronic mild stress and ameliorated olfactory bulbectomy-induced locomotor hyperactivity [179]; see Table 1. Additionally, administration of an alpha5-containing $GABA_AR$ positive allosteric modulator reduced behavioral deficits following chronic unpredictable mild stress, when injected 30 min prior to testing [180]. Further studies will be required to understand the exact impact of altered GABA levels to the symptoms of depression, as well as the effects of $GABA_A$ receptor agonists, antagonists, and inverse agonists on $GABA_A$ receptor function and excitatory-inhibitory balance.

Inhibition of pre-synaptic metabotropic glutamate receptors: The metabotropic glutamate receptor family (mGluRs) is comprised of eight different receptor subtypes ($mGluR_1$-$mGluR_8$), which are divided into three main groups (group I: $mGluR_1$ and $mGluR_5$; group II: $mGluR_2$ and $mGluR_3$; group III: $mGluR_4$, $mGluR_6$, $mGluR_7$ and $mGluR_8$). Pre-clinical studies have reported efficacy of group II metabotropic glutamate

receptor ($mGluR_{2/3}$) antagonists in reducing behavioral despair in the acute forced-swim test tested 30- to 60-min following drug administration [181–183] and decreasing escape failures in the learned helplessness paradigm [184]. Group II metabotropic glutatmate receptors are expressed at hippocampal, synaptic, mossy fiber-CA3 pyramidal cells and at excitatory synapses in the PFC [185]. $mGluR_2$ receptors are primarily localized peri-synaptically in close proximity to the pre-synaptic terminals [186, 187], where they act as auto-receptors to decrease synaptic glutamate transmission when activated, presumably serving as a homeostatic mechanism to prevent excessive glutamate release [188, 189]. In contrast, $mGluR_3$ receptors are primarily localized to glial cells [190] and their activation inhibits astrocyte growth [191] and increases glutamate transporter proteins [192], thus indirectly decreasing extracellular glutamate levels.

$mGluR_{2/3}$ inhibition has been shown to elicit rapid antidepressant actions in preclinical studies, similar to ketamine. In particular, a single administration of an $mGluR_{2/3}$ antagonist reduced immobility time in the 24-h forced-swim test [193], decreased time delay until food consumption in the novelty-suppressed feeding test [194, 195], rapidly reversed chronic stress-induced decreases in sucrose preference - which was sustained for at least 10 days - [196] and reversed chronic corticosterone-induced behavioral deficits [197] in rodents (see Table 1). In addition, $mGluR_{2/3}$ blockade reversed the decrease in sucrose preference produced by chronic social defeat stress in mice [198]. While a large (N= 310 patients) clinical trial of a negative allosteric modulator of $mGluR_2$ (RG1578; decoglurant) failed to demonstrate antidepressant responses compared to placebo [see abstract: 199] (see Table 2), no measure of target engagement was included in this trial and therefore additional studies are needed to determine the potential of $mGluR_{2/3}$ antagonists in the treatment of treatment-resistant depression.

4.2.2. Inhibition of long-term depression and induction/enhancement of long-term potentiation—There are two main forms of activity-dependent synaptic plasticity: long-term depression (LTD), characterized by a persistent decrease in synaptic efficacy, and long-term potentiation (LTP) [200], characterized by a persistent increase in synaptic efficacy [201]. NMDAR activation is typically required for the induction of both LTP and LTD, although NMDAR-independent mechanisms of triggering LTP have been also described [202]. Chronic stress was shown to result in enhancement of LTD and a reduction of LTP, leading to synaptic hypo-function, neuronal loss, as well as decreased spine density and length/number of dendritic branches at some, but not all, synapses in the PFC and hippocampus of rodents [55, 203–209]. Induction of LTP (and inhibition of LTD) have been implicated in antidepressant behavioral responses [210], including the ability of SSRIs to strengthen excitatory synapses [211].

Blocking the NMDAR with acute application of ketamine (10 μM) on rat hippocampal slices prevents induction of LTP [212], and can be predicted to inhibit induction of LTD. Administration of ketamine or (*2R,6R*)-HNK occluded the induction of LTP in the nucleus accumbens and ventral tegmental area 24 h post-injection in mice [213]. However, ketamine paradoxically enhances LTP in hippocampal brain slices taken 24 h after a single *in vivo* administration in rodents [57, 212]. Therefore, ketamine appears to exert differential effects *in vivo* and *in vitro* in terms of LTP induction. One factor to consider in regard to this

paradox is the lack of metabolism of ketamine to its HNK metabolites *in vitro* [214] and/or that enhanced glutamatergic neurotransmission (i.e., increased extracellular glutamate levels [147], increased glutamate cycling [149]) might not occur in slices. Another important factor is the relatively rapid (within 2 h post-injection) clearance of ketamine from the brain *in vivo* [45]. Finally, the degree of NMDAR inhibition *in vivo* produced by antidepressant-relevant concentrations of ketamine is uncertain, while in slices, concentrations of ketamine used may block the NMDAR both on GABAergic interneurons, as well as on glutamatergic pyramidal neurons.

GLYX-13 administered *in vivo* was shown to reduce hippocampal LTD and to simultaneously enhance the magnitude of LTP induced in rat slices [215, 216], possibly via a preferential activation of the GluN2B-containing NMDARs [215]. Importantly, GLYX-13 reverses chronic stress-induced reduction in NMDAR-dependent LTP [217], which is a mechanism hypothesized to mediate its antidepressant actions. Moreover, similar to ketamine, GLYX-13 enhances hippocampal LTP in brain slices taken 24 h and 7 days following a single *in vivo* injection in rodents [218].

Group II metabotropic glutamate receptor activation is required for the expression of hippocampal LTD and induces a bi-directional inhibition of LTP [188, 189]. In contrast to $mGluR_2$ receptors, activation of $mGluR_3$ receptors is critical for the expression of LTD, but it is not important for LTP [219]. It can therefore be hypothesized that inhibition of $mGluR_{2/3}$ receptors might produce rapid antidepressant actions via blockade of the presynaptic $mGluR_2$ autoreceptors, thereby promoting induction of LTP/synaptic strengthening via a disinhibition of excitatory neurotransmission. Furthermore, administration of $mGluR_{2/3}$ antagonists in rodents increases PFC glutamate levels [220], which might be involved in the antidepressant actions of these drugs via the activation of the AMPAR, as described below.

