Glutamatergic Modulators: The Future of Treating Mood Disorders?

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Mood disorders such as bipolar disorder and major depressive disorder are common, chronic, and recurrent conditions affecting millions of individuals worldwide. Existing antidepressants and mood stabilizers used to treat these disorders are insufficient for many. Patients continue to have low remission rates, delayed onset of action, residual subsyndromal symptoms, and relapses. New therapeutic agents able to exert faster and sustained antidepressant or mood-stabilizing effects are urgently needed to treat these disorders. In this context, the glutamatergic system has been implicated in the pathophysiology of mood disorders in unique clinical and neurobiological ways. In addition to evidence confirming the role of the glutamatergic modulators riluzole and ketamine as proof-of-concept agents in this system, trials with diverse glutamatergic modulators are under way. Overall, this system holds considerable promise for developing the next generation of novel therapeutics for the treatment of bipolar disorder and major depressive disorder. (HARV REV PSYCHIATRY 2010;18:293–303.)

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INTRODUCTION

Mood disorders such as bipolar disorder (BPD) and major depressive disorder (MDD) are chronic, disabling psychiatric disorders generally associated with unfavorable outcome and impairment in diverse areas. Indeed, the World Health Organization’s (WHO) Global Burden of Disease projects that mood disorders will be the leading cause of disability worldwide within the next decade. Furthermore, available therapeutic options for the treatment of mood disorders are often insufficient for effectively managing the acute episodes, relapses, and recurrences that are the hallmarks of these disorders, or for restoring premorbid functioning. Consequently, increased rates of recurrences and persistent subsyndromal depressive symptoms, functional impairment, cognitive deficits, and disability are commonly present. It is estimated that less than one-third of patients with MDD achieve remission with an adequate trial of a standard antidepressant after 10–14 weeks of treatment. The situation is similarly sobering for BPD, where a sizable proportion of patients fail to respond to or tolerate currently available therapeutics, especially for the treatment and maintenance of bipolar depression. The presence of unpleasant side effects may also limit adherence in subjects with mood disorders.

There is consequently a critical, unmet need to both identify and test novel drug targets for mood disorders in order to develop more effective treatments. It is a critical public health concern that the next generation of treatments
for mood disorders be more effective, better tolerated, and more rapidly acting than currently available medications, which have predominantly targeted the monoaminergic system. 4 This article reviews the diverse findings implicating the glutamatergic system in the pathophysiology of mood disorders, and examines that system’s promise for developing the next generation of novel therapeutics.

THE FUNCTIONAL AND DYSFUNCTIONAL GLUTAMATERGIC SYSTEM IN MOOD DISORDERS

Glutamate is the most abundant excitatory neurotransmitter in the brain. It acts on three different cell compartments—presynaptic neurons, postsynaptic neurons, and glia—that characterize the “tripartite glutamatergic synapse” 11 (see Figure 1). This integrated, neuronal-glial synapse is complex and directly involves the release, uptake, and inactivation of glutamate by different glutamate receptors (see text box) and other targets with potential clinical relevance, such as voltage-dependent ion channels and amino acid transporters.

Since the initial identification of glutamate as a neurotransmitter in 1959, many studies have provided important insights into the role of the glutamatergic system in the pathophysiology and therapeutics of psychiatric disorders. The involvement of the glutamatergic system in mood disorders was first proposed based on preclinical data with N-methyl-D-aspartate (NMDA) antagonists. 12 Early
Glutamatergic Modulators

Glutamate Receptors and Genes

**Ionotropic Glutamate Receptors**
- AMPA: GluR1, GluR2, GluR3, GluR4 (GRIA1, GRIA2, GRIA3, GRIA4)
- NMDA: NR1, NR2 A-D, NR3 A-B (GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A)
- Kainate: GluR5, GluR6, GluR7, KA1, KA2 (GRIK1, GRIK2, GRIK3, GRIK4, GRIK5)

**Metabotropic Glutamate Receptors**
- Group I (excitatory G-protein coupled)
  - mGluR1 (A-D) (GRM1)
  - mGluR5 (A-B) (GRM5)
- Groups II and III (inhibitory G-protein coupled)
  - mGluR2 (GRM2)
  - mGluR3 (GRM3)
  - mGluR4 (A-B) (GRM4)
  - mGluR6 (GRM6)
  - mGluR7 (A-B) (GRM7)
  - mGluR8 (A-B) (GRM8)

AMPA, -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; Glu, glutamate; NMDA, N-methyl-D-aspartate; m, metabotropic; GluRn, glutamate receptor no. n; KA, kainate.

