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Antidepressant actions of ketamine: from molecular mechanisms to clinical practice

Lisa M. Monteggia¹ and Carlos Zarate Jr.²

¹Department of Neuroscience, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9111, USA

²Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, and Department of Health and Human Services, Bethesda, Maryland, USA

Abstract

In the past decade the emergence of glutamate N-methyl-D-aspartate (NMDA) receptor blockers such as ketamine as fast-acting antidepressants fostered a major conceptual advance by demonstrating the possibility of a rapid antidepressant response. This discovery brings unique mechanistic insight into antidepressant action, as there is a substantial amount of basic knowledge on glutamatergic neurotransmission and how blockade of NMDA receptors may elicit plasticity. The combination of this basic knowledge base and the growing clinical findings will facilitate the development of novel fast acting antidepressants.

Introduction

Major depressive disorder is a devastating mental disorder. Fortunately, there are treatment options of which antidepressant medications are most commonly used. Current antidepressant drugs target the monoamine system and typically require several weeks to mediate an antidepressant response, with the latest clinical findings suggesting they are not efficacious in at least one-third of patients. There is a critical unmet need for antidepressants with a rapid onset of action, particularly in patients that do not respond to traditional antidepressants of which many are at an increased risk of suicide.

Therefore clinical data demonstrating that a low dose of ketamine, a noncompetitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, could mediate a rapid

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Correspondence: Lisa M. Monteggia, Department of Neuroscience, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9111, Tel 214-648-5548, lisa.monteggia@utsouthwestern.edu.

Disclosure

Dr Zarate is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. Dr Zarate has assigned his rights in the patent to the US government but will share a percentage of any royalties that may be received by the government.

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antidepressant response in patients with major depression¹⁻³ including treatment resistant depression^{2,3} and bipolar depression^{4,5} was met with great interest. These clinical data showed that ketamine could elicit a rapid antidepressant response within two hours with effects lasting up to two weeks in some patients. In addition, rapid antisuicidal effects have been reported with ketamine^{2,5-7}. Ketamine has a half-life of approximately three hours^{8,9} suggesting that it is not persistent blockade of NMDA receptors that mediate the antidepressant response but rather synaptic plasticity mechanisms or active metabolites of ketamine that are involved in the longer term behavioral effects.

Synaptic and neuronal basis of ketamine action

It is relatively straightforward to envision how activation of NMDA receptors lead to synaptic and behavioral plasticity whereas how an NMDA receptor blocker can elicit plasticity is more difficult to account for using canonical activity dependent neuronal signaling pathways. The action of a blocker implies that there is an ongoing tonic activity of NMDA receptors that leads to certain signaling events, which in turn are suppressed by the blocker that either inhibits these signaling events and/or leads to desuppression of an alternative pathway. To explain this rather unusual behavioral effect of ketamine at the neuronal level, studies to date have focused on two possibilities. One hypothesis posits that NMDA receptors present on inhibitory interneurons are tonically active and thus drive inhibition onto excitatory networks. Blockade of these NMDA receptors leads to a decrease in the activity of these interneurons and ultimately to a decrease in inhibition that in turn “disinhibits” excitatory networks. This form of regulation has been previously proposed for the action of high dose of ketamine and other NMDA receptor blockers as a glutamatergic theory of schizophrenia¹⁰. Some studies on ketamine as an antidepressant have based their reasoning on this pathway as the potential link between NMDA receptor blockade and subsequent regulation of neuronal plasticity events. However, genetically deleting the obligatory NR1 subunit of the NMDA receptor from inhibitory interneurons does not alter ketamine antidepressant responses in mouse models¹¹ whereas mice lacking the NMDA receptor NR2B subunit on excitatory cortical neurons do not produce an antidepressant response to ketamine¹². However, an alternative hypothesis has been proposed in light of recent studies showing that global suppression of inhibition as well as suppression of glutamate α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity does not elicit a rapid antidepressant effect¹³.

The second hypothesis of how ketamine triggers an antidepressant response suggests a more synapse specific effect of ketamine as the underlying basis for its rapid behavioral effect. These studies suggest that low dose ketamine blocks NMDA receptors at rest resulting in specific effects on downstream intracellular signaling. This model proposes that blockade of spontaneous NMDA receptors results in inhibition of eukaryotic elongation factor (eEF2) kinase and a resulting decrease in phosphorylation of eEF2 that desuppresses protein translation resulting in an upregulation of brain-derived neurotrophic factor (BDNF) that triggers insertion of AMPA receptors and other traditional synaptic plasticity processes. These studies demonstrated that pharmacologically inhibiting the eEF2 kinase was sufficient to trigger a rapid and long lasting antidepressant response independent of blocking NMDA

receptors¹³. Importantly, ketamine did not elicit an antidepressant response in eEF2 kinase knockout, BDNF knockout or the AMPA receptor subunit, GluA2 knockout mice^{13,14}.