4.3. Synaptogenesis

A convergent hypothesis for the actions of rapid-acting antidepressants is that administration of these agents leads to a restoration of synapse number following depression-induced synaptic loss and changes in neuronal morphology. There is evidence showing decreased clustering of neurons [221], reduced neuronal size and glial cell density [222–225], decreased cortical thickness [225], as well as decreased soma size of pyramidal neurons [226] in the PFC, anterior cingulate cortex and/or hippocampus in post-mortem brain tissue from major depressed patients. Moreover, evidence shows that the density of dendritic spines and the extent of dendritic branching in the PFC and hippocampus of chronically-stressed rodents are reduced [227–233]. Although findings in post-mortem brain tissue have limitations due to poor fixation and tissue condition, loss of synapses were also observed in the PFC of patients with depression using electron microscopy [234].

Long-term, but not short-term monoamine-based antidepressant treatment restores dendritic atrophy induced by chronic stress in rodents [235]. In contrast to the need for long-term administration of conventional antidepressants to induce neuronal remodeling, ketamine rapidly reverses the reduction in the number of dendritic synaptic connections following chronic stress in the PFC of rodents [42], consistent with a promotion of the formation of

new synapses. This increase in mature spine density was observed 24 h following a single ketamine administration [42]. The same authors also showed that ketamine produced an increase in the amplitude and frequency of serotonin- and hypocretin-induced excitatory post-synaptic currents in the PFC of rats [42]. Recently, Cavelleri *et al.* (2017) demonstrated that a 60-min exposure of mouse mesencephalic and human induced pluripotent stem cells-derived dopamine neurons to ketamine (1–10 μM) and (*2R,6R*)-HNK (0.5 μM) increased dendritic arborization and soma size of both these cell populations [236].

Similar to ketamine, scopolamine administration has been reported to rapidly increase synaptogenesis in conjunction with its antidepressant behavioral responses in rats [85]. Likewise, the $mGluR_{2/3}$ antagonist MGS0039 also reverses chronic-stress-induced decreases in spine density in the prelimbic area of the mPFC and hippocampus of mice [198]. GLYX-13 also rapidly increases spine number and function in layer 5 neurons of the mPFC [128]. In addition, electroconvulsive shock increases dendritic branching in the dentate gyrus [237] and 24 h of sleep deprivation increases the number of spines in the PFC, but not hippocampus, of rats [238]. Finally, sub-chronic administration of $5\text{-}HT_{2C}$ receptor antagonists (RS102221 and SB242084) induces fast-onset (after 5 days of administration) antidepressant actions following chronic mild stress that was associated with a reversal of stress-induced dendritic atrophy in the mPFC of mice [239]. These findings suggest that increases in spine density and strengthening of neuronal connections are critical mechanisms underlying rapid antidepressant behavioral responses. Increases in synaptic spine densities were shown to be preceded by an activation of the mechanistic target of rapamycin (mTOR) [240], as described below.

5. Downstream pathways involved in rapid antidepressant actions

5.1. Activation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPAR)

Changes in AMPA-preferring glutamate receptors (AMPARs) play a major role in the expression of plasticity at excitatory synapses [241]. Enhancement of synaptic glutamatergic neurotransmission is largely mediated by an increase in the number and/or conductance of post-synaptic AMPARs [242, 243]. The role of AMPAR-mediated plasticity in rapid antidepressant actions is a topic of great interest. Important considerations to understand the role of AMPARs in rapid antidepressant actions is to distinguish between changes in AMPAR *activation* occurring during the induction of the antidepressant response, and changes in AMPAR *number or function* in the expression of a persistent antidepressant response, when the drugs have been metabolized and are no longer in the system.

There is considerable evidence that AMPAR activation is required for the *induction* of a rapid antidepressant response. In rodent pre-clinical studies, administration of the AMPAR antagonist NBQX, prevents the antidepressant actions of ketamine [45, 47, 64, 195, 244–247], GluN2B-NMDAR antagonists [47], 4-chlorokynurenic acid [46], GLYX-13 [57], scopolamine [85, 248], $mGluR_{2/3}$ antagonists [244, 249], $GABA_AR$-NAMs [164], and (*2R, 6R*)-HNK [45]. Importantly, NBQX pre-treatment does not block the antidepressant actions of monoamine-based antidepressants [47, 250].

A marker of enhanced AMPAR activation during the induction of the antidepressant response is an increase in synchronous oscillatory high frequency EEG activity [251–253]. In fact, most of the agents exerting rapid antidepressant actions in clinical and/or pre-clinical studies, including ketamine [45, 114, 254], AZD6765 [114], $mGluR_{2/3}$ antagonists [255], 4-chlorokynurenine (Zanos, P. and Gould, TD unpublished data), alpha5-selective GABA-NAMs [164] and (*2R,6R*)-HNK [45], were reported to enhance surface EEG power in the gamma frequency band (30 – 80 Hz) measured in the frontal cortex. Notably, NBQX pre-treatment prevented not only the increases in gamma activity, but also the persistent behavioral consequences of (*2R,6R*)-HNK [45] and alpha5-selective GABA-NAMs [164]. Because gamma activity strongly depends on the balance of synaptic excitation and inhibition [256], it is possible that NBQX prevents the antidepressant effects of ketamine and other putative rapid-acting antidepressants by disrupting gamma oscillations.

Gamma oscillatory activity is known to favor induction of activity-dependent synaptic plasticity [256]. One hypothesis for how gamma oscillations might induce a change in behavioral state is through an activity-dependent strengthening of abnormally weakened excitatory synaptic networks, particularly those associated with reward and affect regulation [124]. Acute rhythmic optogenetic activation of the PFC, in the absence of any pharmacological manipulation, exerts an acute antidepressant-like effect in the forced swim test in mice [257] and sustained ketamine-like antidepressant response in the forced swim test 24-h after stimulation in rats [258]. These findings suggest that monitoring EEG activity may be of use to predict novel rapid antidepressant compounds and which patients are likely to respond to this treatment.

There is also considerable evidence that changes in AMPAR number and function underlie the *expression* of a persistent antidepressant response, long after the rapid-acting agent has been cleared. Similar to mechanisms underlying LTP induction, ketamine administration results in a rapid upregulation of cell surface expression of the GluA1 subunit of the AMPAR, in the mPFC and hippocampus of stress-naive rodents [57, 259], as well as an increase in the number of synaptoneurosomal GluA1-AMPAR subunits in the same brain regions 24 h post-injection [42, 45, 128]. Similar, albeit more slowly occurring, changes in AMPAR function are observed at stress-weakened synapses after long-term, but not short-term, SSRI administration in rodents [210].