Studies showed altered glutamate levels in serum and cerebrospinal fluid from patients with mood disorders (reviewed in Machado-Vieira R et al.).

In the last decade, accumulating evidence from diverse studies suggests that the glutamatergic system plays a critical role in both MDD and BPD. Postmortem studies describe altered glutamate levels in diverse brain areas in individuals with mood disorders. In addition, elevated glutamate levels in the occipital cortex and decreased levels in the anterior cingulate cortex appear to be the most consistent findings in nuclear magnetic resonance spectroscopy studies of individuals with mood disorders. It is important to note that dysfunctions in glutamate levels and regulation are more complex than the simplistic view of either increased or decreased levels associated with mood disorders; indeed, both higher and lower levels have been described in different brain areas by imaging studies. Recently, magnetic resonance spectroscopy data evaluating glutamate/glutamine levels—which indirectly assess activity of the neuronal-glial cycle—have also provided important new insights into its dynamic regulation in mood disorders. Notably, the glutamate-glutamine cycle plays a critical role in the regulation of synaptic plasticity, learning, and memory.

Broadly, synaptic plasticity refers to the cellular process that results in lasting changes in the efficacy of neurotransmission. More specifically, it refers to the variability of the strength of a signal transmitted through a synapse. Neuroplasticity is a broader term that includes changes in intracellular signaling cascades and gene regulation, modifications of synaptic number and strength, variations in neurotransmitter release, modeling of axonal and dendritic architecture, and, in some areas of the central nervous system, the generation of new neurons. In recent years, research has linked mood disorders with structural and functional impairments related to neuroplasticity in various regions of the central nervous system. Thus, agents capable of increasing cellular resilience within the complex and interconnected dynamics between glutamate release and uptake in the tripartite glutamatergic synapse, while concomitantly targeting downstream signaling pathways involved in neuroplasticity, are promising novel therapeutics for the treatment of mood disorders. Here, we describe recent findings regarding glutamatergic-based novel therapeutics for mood disorders; these treatments target glutamate receptors, ionic channels, transporters, and postsynaptic proteins that regulate intra- and intercellular glutamate dynamics (Figure 1).

**Excitatory Amino Acid Transporters and Vesicular Glutamate Transporters**

Glutamate clearance from the extracellular space takes place mostly through the high-affinity excitatory amino acid transporters (EAATs). Decreased expression of diverse EAATs has been observed in postmortem studies of subjects with mood disorders (Figure 1). Increased expression of these transporters (e.g., as induced by β-lactam antibiotics) has been found to induce antidepressant-like effects. Mood stabilizers such as valproate and lamotrigine also similarly upregulate EAAT activity, albeit through a potentially different mechanism. In contrast, EAAT antagonism induced depressive effects and altered circadian activity in preclinical models.

Regarding the role of vesicular glutamate transporters (VGLUTs) in mood disorders, a recent postmortem study noted significantly decreased VGLUT1 mRNA expression in both MDD and BPD patients. Similarly, reduced...
VGLUT1 expression has been associated with increased anxiety, depressive-like behaviors, and impaired long-term memory. Preclinical studies have found that diverse antidepressants increase VGLUT expression in the limbic system, and a similar effect was observed after lithium treatment—a mechanism that may be involved in lithium’s protective effects against glutamate-induced excitotoxicity. Diverse compounds that target VGLUTs are now in development. This novel class of compounds is expected to induce therapeutic effects by buffering increased glutamatergic release.