NMDA receptor blocker memantine does not elicit a rapid antidepressant effect

The validity of this second mechanism is bolstered by recent data delineating why the clinically better tolerated noncompetitive NMDA receptor antagonist, memantine, does not induce a rapid antidepressant response in treatment resistant depressed patients^{3,15,16}. Recent work has demonstrated that memantine has a negligible ability to block NMDA receptors under resting conditions under physiological levels of magnesium and does not initiate this specific intracellular pathway linked to spontaneous neurotransmission mediated activation of NMDA receptors¹⁷. This differential effect of ketamine and memantine on blockade of NMDA receptors activated at rest extends to key signaling differences where memantine does not alter the levels of phosphorylation of eEF2 or subsequent expression of BDNF, key determinants of ketamine mediated antidepressant efficacy. These data further the previous work on the importance of NMDA receptor activity at rest and this specific intracellular signaling pathway on mediating the rapid antidepressant action of ketamine and start to provide crucial data on the requirements for NMDA receptor antagonist effects on neurotransmission to mediate the antidepressant response.

A finding that has emerged from these studies is that BDNF appears to be a common denominator between fast-acting and classical antidepressants. Ketamine requires BDNF signaling to elicit an antidepressant effect, in that ketamine does not elicit an antidepressant response in inducible BDNF KO or conditional TrkB mice¹³ or in mice that have the BDNF Val66Met mutation¹⁸. Previous data has demonstrated that traditional antidepressants also require BDNF in mediating an antidepressant effect in preclinical animal models^{19–21}. BDNF is a prevalent growth factor in the brain that can impact synaptic plasticity processes as well as neurotransmission²². BDNF can bind to its high affinity receptor, TrkB, and activate several downstream transduction pathways that include mTOR as well as others. Recent data has shown that ketamine triggers activation of phosphorylation of mTOR in mediating an antidepressant response and that rapamycin blocks the ketamine behavioral effect 24 hours later²³ although not at 30 minutes¹³. BDNF is one of the most potent endogenous activators of mTOR, an important integrator of downstream neuronal signaling, which can then impact synaptic mechanisms and may be involved in the long-term behavioral effects of ketamine.

The finding that ketamine can trigger a rapid antidepressant response has provided a fresh perspective to the depression field. The idea that an antidepressant response can be generated in a manner distinct from monoamines suggests that there is more than one way to trigger an antidepressant response and that it is now feasible to develop antidepressants with a rapid antidepressant response. However, there are many unanswered questions that are important as we work towards the development of next generation antidepressants. There is a critical need to delineate the exact synaptic circuits involved in mediating an antidepressant response. The focus to date has been on the hippocampus and prefrontal cortex, two areas that appear critical for ketamine action but undoubtedly are not the only

regions. It will also be important to identify a specific site of ketamine action that can be targeted by therapeutics. It will also be critical to better understand the specific eEF2 kinase pathway in mediating an antidepressant response, as it may be possible to design compounds to target specific sites along this signaling pathway to bypass NMDA receptors and thus avoid undesirable effects of NMDA receptor blockade.

New clinical perspectives

While exciting preclinical studies are underway to further delineate the mechanism of ketamine's rapid antidepressant effect, several other avenues are being explored clinically. Some of these paths include maintenance strategies of ketamine's response, developing NMDA receptor modulators with lower liability for producing psychotomimetic and dissociative side effects, and use of ketamine and other rapid acting agents in developing clinical and human biomarkers of treatment response.

Regarding the first point, maintenance strategies being examined include the use of riluzole, an FDA-approved medication for the treatment of amyotrophic lateral sclerosis. Riluzole is a glutamate modulator²⁴ with preliminary efficacy as monotherapy and adjunctive therapy in patients with treatment-resistant MDD²⁵. However, two studies did not find that riluzole prolonged the initial antidepressant effects of ketamine over the course of 4 weeks^{26,27}. Future studies post-ketamine relapse prevention strategies include traditional antidepressants, mood stabilizers (because both ketamine and lithium are glycogen synthase kinase-3 (GSK-3) inhibitors^{28,29}, antipsychotics, electroconvulsive therapy, and evidence based psychotherapy. In addition, repeat doses of ketamine are being attempted with encouraging results^{30*} although controlled and long-term safety data is lacking.