Similar effects were reported in the PFC and/or hippocampus of rodents following administration of a selective GluN2B antagonist [42], GLYX-13 [128] or (*2R,6R*)-HNK [45]. Chronic stress-induced decreases in hippocampal GluA1 expression are also rapidly reversed following a single dose of a selective GluN2B antagonist [90] or an alpha5-selective GABA-NAM [162]. An increase in AMPAR expression in specific synapses is likely to be indicative of a potentiation of AMPAR-mediated synaptic transmission following administration of rapid-acting antidepressants. [211] Indeed, electrophysiological experiments indicate that ketamine application enhances AMPAR-mediated synaptic transmission in pyramidal neurons of mPFC [260] and CA3 region of hippocampus [261] of stress-naive rats.

In addition to the GluA1 subunit involvement, GluA2 subunit of the AMPAR (GluA2) surface expression is increased after 4–8 h of sleep deprivation in the cortex and hippocampus of rats [262, 263] and following a single administration of ketamine in the hippocampus of mice [43, 45]. Synaptoneurosomal GluA2 levels were also increased 24 h after (*2R,6R*)-HNK administration [45]. GluA2 subunits may 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 and these mice did not manifest antidepressant responses to ketamine in the acute (30-min) forced-swim test [259].

There is evidence that rapid-acting antidepressants exert acute effects on AMPAR function. Application of ketamine to hippocampal slices induces AMPAR-mediated synaptic potentiation in the CA1 region [264], even in the absence of ongoing synaptic stimulation [43, 259]. Similar to ketamine, application of (*2R,6R*)-HNK increases AMPAR-mediated excitatory post-synaptic potentials recorded from the CA1 region of hippocampus [45] at a concentration that does not alter the NMDA-evoked responses in brain slices [45] or hippocampal cell cultures [107, 108]. However, there is no evidence indicating that these actions are a direct effect of ketamine or its metabolite on the AMPARs.

The involvement of AMPAR activation in the antidepressant actions of rapid-acting drugs is further supported by pre-clinical findings showing that positive allosteric modulators of the AMPAR [265–267] and AMPAR agonists (including AMPA itself) [247, 268] decrease behavioral despair in the acute forced-swim test and the demonstration of an enhanced antidepressant potency (increased sucrose preference) of ketamine when administered in combination with AMPA in a putative rat model of depression [268]. Nevertheless, the effects of AMPAR agonists and positive modulators in better validated animal tests (as discussed earlier) have not been yet reported.

5.2. Brain-derived neurotrophic factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a growth factor regulating functional neuronal connections and synaptic plasticity in the central nervous system [269–272]. It has long been postulated that BDNF signaling via its primary receptor, tropomyosin receptor kinase B (TrkB), is deficient in major depression and that elevation of BDNF-trkB signaling contributes to antidepressant activity [44, 273–280]. For example, long-term administration of monoamine-acting antidepressants was reported to increase BDNF transcription in the hippocampus in rats [281]. In addition, chronic antidepressant treatment [282] and ECT [273, 283] reverse a deficit in serum BDNF levels in major depressed patients. Deletion of hippocampal BDNF attenuates antidepressant efficacy of classical antidepressants in rodent models [284, 285], and the BDNF receptor TrB is required to exert antidepressant actions of typical antidepressants [286]. Moreover, systemic or intra-hippocampal administration of BDNF exerts antidepressant-like effects [287–289], while over-expression of BDNF in the hippocampus leads to resilience to chronic stress [290]. Activation of TrkB is necessary for these behavioral actions [291, 292]. It should be noted though that the effects on BDNF-TrkB signaling are region-specific since there is evidence showing that enhanced BDNF-

TrkB signaling in the mesolimbic dopaminergic system results in a depressive phenotype in rodents [293, 294].

Brain-derived neurotrophic factor signaling has been postulated to underlie ketamine's and scopolamine's antidepressant actions. In particular, ketamine did not exert antidepressant actions in mice with forebrain-specific *Bdnf* gene knockdown [43] and intra-mPFC infusion of a BDNF-neutralizing antibody abolished ketamine's antidepressant actions [295]. In addition, mice expressing the human *BDNF*^{Val66Met} (rs6265) single nucleotide polymorphism (SNP), which are characterized by deficits in BDNF processing and activity-dependent BDNF release [296], show attenuated responses to ketamine [297] and scopolamine [298]. Similar dependence on BDNF-TrkB signaling has been observed for GLYX-13 [299] and (*2R,6R*)-HNK (R.S.D., unpublished data). In line with these data, patients suffering from major depression carrying the Val66Met rs6265 allele (both Val/Met and Met/Met) showed as less robust antidepressant response to ketamine compared to homozygous Val/Val individuals (~20–24% of Met carriers showed an improvement *versus* 40% of Val/Val carriers) [300].

Although classical antidepressants require several weeks of administration to induce BDNF-related changes, ketamine administration was reported to rapidly (within 30 min of administration) increase total BDNF protein levels [43, 301] and to enhance BDNF levels in synaptoneurosomal fractions 24 h following administration [45] in the hippocampus of rodents. Similarly, (*2R,6R*)-HNK administration increases hippocampal synaptoneurosome BDNF levels at 24 h post-injection in mice [45]. There is also considerable evidence showing increased BDNF levels following electroconvulsive shock in the hippocampus of rodents [237, 281, 302–309]. Finally, sub-chronic (5 days) administration of a 5-HT_{2C} antagonist [239], as well as partial activation of the $GABA_A$ receptor (via inhibition of GLO1) [179], increase BDNF protein levels in the mPFC and/or hippocampus of mice. In addition, administration of ketamine, GluN2-NMDAR antagonists, $mGluR_{2/3}$ antagonists and electroconvulsive shock reverse chronic stress-induced reduction in BDNF levels in the PFC [95, 198] and hippocampus [198, 310–312] of rodents, suggesting that BDNF induction could be considered as a marker of rapid antidepressant efficacy. Short-term (6–48 h) sleep deprivation has been shown to both increase [303, 313] or decrease [314, 315] hippocampal BDNF levels in stress-naïve rats, and has been shown to restore decreased BDNF levels in the hippocampus following chronic stress [316]. Moreover, although scopolamine administration has been shown to exert its antidepressant actions via a mechanism requiring activity-dependent increased BDNF release [298], there are controversial results showing decreased BDNF levels following scopolamine administration [317–322]. Ketamine and other putative rapid antidepressant drugs also increase the phosphorylation (activation) of hippocampal and/or mPFC TrkB [43, 198, 298], suggesting a BDNF-TrkB-dependent mechanism of rapid antidepressant action. Notably, there is also evidence that isoflurane, an anesthetic drug, may possess relatively rapid antidepressant actions in treatment-resistant patients [323–325] and antidepressant behavioral responses in the learned helplessness and the novelty-suppressed feeding tests in rodents [326], plausible via a TrkB-dependent mechanism [326]. Further studies are required to assess for additional mechanisms whereby rapid and/or sustained antidepressant actions of isoflurane exposure may converge with other rapid-acting antidepressants.