**Ionotropic Glutamate Receptors**

Several studies have shown that ionotropic glutamate receptors play an important role in mood regulation. The NMDA receptors (NMDARs) have a slower and more prolonged postsynaptic current than the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA)/kainate receptors, but all ionotropic glutamate receptors exhibit fast receptor deactivation and dissociation of glutamate. These cellular effects may underlie the specific therapeutic profile of AMPA and NMDA modulators, mostly characterized by their rapid antidepressant effects. It has recently been proposed that both NMDA antagonism and AMPA receptor (AMPA) activation are involved in ketamine’s rapid antidepressant effects (see below for a more detailed discussion). Given the ability of AMPARs to induce a more rapid dissociation of glutamate, the proper balance in this dynamic and complex turnover may account for ketamine’s unique therapeutic effects.

With regard to dysregulation of AMPARs, decreased levels of AMPAR subunits (glutamate receptor (Glu)R 1, GluR2, and GluR3; see text box) have been reported in the prefrontal cortex and striatum of subjects with mood disorders. Also, abnormal metabotropic (m) GluR3 expression has been reported in suicidal subjects with BPD—a finding that was not replicated in a subsequent study. In line with these results, transgenic animals with lower GluR1 expression exhibit increased depressive-like behaviors.

Therapeutically, AMPAR potentiators have been tested in various neuropsychiatric disorders and are a promising new class of agents for the treatment of mood disorders. AMPAR potentiators include benzothiazides (e.g., cyclothiazide), benzylopiiperidines (e.g., CX-516), and bipyridylsulfoxonamides (e.g., LY392098). These agents play a key role in modulating activity-dependent synaptic strength and behavioral plasticity. Furthermore, several preclinical studies found that the antidepressant-like effects of some AMPAR potentiators were also associated with improved cognitive functioning (reviewed in Miu et al., Black, Lynch, and O’Neill et al.). In contrast to the antidepressant-like properties seen with AMPAR potentiators, AMPAR antagonists (e.g., the anticonvulsant talampanel) are believed to have antimanic properties. To date, no placebo-controlled clinical trials with AMPAR potentiators for the treatment of depression or AMPA antagonists for the treatment of mania have been published.

Regarding the role of NMDARs in mood disorders, a series of elegant studies conducted over a decade ago used tricyclic antidepressants to demonstrate that NMDARs may represent a final common pathway of antidepressant action, one that is particularly associated with faster onset. Building on these findings, studies have described altered NMDAR binding and expression in individuals with MDD and BPD. Also, polymorphisms of GRIN1, GRIN2A, and GRIN2B (see text box) have been shown to confer susceptibility to BPD, further supporting a role for these targets in the pathophysiology of this disorder.

Diverse preclinical and clinical studies have found that NMDA antagonists produce rapid antidepressant effects. For instance, one preclinical study observed antidepressant-like effects with a selective NMDAR-2B antagonist, and other brain-penetrant NMDAR-2B antagonists are currently in development. These preclinical findings are supported by a recent, double-blind, randomized, placebo-controlled clinical trial evaluating the NMDAR-2B subunit–selective antagonist CP-101,606, which induced significant and relatively rapid antidepressant effects (by day 5) in patients with treatment-resistant MDD, but with evidence of psychomimetic properties. Additional clinical studies with NMDAR-2A and -2B antagonists in MDD are under way.

It is important to mention that while dramatic clinical therapeutic effects were observed with the high-affinity NMDA antagonist ketamine in MDD (see below), a placebo-controlled study of the low-to-moderate affinity, noncompetitive NMDA antagonist memantine (oral dosing) found no antidepressant effects. These findings suggest that high affinity and IV administration may be key factors for achieving rapid antidepressant effects with this class of agents.

Kainate receptors activate postsynaptic inhibitory neurotransmission. These effects play a crucial role in calcium metabolism, synaptic strength, and oxidative stress, all of which are associated with the pathophysiology of MDD and BPD. A recent, large, family-based association study evaluating the kainate GRIK3 gene described linkage disequilibrium in MDD. Likewise, elevated GRIK3 DNA-copy number was observed in individuals with BPD, relatively, a common variant in the 3’UTR GRIK4 gene was found to protect against BPD. Interestingly, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and Munich Antidepressant Response Signature (MARS) projects
also found that individuals with MDD who had a GRIK4 gene polymorphism (rs1954787) were more likely to respond to treatment with the antidepressant citalopram.72 In preclinical studies, GluR6 knockout mice displayed increased risk-taking and aggressive behaviors, as well as hyperactivity, in response to amphetamine—manic-like behaviors that decreased after chronic lithium treatment.73 These promising findings have led to increased interest in developing kainite receptor modulators, but, to date, no such compounds have been evaluated in the treatment of mood disorders.

