The Role of Glutamate in Mood Disorders: Results from the Ketamine in Major Depression Study and the Presumed Cellular Mechanism Underlying its Antidepressant Effects

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In this article, we first review a study showing that the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine leads to rapid, robust, and relatively sustained antidepressant effects in patients with treatment-resistant major depression. We then discuss our hypothesis that the therapeutic effects of monoaminergic antidepressants and ketamine may be mediated by increased AMPA-to-NMDA glutamate receptor throughput in critical neuronal circuits. We hypothesize that ketamine directly mediates this throughput, whereas monoaminergic antidepressants work indirectly and gradually; this may explain, in part, the lag of onset of several weeks to months that is observed with traditional antidepressants.

Introduction

Mood disorders (major depressive disorder [MDD] and bipolar disorder [BPD]) are serious, debilitating, recurring psychiatric disorders that affect the lives of millions worldwide. Individuals afflicted with these disorders commonly experience high rates of relapse, persistent residual symptoms, functional impairment, and diminished well-being [1,2]. Furthermore, although there is a wide selection of medications for patients afflicted with these conditions [3,4], a large effectiveness study in outpatients with MDD (STAR*D) [4] found that only about one third of patients achieved substantial improvement (remission) with an adequate trial of a standard antidepressant after approximately 2 months of treatment.

Despite the devastating impact that mood disorders have, knowledge about these disorders' fundamental pathophysiology remains obscure, and such an understanding is essential to developing therapeutics that are more effective and work more rapidly than current ones. The brain systems that have received the most consideration in neurobiologic studies of mood disorders have been the monoaminergic (ie, serotonergic, noradrenergic, dopaminergic) systems; current antidepressants are based on these neurotransmitters. Although most antidepressants exert their initial effects by increasing the intrasynaptic levels of serotonin and/or norepinephrine, the resolution of core depressive symptoms becomes manifest only after weeks of administration. This suggests that alterations in downstream signaling cascades likely are the relevant targets ultimately responsible for their therapeutic effects. These observations have led to the appreciation that whereas dysfunction within the monoaminergic neurotransmitter system is likely to have an important role in mediating some aspects of mood disorders' pathophysiology, it likely represents the consequences of other more key abnormalities [5,6].

In recent years, research has linked mood disorders to structural and functional impairments related to neuroplasticity in specific brain regions. Structural brain imaging studies have demonstrated decreased grey matter volume in prefrontal cortical regions, whereas corresponding postmortem studies have found reductions in glial cell counts and/or neuron size in the same prefrontal cortical regions, amygdala, basal ganglia, and dorsal raphe nuclei. Contemporary theories about the neurobiologic underpinnings of mood disorders posit that neuroplasticity deficiency and cellular resilience may lie behind their pathophysiology and that antidepressants exert major effects on signaling

pathways that regulate neuroplasticity and cell survival (reviewed in [7]). Neuroplasticity refers to the processes responsible for modeling of axonal and dendritic architecture, thus providing the necessary structural support for neurochemical signals to propagate downstream. The glutamatergic system's role in the pathophysiology and treatment of mood disorders has been explored in earnest only recently. Available evidence suggests that alterations in the glutamatergic system's activity likely contribute to deficiencies in brain neuroplasticity and cellular resilience observed in patients with severe or recurrent mood disorders.

Excitatory amino acid receptors are the principal mediators of excitatory synaptic transmission in the mammalian brain, contributing to important brain functions. In typical circumstances, glutamate has a prominent role in synaptic plasticity, learning, and memory. Glutamate also can be excitotoxic under a range of conditions, resulting in either rapid or delayed neurotoxicity. Glutamate-mediated excitotoxicity has been implicated in several neurodegenerative diseases, including amyotrophic lateral sclerosis, Alzheimer's disease, and Huntington's disease (reviewed in [8–10]).

