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NMDA antagonist treatment of depression

Nolan R Williams and Alan F Schatzberg

Ketamine is a psychoactive anesthetic agent, which has been approved and utilized for various forms of anesthesia over decades. Recently, ketamine has been demonstrated to have robust and rapid antidepressant effects in individuals with treatment-resistant depression. After more than a decade of research, it is unclear what the mechanisms underlying the novel antidepressant effect are. The consensus has centered on NMDA properties of ketamine as a potential factor in the mechanism for antidepressant action. However, this may be a true but partial explanation of the effects of ketamine as a novel antidepressant. It appears that ketamine influences synaptic plasticity and may promote new synapse formation. From a neurocircuitry perspective, ketamine may exert some of its effects on the anterior cingulate.

Address
Department of Psychiatry, Stanford University, 401 Quarry Road, MailCode: 5717, Stanford, CA 94305, United States

Corresponding author: Schatzberg, Alan F (afschatz@stanford.edu)

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Introduction

Depression is often a severely disabling disorder of melancholia or extreme sadness that affects an individual's activities of daily life and social functioning [1]. Depression is a public health problem and a leading cause of disability worldwide [2]. Current psychopharmacologic interventions have demonstrated fairly limited success in large clinical studies [3], and the development of novel antidepressant medications has had mixed results over the last ten years with several unfortunate failures [4]. When depression fails to remit after two adequate trials of a pharmacologic treatment, the condition is termed treatment-resistant depression (TRD) [5] and unfortunately, approximately 41% of patients will meet criteria for TRD [6]. Many of these patients require an interventional psychiatric approach such as ketamine [7].

Because of the clear and urgent need for new medications that are both rapid and efficacious, ketamine has emerged as a promising prototype of a novel antidepressant class [8]. Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist [9]. Ketamine has traditionally been used for induction and maintenance of anesthesia [10]. In 2000, Berman and colleagues discovered that subanesthetic doses of ketamine could reverse severe depressive symptoms in treatment-resistant patients [9]. Numerous controlled trials have replicated this finding [11••,12]. In this brief review, we succinctly address the previous studies and potential factors thought to underlie ketamine as a rapid acting antidepressant. We discuss highlights of the underlying neurobiology of depression with particular emphasis on the anterior cingulate cortex. We also discuss recently discovered molecular pathways involved in synaptogenesis along with biomarkers related to ketamine's rapid action. Last, we discuss other disorders that ketamine has been expanded to as well as the implications of rapid acting antidepressants.

NMDA antagonism and ketamine as a novel antidepressant

For nearly 25 years, ketamine, the NMDA receptor antagonist, has been utilized as a model system for the positive symptoms of schizophrenia [13–16]. While it was known for some time that NMDA was implicated in the pathophysiology of depression [17,18], the speed and efficacy of ketamine's effect in major depression was surprising [9]. After a few hours of experiencing the psychoactive effects, the antidepressant effect sets in [19•] and can last around a week on average,much longer than the terminal half-life [20]. There have been six major placebo-controlled trials of ketamine in MDD and bipolar depression [9,11••,12,21–23]. Every group infused intravenous ketamine for 40 min with a total dose of 0.5 mg/kg except for the Sos *et al.* study, which used an intravenous loading ketamine dose of 0.27 mg/kg infused over 10 min and then a maintenance dose of 0.27 mg/kg over 20 min [23]. For all of these studies, the antidepressant effects were apparent within 2–4 hours and sustained for an average of 4–7 days. There was a reported response rate of around 40–60% at the 24-hour postinfusion timepoint. In general, ketamine as an antidepressant has been demonstrated to be well-tolerated with only mild, transient adverse effects observed [20].

One major trial design difficulty has been adequate blinding which has been partially solved with the use of midazolam as an active comparitor [11••]. Another limitation is the abbreviated range of efficacy, which has been demonstrated to be extended with a multiple dosing schedule [24–28]. The safety of administering

multiple doses of ketamine for extended periods of time is unclear [29•].