Metabotropic Glutamate Receptors

Genetically-induced decreases in expression of mGluRs and agents that target mGluRs—especially Group II and III mGluR modulators—have consistently been found to induce anxiolytic, antidepressant, and neuroprotective effects in preclinical models.74–86 In particular, Group I and II mGluR antagonists such as MPEP (2-methyl-6-[phenylethynyl]-pyridine) and MGS-0039 had antidepressant-like and neuroprotective effects in animal models.81–84 Similar effects were observed with selective Group III mGluR agonists.77,79,85 Several compounds that modulate mGluRs are currently under development for treating MDD.

Postsynaptic Density Proteins

Other potentially relevant targets involving the glutamatergic synapse include the postsynaptic density (PSD) proteins. These proteins (PSD95, SAP102, and others), which interact with ionotropic glutamate receptors at the synaptic membrane, modulate receptor activity and signal transduction. For instance, NMDAR activation interacts directly with PSD95, thereby playing a critical role in the regulation of membrane trafficking, clustering, and downstream signaling events. In mood disorders, decreased PSD95 levels were observed in the dentate gyrus of individuals with BPD.53 In individuals with MDD, PSD95 levels were found to be significantly increased in the limbic system.86 SAP102, which interacts primarily with the NMDAR-2B subunit, has been shown to decrease NMDAR-2B subunit expression in individuals with mood disorders, a finding that was correlated with decreased expression of NMDAR subunits in the limbic system.24,87,88 While these findings suggest that PSD proteins may interact with NMDARs in the pathophysiology of mood disorders, currently no compounds specifically targeting PSD proteins have been developed.

RILUZOLE AND KETAMINE: PROTOTYPES FOR NEW, IMPROVED GLUTAMATERGIC MODULATORS FOR TREATING MOOD DISORDERS

Riluzole

The glutamatergic modulator riluzole is currently approved by the U.S. Food and Drug Administration for treating amyotrophic lateral sclerosis. It has both neuroprotective and anticonvulsant properties due to its ability to inhibit glutamate release and enhance both glutamate reuptake and AMPA trafficking.89 Studies have also shown that it protects glial cells against glutamate excitotoxicity.90 Riluzole’s antidepressant effects have been investigated in open-label studies. In the first study, 19 patients (68%) with treatment-resistant MDD completed the trial, and all showed significant improvement at week 6.91 In the second study, 14 patients with bipolar depression received riluzole adjunctively with lithium; they experienced a 60% overall decrease in Montgomery-Åsberg Depression Rating Scale scores across the eight weeks of treatment and a significant improvement on that scale by week 5.92 In another study, riluzole (50mg/twice daily) was tested as add-on therapy in individuals with MDD; significant antidepressant effects were noted after one week of treatment, with a considerable decrease (36%) in Hamilton Depression Rating Scale scores observed among completers.93 Open-label trials also suggest that riluzole may be effective in treating generalized anxiety disorder and obsessive-compulsive disorder.94,95 Double-blind, placebo-controlled clinical trials are necessary to confirm the promising findings of these open-label studies.

In addition to the clinical evidence, animal studies have shown that long-term use of riluzole induces antidepressant- and antimanic-like behaviors in rodents.96,97 It is important to note, however, that despite its efficacy, no evidence suggests that riluzole acts more rapidly than existing antidepressants, though it may be a reasonable therapeutic option in treatment-resistant cases.