Because of glutamate's possible role in central nervous system injury and neurodegenerative diseases, an assortment of therapeutic strategies is being investigated in an effort to more tightly regulate glutamate brain levels and/or better modulate its neurotransmission. In preclinical models, several of these strategies exert significant neuroprotective effects [11]. Although mood disorders are not typical neurodegenerative diseases per se, recent neuroimaging studies in patients with MDD and BPD have found morphometric alterations indicative of cell loss and/or atrophy (reviewed in [12]). Testing the efficacy and safety of neuroprotective treatment strategies in patients with recurrent mood disorders may yield a better understanding of the neurobiological processes involved in these disorders, as well as lead to the development of improved treatments. One of them, a glutamatergic modulator, the N-methyl-D-aspartate (NMDA) antagonist ketamine, demonstrated notable antidepressant effects in patients with severe depression; it is this review's focus.

Glutamate is widely distributed throughout the brain, and strict regulation of its levels is necessary to assure that glutamatergic excitation occurs within normal limits. Otherwise, excitotoxicity ensues. Glutamate exerts its action at the presynaptic and postsynaptic levels through the stimulation of specific receptors that can be classified by structural characteristics. The first group, called "ionotropic glutamate receptors," are ion channels that, when activated, open the channel pore and allow certain ions to flow freely into the cell. This opening of the pore changes the neuronal surface's polarization and also activates intracellular signaling cascades. The ionotropic glutamate receptors are NMDA, AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid), and kainate (KA). The second group, called "metabotropic receptors," are G-protein–coupled receptors that exert their action directly through second messenger pathways. This review focuses mainly on NMDA and AMPA glutamate receptors, which are believed to have a large role in the mechanism of ketamine's antidepressant action.

NMDA and AMPA receptors

The NMDA receptor channel is composed of the combination of NR1, NR2 (NR2A–NR2D), and NR3 (NR3A and NR3B) subunits. Glutamate's binding site has been found in the NR2 subunit, and the NR1 subunit is the site for the coagonist glycine. Within the ion channel, two sites have been identified: the "s" site and the phencyclidine (PCP) site; the latter is ketamine's binding site.

AMPA receptors mediate the fast, rapidly desensitizing excitation at the majority of synapses and are responsible for the early response to glutamate in the synapse. Their activation opens the pore, permitting the inward flow of sodium and resulting in the neuronal membrane's depolarization. This modification in the intracellular charge sets free the Mg^{2+} cation plug from the NMDA receptor ionic channel, permitting the entrance of Ca^{2+} through the pore. The AMPA receptors are composed of four subunits (GluR1–GluR4). At mature synapses, AMPA receptors are usually coexpressed with NMDA receptors, where in concert they contribute to the synaptic plasticity processes involved in learning, memory, and neuroprotection [13,14].

Evidence for Glutamate's Role in the Pathophysiology of Mood Disorders and Mechanism of Action of Antidepressants

Data exist suggesting that glutamate is implicated in the pathophysiology of mood disorders, although this evidence is largely indirect and consists of imaging and postmortem studies. Glutamatergic alterations have been reported in the serum, cerebral spinal fluid (CSF), and brain tissue of individuals afflicted with mood disorders. However, plasma [15–17], serum [18], and CSF [19,20] studies of peripheral glutamate levels are difficult to interpret because of problems with medication exposure and the inability to identify the source of the glutamate (central vs peripheral) [21,22]. Proton magnetic resonance spectroscopy (^{1}H-MRS) is currently the most direct way of assessing brain glutamate content. Studies conducted with this imaging modality suggest elevated glutamate levels in the occipital cortex of depressed patients, with decreased levels in the anterior cingulate cortex and, possibly, other frontal regions.

Currently, there are more data to support glutamate's involvement in the mechanism of antidepressant action than in the pathophysiology of mood disorders. It has been argued that the NMDA receptor serves as

a final common pathway of antidepressant action. Clinical response to antidepressant drugs requires chronic administration, and there is usually a delayed onset in core depressive symptom relief. Therefore, chronic administration of antidepressant drugs' effects on NMDA receptor function may be more relevant to clinical antidepressant action (reviewed in [10]). Current monoaminergic-based antidepressants, including the tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), decrease NMDA receptor function. If antagonism at the NMDA receptor-channel complex is related to the mechanisms underlying antidepressant action, then NMDA antagonists ought to exhibit antidepressant properties. Furthermore, direct targeting of the NMDA receptor should result in more rapid antidepressant effects. A growing body of preclinical work suggests that that NMDA receptor antagonists have antidepressant properties (reviewed in [10]). Dizocilpine (MK-801), a use-dependent channel blocker, and CGP 37849, an NMDA receptor antagonist, have shown antidepressant properties in preclinical studies, either alone or combined with traditional antidepressants [23–29].