5.2.1. Eukaryotic elongation factor 2 (eEF2)—Increased BDNF signaling following ketamine administration has been proposed to depend on decreases in the spontaneous activation of postsynaptic NMDARs [43]. Under physiological conditions, NMDAR-dependent activation of eukaryotic elongation factor 2 kinase (eEF2K), which is involved in protein synthesis and synaptic plasticity [327], causes an inactivation (phosphorylation) of its substrate protein, eEF2 (Thr 56), leading to the blockade of the elongation phase of protein synthesis and thus inhibition of protein translation [328, 329]. Ketamine is proposed to block NMDAR-mediated spontaneous activation of eEF2K, thereby causing a de-phosphorylation of eEF2 and a consequent de-suppression of protein synthesis and enhancement of BDNF translation [43]. This hypothesis is supported by the finding that administration of eEF2K inhibitors induces antidepressant behavioral responses in mice using the 30-min forced-swim test [43]. Administration of (*2R,6R*)-HNK [45] also decreases phospho-eEF2 (Thr 56) levels in the hippocampus of mice 1 and 24 h after administration, suggesting that this pathway could be triggered independently from NMDAR inhibition. Sub-chronic administration of 5-HT_{2C} antagonists or GLYX-13 also decreases phospho-eEF2 (Thr 56) levels in the mPFC [239] and reduce the chronic stress-induced enhancement of phospho-eEF2 (Thr 56) in the hippocampus of mice [330], respectively, further challenging NMDAR inhibition-dependency for these downstream changes. Indeed, there are multiple mechanisms other than NMDAR inhibition that could be responsible for a de-phosphorylation of eEF2 [331–334]. Finally, 8 h of sleep deprivation cause a robust increase in phospho-eEF2 (Thr 56) levels in the PFC and hippocampus of rats [335]. Decreased phospho-eEF2 levels alone may not be sufficient for exerting rapid-acting antidepressant actions. Opal *et al.* demonstrated that sub-chronic (5-day) administration of citalopram did not exert antidepressant actions in mice, even though it significantly reduced phospho-eEF2 (Thr 56) levels in the mPFC [239].

5.2.2. Mechanistic target of rapamycin (mTOR)—Enhanced BDNF release and activation of TrkB trigger downstream pathways via an activation of the phosphatidylinositol 3-kinase (PI3K), which in turn translocates Akt (protein kinase B) to the plasma membrane [336]. TrkB activation can also induce activation of the downstream (mitogen-activated protein kinase) MAPK/Erk signaling pathway. Both pathways promote protein synthesis through activation of the mechanistic target of rapamycin complex 1 (mTORC1) [337]. Among the mTOR-regulated proteins are several that regulate neurogenesis and dendrite spine growth via phosphorylation of the synaptic p70S6 kinase and suppression of 4E binding proteins (4EBP) [338–340].

mTORC1 signaling has been implicated in rapid antidepressant actions. In particular, administration of ketamine [42, 52, 247, 341–344], $mGluR_{2/3}$ antagonists [196], GluN2B-NMDAR antagonists [42], GLYX-13 [128, 330], scopolamine [85], 7-chlorokynurenic acid [97] and 5-HT_{2C} antagonists [239] induces a fast-onset increase in levels of phospho-mTOR (Ser 2448), phospho-p70S6 kinase (Thr 389), and phospho-4EBP1 (Thr 37/46) in the hippocampus and/or mPFC of rodents. Enhanced mTORC1 signaling following administration of ketamine is transient [42], indicating that acute activation of mTORC1 and thus protein translation may transiently induce synaptic plasticity responsible for the prolonged effects of ketamine. mTORC1 activation was shown to be necessary for the

behavioral antidepressant responses of ketamine, scopolamine, GLYX-13 and $mGluR_{2/3}$ antagonists. Specifically, pre-treatment with the selective mTORC1 inhibitor rapamycin blocks ketamine-induced synaptic molecular changes [42], as well as the antidepressant actions of ketamine, scopolamine, Ro 25–6981, GLYX-13 and $mGluR_{2/3}$ inhibition in rodents [42, 85, 128, 193, 345]. Importantly, AMPAR inhibition prior to ketamine administration not only blocks its antidepressant actions, but also blocks ketamine-induced actions on mTORC1 signaling [42]. There is evidence that chronic SSRI administration does not induce mTORC1 activation [42] (but see [239]), suggesting that mTORC1 is a point of convergence that is uniquely activated by rapid-acting antidepressants.

In addition to the direct activation through the BDNF/TrkB pathway, it is hypothesized that mTORC1 activation could also occur via alternate pathways. One alternate is upstream phosphorylation-dependent deactivation of glycogen synthase kinase-3 (GSK-3). GSK-3, which has two isoforms, α and β, with similar but not identical functions, has been extensively linked with the antidepressant actions of lithium [346, 347] and has been implicated in the rapid antidepressant actions of ketamine [51]. Ketamine administration increases the levels of phosphorylated GSK-3β (Ser 9) in the PFC and/or hippocampus in rodents [39, 51, 348]. Mice carrying a knock-in mutation of both α and β isoforms of GSK-3 that prevents their kinase activity do not show antidepressant behavioral responses to ketamine [51], and lack ketamine-induced upregulation of cell surface GluA1 in the hippocampus [349]. Moreover, when lithium (a non-selective GSK-3 inhibitor) is co-administered with ketamine at sub-effective doses, it induces an activation of the mTORC1 signaling pathway, phosphorylation of GSK-3, synaptogenesis and greater antidepressant effects [39], indicating that a convergent mechanism between mTORC1 signaling and GSK-3 might be involved in ketamine's rapid antidepressant actions. Similar to ketamine, a single electroconvulsive shock enhances phosphorylation of GSK-3β (Ser 9) in the PFC and/or hippocampus of rodents [350–352].