With regards to other NMDA antagonists, the NMDARs are tetrameric proteins comprising NR1 and NR2 subunits; four different NR2 subunits (NR2A-D) exist in the brain. A significant reduction in NR2A and NR2B subunit expression was found in the prefrontal cortex (PFC) of patients with MDD³¹. In a previous study, it was found that the subunit selective NR2B receptor antagonist Ro25-6981 exerted antidepressant-like properties in mice^{23,32}. In a clinical study, Preskorn and colleagues found that a single i.v. infusion of the NR2B receptor antagonist CP-101,606 (Traxoprodil) produced antidepressant effects within five days in patients with TRD-MDD³³. Subsequently an oral formulation of a selective NR2B receptor antagonist (MK-0657; 4–8 mg/day) in a randomized, double-blind, placebo-controlled, pilot study in unmedicated patients with TRD-MDD was found to have antidepressant properties as early as day 5 in the treatment group compared to placebo³⁴ with no psychotomimetic effect observed. More recently, a randomized, double-blind, placebo-controlled pilot study evaluating the potential rapid antidepressant efficacy and tolerability of a single i.v. infusion of the low-trapping NMDAR antagonist AZD6765 (150 mg) in 22 patients with TRD-MDD was conducted. Within 80 minutes, MADRS scores improved in subjects receiving AZD6765 compared with placebo and no psychotomimetic effect was found, but this improvement only lasted two days³⁵; the antidepressant efficacy of AZD6765 in TRD-MDD was independently demonstrated in a subsequent study³⁶. The studies with non-ketamine NMDAR antagonists demonstrate two critical things. First, that rapid antidepressant effects can be attained without psychotomimetic effects. Second, that

the antidepressant effects are not as robust and durable as those observed following ketamine, underscoring the need for additional studies with other glutamatergic modulators or downstream effectors of ketamine action.

Predictive biomarkers are being studied with the goal of differentiating treatment responders and non-responders to antidepressants^{37,38}. Until recently, these studies were limited to monoaminergic-based antidepressants and thus were likely to generate insights associated with only these treatments, which are known to have a lag of onset of action and are clinically ineffective for many patients; such studies also tend to be long, have high dropout rates, and are associated with risk of non-compliance. Rapid-onset antidepressants and novel targets offer a unique opportunity to study potential clinical and neurobiological biomarkers of treatment response within a limited time period³⁹. Clinical predictors of ketamine response in treatment-resistant depression are being examined⁴⁰. For example, greater improvement in depressive symptoms was associated with a higher body mass index at 230 minutes and day 1, and family history of alcohol use disorder in a first-degree relative at day 1 and day 7. A number of biomarkers have also been explored in the context of ketamine treatment including peripheral measures, genetics, neuroimaging, sleep, and electrophysiology of studies. Many of these are promising but are in need of replication^{39–41}.

Conclusions

In this review, we have provided an overview of the antidepressant mechanism of ketamine, clinical studies with ketamine, and its use in shaping the development of next generation treatments with rapid antidepressant efficacy. Although, considerable progress has been made within a relative short period of time towards this goal, much more knowledge is needed. Indeed, a number of avenues are being pursued including mechanistic preclinical studies, clinical trials with different formulations of ketamine as well as more selective and apparently better tolerated non-ketamine NMDA antagonists and other non-NMDA glutamatergic modulators. In this regard it will be critical to fully delineate the specific synaptic mechanisms underlying ketamine action as this information will likely uncover additional synaptic proteins that can be targeted to elicit a rapid antidepressant response⁴². Finally, there appears to be a potential benefit to patients with ketamine in treatment-resistant depression in the community. However, further studies into ketamine's safety and feasibility are needed to determine its ultimate clinical utility⁴³.

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Highlights

Ketamine elicits a rapid antidepressant response in depressed individuals

Blockade of NMDA receptors inhibits eEF2K desuppressing BDNF and leading to an increase in synaptic plasticity

Some glutamatergic blockers also elicit antidepressant effects although they are not as robust and durable as ketamine

Predictive biomarkers to ketamine treatment are being explored