Clinical Evidence for the Efficacy of NMDA Receptor Complex Modulators in Mood Disorders

Although the preclinical studies support the glutamatergic system's role in the mechanism of antidepressant action, ultimately it will be the studies conducted with NMDA receptor modulators in patients with mood disorders that will prove this system's relevance in antidepressant action. This paper focuses only on treatments that have effects on the NMDA receptor complex (eg, partial agonists [D-cycloserine], NMDA antagonists [memantine, ketamine]) and not on other glutamatergic modulators (eg, inhibitor of glutamate release, riluzole). Riluzole was recently reported to have antidepressant effects in patients with major depression and bipolar depression [30,31].

Partial agonists at the glycine site on the NMDA receptor: cycloserine

Cycloserine is a broad-spectrum antibiotic reportedly with antidepressant properties. Preclinical data suggest that cycloserine has a dose-dependent biphasic effect; at low doses (< 150 mg/d), it behaves as an agonist, whereas at higher doses (> 500 mg/d), it has an antagonist effect at the NMDA receptor. Van Berckel et al. [32,33] found that at doses of 15, 50, and 150 mg/d, cycloserine was unsuccessful in eliciting neuroendocrine response as evaluated by cortisol, prolactin, and luteinizing hormone plasma levels in healthy volunteers. Conversely, 500 mg/d did increase luteinizing hormone plasma levels, but not that of cortisol and prolactin. Preclinical studies of cycloserine in mood disorders show antidepressant-like properties in rodent models of depression [34–36]. However, a recent double-blind, placebo-controlled, 6-week crossover study involving 22 patients with treatment-resistant MDD found that D-cycloserine at 250 mg/d, when added to other antidepressants, was ineffective in treatment-resistant MDD [37]; however, it is possible that the doses studied were too low.

NMDA receptor antagonists

Amantadine

Amantadine is a well-tolerated, noncompetitive, selective NMDA antagonist with dopamine agonist and antiviral properties. At high doses, amantadine reduces NMDA receptor function by approximately 50%, an effect attributed to its instability within the NMDA receptor channel.

Although some preclinical and clinical studies suggest that amantadine may have antidepressant-like properties, this drug's utility in further delineating the glutamatergic system's role, particularly that of the NMDA receptor, is limited because of its effects on the dopamine system (reviewed in [10]).

Memantine

Memantine is a derivative of amantadine, a low-affinity, noncompetitive, open-channel NMDA antagonist. Memantine is well-tolerated and is used to treat Alzheimer's disease and other types of dementia, in which it has been shown to enhance cognition and minimize clinical deterioration [38].

Preclinical studies have described a dose-dependent decrease in the immobility time in the forced swim test (FST) in rats following memantine administration. A synergistic effect was seen when imipramine and fluoxetine were administered jointly with memantine in the FST in rats. A recent double-blind, placebo-controlled trial of memantine in patients with MDD [39] found no significant antidepressant effects, although it is possible that such effects may occur using much higher doses of memantine or if administered in combination with other agents. Another possibility is that higher-affinity NMDA antagonists are necessary for antidepressant properties to become manifest; thus, ketamine was deemed the next appropriate candidate NMDA antagonist to test in major depression.

Ketamine

Ketamine is an NMDA receptor antagonist and a derivative of PCP. Ketamine's primary mechanism of action is blocking the NMDA receptor at the PCP site within the ionotropic channel. In contrast to memantine, ketamine has 1) higher affinity for the NMDA receptor, 2) much slower open-channel blocking/unblocking kinetics, 3), a different type of channel closure (ie, "trapping block" as opposed to "partial trapping" properties) [40], and 4) different NMDA subunit selectivity [41–43]. Some of these properties may explain why ketamine and not memantine was found to

have significant antidepressant actions. Clinically, ketamine is a popular agent for emergency department procedural sedation in children, with ample evidence to support its safety and efficacy [44], although its psychotomimetic side effects have led to misuse among teenagers.