6. Conclusion

Elucidation of the neurobiological underpinnings of ketamine's rapid and persistent antidepressant actions has been a major recent research focus in psychopharmacology, with the expectation that knowledge gained from such studies will lead to the development of novel pharmacotherapies for the effective, rapid treatment of depression [124]. Here we discussed clinical and pre-clinical findings demonstrating rapid-onset antidepressant actions of ketamine and other promising candidate drugs. We have reviewed convergent mechanisms of actions underlying the induction of rapid antidepressant efficacy including NMDAR modulation, synaptic plasticity strengthening, and synaptogenesis, as well as the common downstream effector pathways such as AMPAR activation, enhanced BDNF-TrkB signaling, de-phosphorylation of eEF2, and activation of mTORC1. Pre-clinical and/or clinical findings suggest that other compounds, including scopolamine, (*2R,6R*)-HNK, GLYX-13, 4-chlorokynurenine, GluN2B-NMDAR antagonists, $mGluR_{2/3}$ antagonists, and $GABA_A$ receptor negative allosteric modulators also possess fast-onset antidepressant efficacy (see Tables 1 and 2).

It is important to better understand the convergent mechanisms underlying rapid antidepressant efficacy in preclinical models in order to maximize their antidepressant potency and ameliorate any undesirable side effects these drugs may currently display. Although NMDAR inhibition was long assumed to underlie ketamine's antidepressant actions, recent evidence indicates that additional downstream mechanisms are likely to be involved. Indeed, it was recently shown that the (*2S,6S;2R,6R*)-HNK metabolite of ketamine is essential for its antidepressant actions and that (*2R,6R*)-HNK possesses robust antidepressant efficacy with low potency at the NMDAR [45, 107, 108, 353, 354].

A well-acknowledge point of convergence between distinct mechanistic hypotheses is the required activation of AMPARs for the emergence of rapid antidepressant actions. AMPAR activation promotes activation of downstream signaling pathways, including BDNF/TrkB signaling and activation of mTORC1, thereby promoting protein synthesis, neosynaptogenesis, and restoration of synaptic function in reward and mood-related circuits, where its impairment contributes to the symptoms of depression [355, 356]. The ultimate result of these processes is a sustained potentiation of excitatory synapses in cortico-mesolimbic brain circuits involved in the maintenance of mood and appropriate reactivity to stress [124].

Rapid-acting antidepressants hold a promising future for the effective treatment of depression. Although ketamine is increasingly being used as a treatment [357], there is not a single rapid-acting antidepressant medication that is approved for the treatment of major depression to date. (*S*)-ketamine and GLYX-13 are currently in phase III clinical trials for the treatment of depression. However, a significant amount of research remains to be performed to delineate the exact mechanisms responsible for the emergence of rapid antidepressant efficacy and to define the most efficacious dose regimens for achieving the desired clinical effects, with fewer side effects. Moreover, future clinical studies should aim to include measures that will indicate whether drugs are active at the proposed target *in vivo* (i.e. target engagement), in order to make definitive conclusions regarding mechanism of action and to properly interpret the relevance of negative findings. The identification of additional putative rapid-acting antidepressants in pre-clinical tests that lack ketamine-like side effects, including ketamine's metabolite (*2R,6R*)-HNK, which does not possess NMDAR inhibition-mediated side effects in rodents, opens new paths for the treatment of depression. An important aspect for consideration and an area of future research is the tolerability and efficacy of these treatments following long-term administration. It is important to identify rapid-acting antidepressant medications that can be routinely administered to depressed patients and provide rapid and sustained relief of their mood symptoms without detrimental effects associated with chronic use. Additionally, work is needed to determine approaches that may extend the therapeutic effects of rapid-acting drugs such as ketamine and avoid either short-term or long-term relapse.

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Key points

- Multiple mechanisms have been proposed to explain the rapid antidepressant actions of ketamine and other drugs.
- Proposed mechanisms underlying rapid antidepressant action are not mutually exclusive but may act in a complementary manner, resulting in rapid changes in synaptic plasticity, and sustained strengthening of excitatory synapses in limbic brain regions.
- There are a number of pre-clinically validated targets beyond *N*-methyl-D-aspartate receptor inhibition that provide hope for the development of novel rapid-acting antidepressants.

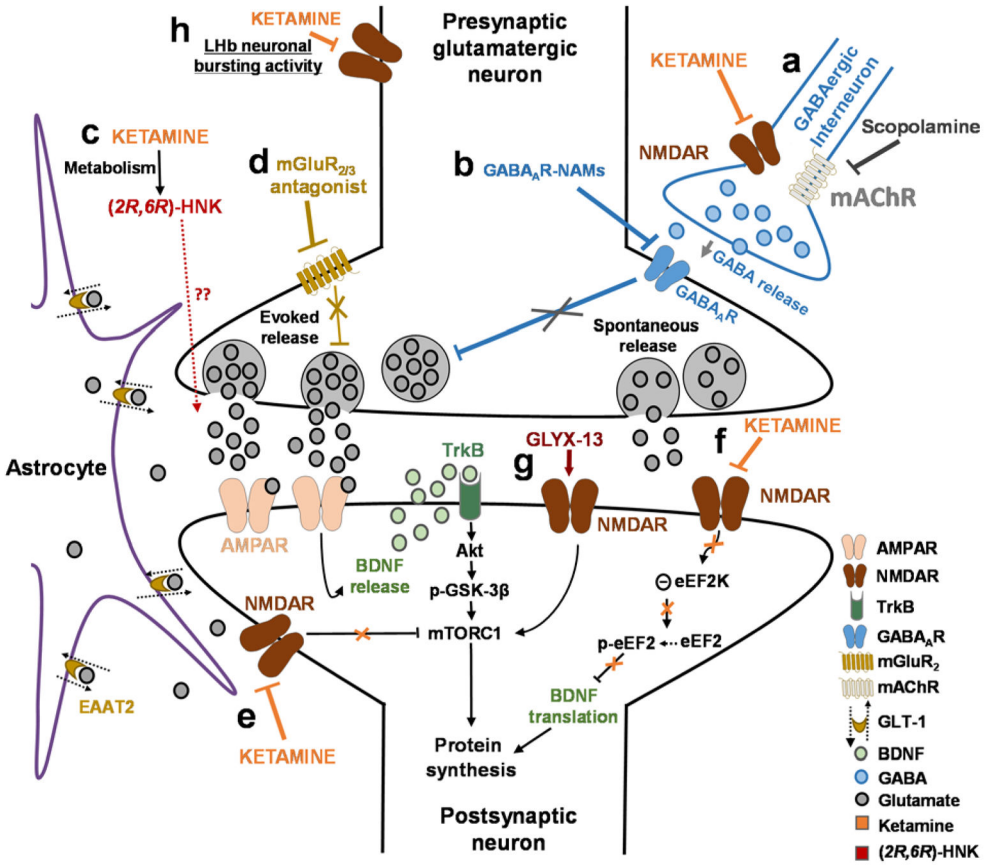

Figure 1. Proposed mechanisms of action of ketamine and other putative rapid-acting antidepressant