NMDA antagonism and plasticity

Synaptic plasticity refers to the activity-dependent modification of the efficacy and/or strength of synaptic transmission and is thought to play a key role in the early development and maintenance of neural circuitry [30]. Synaptic plasticity may play a major role in the potential factors the antidepressant effects of ketamine along with the recovery from the depressive episode [31]. It is clear that if stress and depression occur for a prolonged period of time [32], this prolonged state has been associated with neuronal atrophy [33] and synaptic depression [34,35]. Brain-derived neurotrophic factor (BDNF) regulates synaptic plasticity, synaptic transmission, and synapse growth. Reduction in the expression of BDNF may be a potential factor to depression [36,37]. Upregulation of BDNF plays a potential factor in antidepressant treatment mechanism [38]. Mammalian target of rapamycin (mTOR) is a protein kinase, which is implicated in protein synthesis-dependent synaptic plasticity. Deficits in the mTOR-dependent translation initiation pathway have been proposed to potentially be a contributing factor in the molecular abnormalities observed in the prefrontal cortical neurons of those individuals with depression [39].

Evidence that traditional antidepressants (such as SSRIs) could influence synaptic plasticity is provided by electrophysiological studies demonstrating that chronic administration of fluoxetine enhances long-term potentiation (LTP) [40]. New therapeutic interventions for rapid depression treatment will likely need to reverse or block the effects of chronic stress on mTOR signaling and synaptogenesis [41] and increase BDNF. In preclinical studies, both increasing BDNF and/or enhancing mTOR produces an antidepressant effect [38,42]. Upregulation of both BDNF and mTOR signaling leads to synaptogenesis of the prefrontal cortical neurons and depression-induced neuronal atrophy reversing effects which may be required for efficacious antidepressant treatment [43].

The acute effects of the drug create the cascade of events that ultimately culminate in the antidepressant effect [19•]. Antagonism of the glutamatergic NMDA receptor by ketamine appears to be one of the first events to occur that triggers the rapid antidepressant effect. Next, there is a rapid increase in presynaptic glutamate release [44] which occurs secondary to presynaptic disinhibition of glutamatergic neurons [45]. The surge of glutamate neurotransmission has been thought to be critical for ketamine's antidepressant effect [45], and lamotrigine has been shown to block the psychoactive effects [46] that may be necessary for the efficacy of ketamine [19•]. Blockade of the NMDA receptor is followed by activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [45,47]. Multiple studies in mouse models have demonstrated that activation of the AMPA receptor is necessary for the antidepressant effects of ketamine [47,48]. Finally, synaptic plasticity and connectivity has been associated with exposure to ketamine through signaling pathways involving BDNF [45,49] and mTOR [50••]. Further evidence of this mechanistic progression is demonstrated if one blocks mGluR2/3 metabotropic receptors, where such a blockade produces mTOR-dependent antidepressant effects similar to ketamine [42].

Biomarkers of ketamine efficacy

Reduced glutamate in the anterior cingulate cortex (ACC) has been observed in MDD patients [51]. Furthermore, adolescents with MDD who are medication-naive are characterized by abnormal function in the ACC during tasks of performance and attention monitoring, suggesting that the pathogenesis occurs early and that these functional abnormalities can be attributed to MDD [52]. Patients with MDD have been demonstrated to have robust increases in pretreatment ACC activity, which has been correlated positively with subsequent rapid antidepressant response to ketamine [53]. In a follow-up study, patients who demonstrated reduced response of the ACC to increased load of working memory went on to demonstrate the largest improvement of symptoms within the first few hours after ketamine administration [54]. Ketamine-induced reduction in anhedonia has been correlated with increased metabolism of glucose in the dorsal portion of the anterior cingulate cortex (dACC). This finding remained significant when controlling for change in total depression score. Ketamine appears to possess anti-anhedonic effect in treatment-resistant depression, which speculatively, may be mediated by the change in metabolic activity of the dACC [55]. In a normal healthy volunteer study of ketamine, there was a correlation between increased metabolic activity in the ACC and dissociation [15].

Dissociative side effects of ketamine as measured by the Clinician Administered Dissociative States Scale (CADSS) have predicted more robust and sustained antidepressant effect [19•]. In depressed subjects, the higher the intensity of psychotomimetic symptoms as measured using the Brief Psychiatric Rating Scale during ketamine administration, the more robust the alleviation of mood symptoms [23]. Several studies have demonstrated that a family history of alcohol dependence is correlated with response to ketamine [56] and is not affected by the level of dissociation [57]. Smaller trials have failed to show any correlation between brain derived neurotrophic factor (BDNF) and ketamine response [58,59], but a more recent, larger study demonstrated a positive relationship. In this larger trial, the relationship was demonstrated between the antidepressant effect of ketamine and peripheral BDNF levels in depressed patients. BDNF (plasma) increased in those who were responders

compared to nonresponders [60]. Higher slow wave sleep activity and BDNF levels act as correlates of mood change following ketamine treatment [61].