Administration of ketamine and related NMDA antagonists has been shown to have anxiolytic and antidepressant effects in animal models of anxiety and depression, as well as in humans [39,45]. In a pilot study by Berman et al. [45], seven patients with treatment-resistant depression showed significant improvement in depressive symptoms within 72 hours of ketamine treatment. Most recently, these findings have been replicated, and ketamine's antidepressant properties were further characterized [46••]. In this study, we found that a single intravenous, subanesthetic dose of ketamine resulted in rapid (within 2 hours) and relatively sustained antidepressant effects in treatment-resistant MDD patients. More details of this study are as follows: after a 2-week drug-free period, 18 patients with recurrent MDD received intravenous infusions of saline solution and ketamine hydrochloride (0.5 mg/kg, over 40 minutes, 1 week apart) using a randomized, double-blind, crossover design. Patients were rated 60 minutes prior to infusion and at 40, 80, 110, and 230 minutes, as well as 1, 2, 3, and 7 days after the infusion. In terms of demographic and clinical characteristics, there were 12 females and six males, and the mean age was 47 years. A total of 61% had a lifetime comorbid anxiety diagnosis, 39% a lifetime diagnosis of any substance abuse or dependence, and 28% a lifetime diagnosis of alcohol abuse or dependence. The mean length of illness was 24 years, the mean duration of the current depressive episode was 34 months, and the mean number of lifetime episodes of depression was seven. Patients were treatment-resistant. In fact, the mean number of lifetime antidepressant trials (not including augmentation trials) was six, and four patients had previously received electroconvulsive therapy (ECT).

Significant improvement in the 21-item Hamilton Depression Rating Scale (HDRS) with ketamine over placebo was noted at every time point from 110 minutes through 7 days. The effect size for the drug difference was very large (d = 1.46; 95% CI, 0.91–2.01) after 24 hours, and moderate to large (d = 0.68; 95% CI, 0.13–1.23) after 1 week (Fig. 1). Improvements with the Beck Depression Inventory and Visual Analogue Scale depression scores paralleled those of the HDRS (data not shown).

On the individual HDRS symptoms, depressed mood, guilt, work and interests, psychic anxiety, suicide, insomnia, general somatic symptoms, genital symptoms, and hypochondriasis improved significantly with ketamine.

One day after infusion, 12 of the 17 (71%) patients treated with ketamine met response criteria, as compared with zero of 14 (0%) on placebo. Five of 17 (29%) on ketamine met remission criteria 1 day after infusion, whereas none reached remission on placebo at the same time point. Six (35%) patients maintained response to ketamine for at least 1 week; two of these maintained response for at least 2 weeks.

The improvement resulting from the ketamine infusion was not merely ketamine-induced euphoria; in fact, the core symptoms of depression were no longer present or significantly attenuated immediately after the ketamine infusion. In support, the psychotomimetic and euphoric effects of ketamine were significantly worse only before the onset of antidepressant effects, which became apparent at 110 minutes.

Side effects occurring more commonly on ketamine than placebo were dissociation/perceptual disturbances, confusion, increases in blood pressure, euphoria, dizziness, and increased libido. The majority of these side effects ceased within 80 minutes after the ketamine infusion. In no case did euphoria or dissociation persist beyond 110 minutes. No serious adverse events occurred during the study.

This study confirmed our hypothesis that NMDA antagonism will lead to significant antidepressant effects. Several interesting points deserve comment. First is the rapidity of onset of antidepressant effect. The antidepressant effect resulting from a single intravenous, subanesthetic dose of ketamine occurred within a few hours instead of several weeks, as occurs with current monoaminergic-based antidepressants. The improvement seen within the first few hours post–ketamine infusion was not a merely an improvement in one or two depressive symptoms, but in many cases, complete remission occurred. Some statements from patients were, "This is the best I've ever been; I had lost all hope after trying all treatments [failed 16 separate antidepressant trials and ECT]," "I no longer have depression; it is as if I had never been depressed in my life." Second is the robustness of the antidepressant effect. In reviews of antidepressant trials involving non–treatment-resistant major depression, response rates at week 8 were 62% for bupropion, 63% for SSRI, and 65% for venlafaxine [47,48]. In the present study involving treatment-resistant patients, these response rates were obtained the day after the ketamine infusion. Figure 2 shows the response rates to ketamine and placebo and contrasts these results with a historical control [48]. Third is the relatively sustained antidepressant effect of a single intravenous infusion. To our knowledge, there has never been a report of any other drug or somatic treatment (ie, sleep deprivation, thyrotropin-releasing hormone, antidepressant, dexamethasone, or ECT) [49–52] resulting in such a dramatic, rapid, and prolonged response with a single administration. A study underway in patients with treatment-resistant major depression found response rates and time of onset of antidepressant effect comparable to our study (Mathews, Personal communication).