(A) Disinhibition hypothesis: ketamine or scopolamine selectively block *N*-methyl-*D*-aspartate receptors (NMDARs) or muscarinic acetylcholine receptors (mAChRs), respectively, expressed on GABAergic inhibitory interneurons, causing a decrease in interneuron activity, which leads to a disinhibition of pyramidal neurons and enhanced glutamatergic firing. **(B) Negative modulators of $GABA_A$ receptors ($GABA_A$R-NAMs)** directly act to reduce pyramidal neuron inhibition. Evoked released glutamate binds to and activates post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR). **(C) Role of ketamine metabolites:** Ketamine exerts NMDAR inhibition-independent antidepressant actions via the action of its metabolite, (*2R,6R*)-hydroxynorketamine (HNK), which acts to promote glutamate release (unpublished data) and AMPAR-mediated synaptic potentiation. **(D) Antagonists of the group II metabotropic glutamate receptors ($mGluR_{2/3}$)** disinhibit the tonic blockade of presynaptic glutamate release, thus enhancing synaptic glutamatergic neurotransmission and thus inducing AMPAR activation. AMPAR activation results in enhanced brain-derived neurotrophic factor (BDNF) release, activation of the tropomyosin receptor kinase B (TrkB) receptor, and a subsequent promotion of protein synthesis via the activation of the mechanistic target of rapamycin complex 1 (mTORC1 complex). **(E) Inhibition of extra-synaptic NMDARs:** Ketamine selectively blocks extra-synaptic GluN2B-containing NMDARs, which are tonically activated by low levels of ambient glutamate regulated by the

glutamate transporter 1 (EAAT2) located on astrocytes. Inhibition of the extra-synaptic GluN2B-NMDARs de-suppresses mechanistic target of rapamycin complex 1 (mTORC1) function, which in turn induces protein synthesis. **(F) Blockade of spontaneous NMDAR activation:** Ketamine blocks NMDAR-mediated spontaneous neurotransmission (miniature excitatory postsynaptic currents – mEPSC), 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 and ultimately protein synthesis. **(G) GLYX-13-induced partial activation of NMDARs:** Activation of the NMDARs is hypothesized to activate mTORC1 and thus to induce protein synthesis. **(H) Inhibition of NMDAR-dependent burst firing activity of lateral habenula (LHb) neurons**: ketamine is proposed to decrease excessive NMDAR-dependent burst firing of LHb neurons linked to depressive symptomatology. All hypotheses propose sustained changes in synaptic plasticity, leading to strengthening of excitatory synapses, being necessary for antidepressant responses. *Abbreviations*: EAAT2, excitatory amino acid transporter 2; GABA, gamma aminobutyric acid; GSK, glycogen synthase kinase

Table 1

Animal tests predictive of rapid antidepressant efficacy

Animal test	Description	Efficacy onset	Rapid-acting antidepressant drugs	Action	Ref.
24-h forced-swim test	Rodents are placed in a water-filled cylinder and their mobility behavior (behavioral despair) is scored. Antidepressant efficacy is noted by decreased immobility compared to the vehicle-treated groups. This timeframe contrasts with testing in the FST at an acute, earlier time point (such as 30 min or 1 h post-treatment) in that drugs are typically no longer present in the brain and exerting direct effects.	• Classical antidepressants: >14 days • Rapid-acting antidepressants: Single administration 24 h prior to testing	Ketamine	NMDAR antagonist	[42–44]
			(*2R,6R*)-HNK	Ketamine metabolite; mechanism not determined	[45]
			Scopolamine	mAChR antagonist	[81, 82]
			GLYX-13	NMDAR agonist	[57, 128]
			4-Cl-KYN	prodrug of the glycineB NMDAR antagonist 7-Cl-KYNA	[46]
			MRK-016	$GABA_A$ receptor negative allosteric modulator	[164]
Novelty-suppressed feeding	Rodents undergo 24–48-h food deprivation and subsequently, the time needed for approaching and biting a food pellet placed in the middle of a highly illuminated arena is measured.	• Classical antidepressants: ~14 days • Rapid-acting antidepressants: Single administration 30–60 min prior to testing	Ketamine	NMDAR antagonist	[49, 52–55]
			(*2R,6R*)-HNK	Ketamine metabolite; mechanism not determined	[45]
			Scopolamine	mAChR antagonist	[81, 82]
			GLYX-13	NMDAR agonist	[128]
			Ro 25–6981	GluN2B-NMDAR antagonist	[42, 47, 55]
			7-Cl-KYNA	$Glycine_B$ NMDAR antagonist	[97]
			4-Cl-KYN	prodrug of the glycineB NMDAR antagonist 7-Cl-KYNA	[46]
Novelty-induced hypophagia	Rodents are food deprived for 24–48 h and food consumption is measured in both the home cage and in a novel anxiogenic environment. Latency to eat, as well as amount of food consumed in the novel arena is recorded and	• Classical antidepressants: ~14 days • Rapid-acting antidepressants: Single administration 30–60 min prior to testing	Ketamine	NMDAR antagonist	[56, 57]
			GLYX-13	NMDAR agonist	[57]
			Ro 25–6981	GluN2B-NMDAR antagonist	[56]