Unanswered questions

The path to drug development as a result of ketamine's discovery as a novel antidepressant has not been straightforward [4]. Some have questioned the unbridled enthusiasm about widely utilizing a drug whose mechanism we do not fully understand before controlled trials are completed [4,29•,62]. Other NMDA antagonist drugs efficacy like memantine [63] and D-cycloserine [64] have not shared ketamine's efficacy or its rapid effects [9], while NMDA partial agonists such as GLYX13 have demonstrated some signals of efficacy [62]. Certainly ketamine's dopamine and opioid properties more closely link with known mechanisms of antidepressant drugs in use [65,66]. Several prominent basic scientists have suggested that ketamine treatment is analogous to lithium and electroconvulsive therapy (ECT) in the sense that searching for its precise mechanism(s) of action are 'doomed to failure' [67]. Certainly, the mechanisms of action of ECT have been difficult to study but certainly not unknowable [68–72], and careful study of ECT [73] has in fact led to improved forms of ECT therapy [74,75].

We would like to suggest an alternative viewpoint. It may be that there is in fact one 'mechanism of action' [62], or rather that there is in fact an 'entourage effect' for which there are several synergistic mechanisms of action [76] that result in a given state [19•] which may in fact be measurable [77]. This concept of an 'entourage effect' of ketamine where NMDA [62,78], opioid [79], and dopamine [80] are all potential factors in the mechanism of ketamine. It may be that these attributes work together in a unique way to cause the apparent, profound antidepressant effect would explain the mixed results of recent attempts to reproduce ketamine's effects [62–64,78] and block them [46]. Continuing with the analogy described above, ECT certainly appears to have multiple effects in brain [81–84], each of which could be the putative mechanism(s) of action. It is likely that the summation of these effects are why ECT has such a broad range of disorders which it is able to treat [85]. Ketamine has a similarly broad range of disorders in which we are seeing strong initial signals of efficacy [86–88]. Given that there are drugs with independent opiate [65,66], dopamine [89], and NMDA [62,78] mechanisms that have been shown to treat depression, it would make sense that a drug which rapidly modifies all three of these neurotransmitters and causes additional downstream effects mentioned above would synergize in a non-linear way to produce such a rapid antidepressant effect that may be the result of a state phenomenon [19•]. Such an approach departs from the binary argument of whether NMDA antagonism is or is not the actual 'mechanism' of ketamine [62], which based on recent attempts at replicating the mechanism, have left the field more confused than before (GLYX13 [62] and AZD6765 [78]).

We argue that in order to get one step closer to solving the problem of what ketamine is doing to treat depression so rapidly, we will need to not only look at the NMDA mechanisms [62] and the other factors potentially contributing to ketamine's effects [29•], but also look at the effects on the underlying mood regulatory circuitry at the level of the circuit [90]. One node in particular, the anterior cingulate, may give clues given that it is statistically significantly correlated with treatment response as described above [54]. The anterior cingulate has one of the highest densities of opioid receptors [91] in the human brain. Additionally, abnormalities of the anterior cingulate appear to be shared in all major psychiatric disorders [92].

Conclusions

Ketamine exerts a rapid, robust effect on depression that has been replicated numerous times. The mechanism is only starting to be discovered. We strongly believe that continued exploration with an open, skeptical perspective is most important for the field to move forward. Like ECT research, ketamine research will likely eventually be fruitful, but it may take some time to understand the potential factors underlying this unique drug. We suggest that other properties of ketamine be further explored, such as the opioid properties [29•]. While the correlation between the psychological effects of ketamine and efficacy are not totally clear, there appears to be some signal that ketamine exerts it antidepressant effects through a variety of mechanisms and these mechanisms together exert an antidepressant effect that is unparalleled in psychiatry [19•,23].

Conflict of interest

Dr. Schatzberg has served as a consultant for Alkermes, Cervel, Clintara, Forum, McKinsey, Myriad Genetics, Neuronetics, Naurex, One Carbon, Pfizer, Takeda, Sunovion, and X-Hale and as a speaker for Merck and Pfizer; he holds equity in Corcept (co-founder), Intersect ENT, Merck, Neurocrine, Seattle Genetics, Titan, and X-Hale; and he is listed as an inventor on pharmacogenetic and mifepristone patents from Stanford University.

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