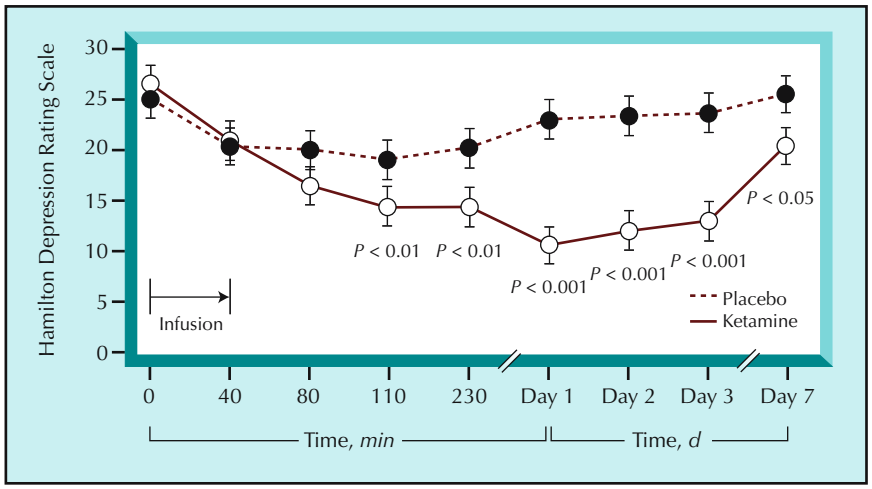

Figure 1. Changes in the Hamilton Depression Rating Scale scores over 1 week.

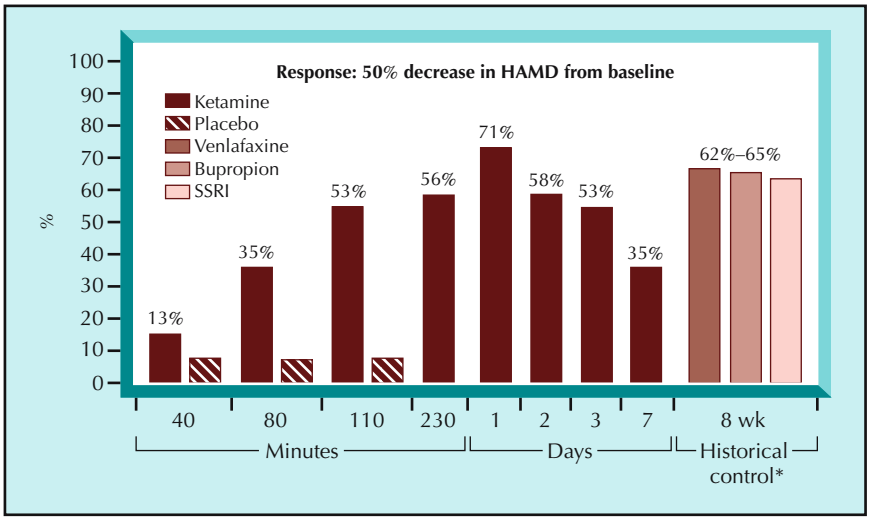

Figure 2. Response rates to ketamine in a double-blind, placebo, crossover trial in patients with treatment-resistant major depression (*N* =18). *Historical control data from Thase et al. [48]. HAMD—Hamilton Depression Rating Scale; SSRI—selective serotonin reuptake inhibitor. (*Adapted from* Reisberg et al. [38].)