Animal test	Description	Efficacy onset	Rapid-acting antidepressant drugs	Action	Ref.
	normalized to home cage consumption.				
Learned helplessness	Rodents manifest escape deficits following inescapable shocks and sub-chronic/chronic, but not acute administration of classical antidepressants is required to reverse this helpless phenotype.	• Rapid-acting antidepressants: Single administration 24 h prior to testing	Ketamine	NMDAR antagonist	[42, 43, 45–51]
			(*2R,6R*)-HNK	N/D	[45]
			Scopolamine	mAChR antagonist	[83, 84]
			GLYX-13	NMDAR agonist	[57]
			7-Cl-KYNA	$Glycine_B$ NMDAR antagonist	[97]
			4-Cl-KYN	prodrug of the glycineB NMDAR antagonist 7-Cl-KYNA	[46]
Olfactory bulbectomy	Surgical removal of the olfactory bulbs induces hyperactivity in rodents exposed to novel arenas, as well as hypersensitivity to stress and disruption of sleep patterns, which are characteristics of human depression.	• Classical antidepressants: ~14 days • Fast-onset antidepressants: 5-day administration	pBBG	cytosolic enzyme GLO1 inhibitor (possibly acting via $GABA_A$ receptor activation)	[179]
			MeGFN	cytosolic enzyme GLO1 inhibitor (possibly acting via $GABA_A$ receptor activation)	[179]
			RS102221	$5\text{-}HT_{2C}$ receptor antagonist	[239]
			SB242084	$5\text{-}HT_{2C}$ receptor antagonist	[239]
Chronic corticosterone-induced anhedonia	Rodents are treated for 4 weeks with corticosterone (25 μg/ml equivalent for mice or 50 μg/ml equivalent for rats), provided in their drinking water, followed by a wean-off phase: 3 days of 12.5 μg/ml and then 3 days of 6.25 μg/ml. Prior to the anhedonia measures, corticosterone is completely removed for a period of 1 week. This induces anhedonia (decreased sucrose preference) and enhance behavioral despair in the forced-swim test.	• Classical antidepressants: ~14 days • Rapid-acting antidepressants: Single administration 24 h prior to testing	(*2R,6R*)-HNK	Ketamine metabolite; mechanism not determined	[45]
			MGS0039	$mGluR_{2/3}$ antagonist	[197]
			LY341495	$mGluR_{2/3}$ antagonist	[197]
Chronic mild stress	Rodents are exposed to a ~4-week regime of daily stressors	• Classical antidepressants: ~14 days	Ketamine	NMDAR antagonist	[43, 55]
			Scopolamine	mAChR antagonist	[81]

Animal test	Description	Efficacy onset	Rapid-acting antidepressant drugs	Action	Ref.
	(including wet bedding, food deprivation, restraint stress, disturbances in sleep cycles and others), which induces anhedonia, which is typically assessed by decreased sucrose preference and other maladaptive phenotypes that are related to core symptoms of depression.	• Rapid-acting antidepressants: Single administration 24 h or 60 min prior to testing • Fast-onset antidepressants: 5-day administration	GLYX-13	NMDAR agonist	[57]
			Ro 25–6981	GluN2B-NMDAR antagonist	[55]
			Infeprodil	GluN2B-NMDAR antagonist	[95]
			7-Cl-KYNA	$Glycine_B$ NMDAR antagonist	[97, 98]
			L, 655–781	$GABA_A$ receptor negative allosteric modulator	[162]
			MRK-016	GABAA receptor negative allosteric modulator	[162] [164]
			pBBG	cytosolic enzyme GLO1 inhibitor (possibly acting via $GABA_A$ receptor activation)	[179]
			MeGFN	cytosolic enzyme GLO1 inhibitor (possibly acting via $GABA_A$ receptor activation)	[179]
			RS102221	5-HT_{2C} receptor antagonist	[239]
			SB242084	5-HT_{2C} receptor antagonist	[239]
Chronic social defeat stress	Rodents are subjected to a ~10-day cycle of physical attack by an aggressive retired-breeder mouse and psychological stress by placing the test mouse in an area next to the aggressive mouse separated by a perforated divider (for sensory contact); this stress paradigm induces anhedonia and social avoidance.	• Classical antidepressants: ~14 days • Rapid-acting antidepressants: Single administration 24 h prior to testing	Ketamine	NMDAR antagonist	[45, 58–61]
			(*2R,6R*)-HNK	Ketamine metabolite; mechanism not determined	[45]
			GLYX-13	NMDAR agonist	[58]
			MGS0039	mGluR2/3 antagonist	[198]

Abbreviations: 4-Cl-KYN, 4-chlorokynurenine; 5-HT, serotonin; 7-Cl-KYNA, 7-chlorokynurenic acid; GABA, γ-aminobutyric acid; GLO1, lactoylglutathione lyase; GluN2B, glutamate ionotropic receptor NMDA type subunit 2B; HNK, hydroxynorketamine; N/D, not determined; mAChR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor.

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Table 2

Completed double-blind, placebo-controlled trials assessing ketamine and other putative rapid-acting antidepressants

Drug	Study design	Drug administration regimen	Placebo	*N*	Patient condition	Primary outcome	Results	Ref
Ketamine	Double-blind, crossover	Single 0.5 mg/kg, 40-min intravenous infusion	Saline	9	Major and bipolar depressed patients	HDRS	• Decrease in depression scores; • Initial effect at 240 min; Sustained for at least 72 h	[20]
	Double-blind, crossover	Single 0.5 mg/kg, 40-min intravenous infusion	Saline	18	Treatment-resistant depressed patients	HDRS	• Decrease in depression scores; • Initial effect at 110 min; Sustained 7 days on average • Maximum effect at 24 h post-infusion (drug effect: 71%; placebo: 0% response)	[21]
	Double-blind, crossover (augmentation to mood stabilizer)	Maintained lithium or valproate therapy + Single 0.5 mg/kg, 40-min intravenous ketamine infusion	Saline	18	Treatment-resistant bipolar depressed patients	MADRS	• Decrease in depression scores; • Initial effect at 40 min; Sustained 3 days on average • Maximum effect at 48 h post-infusion (drug effect: 71%; placebo: 6% response)	[37]
	Double-blind, crossover (augmentation to mood stabilizer)	Maintained lithium or valproate therapy + Single 0.5 mg/kg, 40-min intravenous ketamine infusion	Saline	15	Treatment-resistant bipolar depressed patients	MADRS	• Decrease in depression scores; • Initial effect at 40 min; Sustained 3 days on average	[38]

Drug	Study design	Drug administration regimen	Placebo	*N*	Patient condition	Primary outcome	Results	Ref
							• Maximum effect at 40 min post-infusion (drug effect: 71%; placebo effect: 0%)	
	Double-blind, parallel arm	Single 0.5 mg/kg, 40-min intravenous infusion	Midazolam	73	Treatment-resistant depressed patients	MADRS	• Decrease in depression scores; • Initial effect at 24 h; Sustained 7 days on average • Maximum effect at 24 h post-infusion (drug effect: 64%; placebo: 28% response)	[36]
	Double-blind, crossover	Single 0.54 mg/kg, 30-min intravenous infusion	Saline	27	Major depressed patients	MADRS	• Decrease in depression scores; • Initial effect at 24 h; Sustained 7 days on average • Maximum effect at 24 h	[358]
	Double-blind, crossover	Single 50 mg intranasal administration	Saline	20	Major depressed patients	MADRS	• Decrease in depression scores; • Initial effect at 24 h; Sustained 7 days on average • Maximum effect at 24 h	[24]
	Double-blind, parallel arm (augmentation to SSRIs)	Newly 4-week escitalopram treatment + Single 0.5 mg/kg, 40-min intravenous ketamine infusion	Saline	30	Major depressed patients	MADRS	• By 4 weeks ketamine decreased depression score by 92.3 % *versus*	[359]

Drug	Study design	Drug administration regimen	Placebo	*N*	Patient condition	Primary outcome	Results	Ref
							57.1 % for placebo • Initial effect at 2 h	
	Double-blind	0.5 mg/kg, 40-min intravenous infusion 2–3 times a week over a 15-day period	Saline	67	Treatment-resistant depressed patients	MADRS	• Maintained antidepressant action for at least 15 days	[360]
(*S*)-ketamine	Double-blind, parallel arm	Single 0.2 or 0.4 mg/kg, 40-min intravenous infusion	Saline	29	Treatment-resistant depressed patients	MADRS	• Decrease in depression scores (not dose-dependent); • Initial effect at 2 h; Persisted 35 days (for 0.4 mg/kg dose) • Maximum effect at 24 h (drug response: 64–67%; placebo response: 0%)	[35]
Memantine	Double-blind, parallel arm	Starting dose of 5 mg/day (capsules) up to a maximum of 20 mg/day for a total period of 8 weeks	Saline	26	Major depressed patients	MADRS	• No statistical separation from the placebo control treatment	[110]
	Double-blind	One capsule daily; dosing titration: week 1, 5 mg/day; week 2, 10 mg/day; weeks 3–8, 20 mg/day	Saline	117	Major depressed patients	PANSS	• No statistical separation from the placebo control treatment	[361]
	Double-blind, (augmentation to traditional antidepressant)	Flexible dose 5–20 mg/day (capsules); target dose of 20 mg/day; total augmentation period: 8 weeks	Saline	31	Major depressed patients (partial or non-responsive to their antidepressant)	MADRS	• No statistical separation from the placebo control treatment	[362]
AZD6765 (lanicemine)	Double-blind	Single 100 mg, 60-min intravenous infusion	Saline	34	Treatment-resistant depressed patients	MADRS	• No separation from placebo	[114]

Drug	Study design	Drug administration regimen	Placebo	*N*	Patient condition	Primary outcome	Results	Ref
							at 24 h post-infusion	
	Double-blind	3-week period of 100–150 mg, 60-min intravenous infusions (3 non-consecutive infusions per week) – patients were allowed to be on their prior antidepressant medications	Saline	152	Treatment-resistant depressed patients	MADRS	• Decrease in depression scores at 2 weeks following the last infusion	[114]
	Double-blind, parallel arm	15 intravenous infusions of 50 or 100 mg lanicemine over a 12-week period	Saline	240	Treatment-resistant depressed patients	MADRS	• No significant separation between lanicemine and placebo treatment	[115]
CP-101,606 (taxoprodil)	Double-blind, parallel arm	40 mg paroxetine + 0.75 mg/kg CP-101,606 intravenous infusion for 1.5 h followed by 0.15 mg/kg/h for 6.5 h	Saline	30	Major depressed patients (paroxetine treatment non-responders)	MADRS	• Decrease in depression scores 5 and 8 days post-treatment (8.4 and 6.2 point difference from placebo respectively) • No antidepressant response 48 h post-treatment	[116]
MK-0657 (CERC-301)	Double-blind, crossover	Oral capsules of 4 mg/day and increased 2 mg/day until reaching 8 mg/day; total administration period - 12 days	Saline	5	Treatment-resistant depressed patients	MADRS	• No significant improvement in patients receiving MK-0657 compared with placebo-treated controls • Moderate decrease in HDRS scores on days 5–6, 9–10 and 12	[122]
GLYX-13 (Rapastinel)	Double-blind, parallel arm	Single 1, 5 or 10 mg/kg, 40-min intravenous infusion	Saline	116	Major depressed patients	HDRS	• Decrease in depression scores; • Initial effect at 24 h for all doses; Sustained 14 days on	[127]

Drug	Study design	Drug administration regimen	Placebo	*N*	Patient condition	Primary outcome	Results	Ref
							average (for 1 and 5 mg/kg) • Maximum effect at 24 h; Sustained for at least 7 days	
Scopolamine	Double-blind, crossover	15-min intravenous infusion of 4 μg/kg scopolamine for 7 sessions (3–4 days no-drug intervals between sessions)	Saline	20	Major and bipolar depressed patients	MADRS	• Decrease in depression scores as soon as three days after the first treatment	[76]
	Double-blind, crossover	15-min intravenous infusion of 4 μg/kg scopolamine for 3 sessions (3–5 days no-drug intervals between sessions)	Saline	22	Major depressed patients	MADRS	• Decrease in depression scores as soon as three days after the first treatment • Initial session: drug response: 32%, placebo response: 6.5 % • Second session: drug response: 53%; scopolamine's effect persisted from the initial session	[77]
	Double-blind, crossover	15-min intravenous infusion of 4 μg/kg scopolamine for 3 sessions (3–5 days no-drug intervals between sessions)	Saline	5	Major depressed patients	MADRS	• Decrease in depression scores following a single administration • Sex-dependent antidepressant responses of the drug: 71% response for women; 38% response for men	[78]
RG1578 (decoglurant)	Double-blind, parallel arm	6-week treatment with 5, 15 or 30 mg RG1578	Saline	310	Treatment-resistant depressed patients (on SSRI or SNRI during the study)	MADRS	• No significant improvement in patients receiving	[199]

Drug	Study design	Drug administration regimen	Placebo	*N*	Patient condition	Primary outcome	Results	Ref
							RG1578 compared with placebo-treated controls	

Abbreviations: HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, serotonin-selective reuptake inhibitor