We postulate that the rapid onset of ketamine and its sustained effects are the result of two processes. First, the rapid improvement resulting from ketamine is not the consequence of neuroplastic changes from glutamate modulation, as these changes would not occur within this time frame. Rather they are posited to be due to an increase in AMPA relative to NMDA glutamatergic throughput, which results in increased synaptic potentiation. This point is described in more detail subsequently. Second, early neuroplastic changes most likely explain the sustained effect of a single dose of ketamine.

Ketamine's direct antagonist effects on the NMDA receptor complex are well-known [53]. In addition to being a noncompetitive, nonselective NMDA antagonist, ketamine also produces a presynaptic release of glutamate [54], a property believed to be essential to its antidepressant action [55•]. This increase in glutamate release then preferentially favors AMPA receptors over NMDA receptors because the latter are blocked by ketamine; thus, the net effect of ketamine's antidepressant effect on a cellular level is an increased glutamatergic throughput of AMPA relative to NMDA. Notably, chronic administration of antidepressants also has been shown to augment AMPA receptor surface levels [56]. In addition, AMPA potentiators have antidepressant-like properties in animal models [57]. Thus, we have postulated that the therapeutic effects of monoaminergic antidepressants and ketamine may be mediated by increased AMPA-to-NMDA throughput in critical neuronal circuits. Indeed, in animal behavioral studies, we found that in the FST—a test with fairly high predictive validity in identifying antidepressant compounds—ketamine significantly decreased immobility time. In the same test, 2,3-dihydroxy-6-nitro-7-sulfoamoylbenzo(f)-quinozaline (NBQX; Toronto Research Chemicals, Toronto, Ontario), an AMPA/KA antagonist, had no effects in the FST when administered alone; however, when NBQX was administered immediately before ketamine and imipramine, it abolished the decrease in immobility time with ketamine but not with imipramine [55•]. This finding suggests that, at least in animal models, ketamine's antidepressant-like properties are mediated in part by AMPA receptor throughput.

Conclusions

The investigation of the glutamatergic system to elucidate the etiology of mood disorders and mechanism of antidepressant action is relatively new, but the therapies being developed to treat mood disorders through this system show considerable promise. Most notably, ketamine is a candidate glutamatergic drug that merits continued investigation as a putative model for improved therapeutics. Ketamine is of particular interest because it has been shown to yield rapid and relatively sustained antidepressant effects and is the only known drug or somatic treatment resulting in such a dramatic and prolonged response with a single administration. Its rapid, robust, and consistently reproducible antidepressant effects offer a unique opportunity to better delineate the precise cellular mechanisms involved. A concern to consider when pursuing this line of research with ketamine or other agents targeting other modulatory sites or subunits at the NMDA receptor complex is that adverse events may occur with their acute and mostly chronic use, including neurotoxic effects, cognitive deficits, and psychotomimetic effects. We believe that these adverse events from ketamine are not necessarily insurmountable or are a class effect of all drugs that modulate the NMDA receptor complex [58]. We have taken a series of steps in our ongoing research to address these issues. For example, NR2B antagonists appear to be less vulnerable to neurotoxic, cognitive, and psychotomimetic complications. The NMDA/NR2B receptor subtype also seems to be relevant to the mechanism of antidepressant action and a reasonable target to pursue to develop the next generation of antidepressants. We recently found that Ro 25-6981, a selective NR2B subunit antagonist, has antidepressant-like properties in rodents and that these effects, similar to ketamine, appear in part to be largely mediated through AMPA receptors [55•].

Whether ketamine will be used clinically as an antidepressant treatment in patients with mood disorders remains to be determined. It is clear that ketamine as a pharmacologic tool, despite its side effect profile, will undoubtedly lead to significant insights on the mechanism of antidepressant action. Continuing to explore ketamine's neuropsychopharmacologic properties holds considerable promise for developing new treatments for mood disorders, and for reducing at least some of the morbidity and mortality associated with the traditional antidepressants' delayed onset of action. The fact that currently available antidepressants take weeks to achieve their full effects leaves patients particularly vulnerable to devastating symptoms and the risk of self-harm. Thus, any pharmacologic strategy that could exert a rapid and sustained antidepressant effect within hours or even days could impact public health enormously.

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- •• Of major importance

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