Ketamine

The noncompetitive, high-affinity NMDA antagonist ketamine is a phencyclidine derivative that prevents excess calcium influx and cellular damage by antagonizing NMDARs. In vitro, ketamine increases the firing rate of glutamatergic neurons and the presynaptic release of glutamate.98 Some of these properties are believed to be involved in the compound’s antidepressant effects. AMPAR activation has also been shown to mediate ketamine’s antidepressant-like effects.57 See Figure 2.
Figure 2. Biological correlates of ketamine’s antidepressant effects. BDNF does not appear to be involved in ketamine’s rapid antidepressant effects; however, AMPA relative to NMDA throughput and its potential effects targeting at the PSD may represent a relevant mechanism by which ketamine induces these therapeutic effects. In particular, NR2A and NR2B receptors are believed to mediate these rapid antidepressant effects. Rostral anterior cingulate cortex activity has been implicated in rapid antidepressant response to ketamine infusion. Family history of alcohol dependence in MDD subjects was associated with better short-term outcome after ketamine infusion. ACC, anterior cingulate cortex; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; NR, NMDA receptor; PSD, postsynaptic density.

Similar to other NMDAR antagonists, ketamine induced antidepressant and anxiolytic effects in diverse preclinical studies. An initial clinical study found that seven subjects with treatment-resistant MDD had improved depressive symptoms within 72 hours of ketamine infusion. Subsequently, a double-blind, placebo-controlled, crossover study showed a fast (first two hours after infusion) and relatively sustained antidepressant effect (one to two weeks) after a single ketamine infusion in treatment-resistant patients with MDD. More than 70% of patients responded within 24 hours after infusion, and 35% maintained a sustained response at the end of week 1. Notably, the response rates obtained with ketamine after 24 hours (71%) were similar to those described after six to eight weeks of treatment with traditional monoaminergic-based antidepressants (65%). These findings were subsequently replicated in a different cohort of 26 subjects with treatment-resistant MDD.

A recent study found that ketamine was also associated with robust and rapid antisuicidal effects. Thirty-three subjects with treatment-resistant MDD received a single open-label infusion of ketamine (0.5 mg/kg). Patients were rated at baseline, 40, 80, 120, and 230 minutes post-infusion using the Scale for Suicide Ideation. Scores significantly decreased within 40 minutes of ketamine infusion and remained improved for up to four hours post-infusion. In another study, early antisuicidal effects (within one day) were found with ketamine, and these effects remained significant for several weeks. Due to the public health implications of this finding, future studies evaluating ketamine’s effect on suicidal ideation are warranted. Interestingly, ketamine infusion has also been associated with rapid antidepressant effects during pre- and postoperative states in patients with depression comorbid with pain syndrome or alcohol dependence, as well as during a course of electroconvulsive therapy. Despite these intriguing findings, its sedative and psychotomimetic side effects may limit its clinical use. Although misuse and abuse of therapeutically relevant agents in psychiatry are not new phenomena (e.g., as has occurred with benzodiazepines, anticholinergic...
drugs, and stimulants), an additional limitation of ketamine as a therapeutic agent is that it is one of several abusable “club drugs.”

Alcohol dependence increases NMDAR expression and induces cross-tolerance with NMDAR antagonists. Previous clinical studies found that, compared to healthy controls, subjects with alcohol dependence had fewer perceptual alterations and decreased dysphoric mood during ketamine infusion. This attenuation of ketamine-induced perceptual alterations was also observed in healthy individuals with a positive family history of alcohol dependence. In line with these findings, a recent study from our laboratory found that patients with MDD who had a family history of alcohol dependence had a better short-term outcome (greater and faster improvement in depressive symptoms) after ketamine infusion than subjects with no family history of alcohol dependence. It is also interesting to note that a recent study found that genetic variations in the NMDAR-2A gene are directly associated with alcohol dependence. Thus, the potential mechanisms underlying this different antidepressant response to ketamine in individuals with alcoholism may involve genetic differences in NMDAR subunits, particularly NMDAR-2A binding, which is affected by chronic ethanol exposure.

Other predictors of ketamine response have also been assessed. One recent study tested the hypothesis that magnetoencephalography recordings could provide a neurophysiological biomarker associated with ketamine’s rapid antidepressant effects. Indeed, increased pretreatment rostral anterior cingulate cortex activity was found to be positively correlated with rapid antidepressant response to ketamine infusion in 11 MDD patients versus healthy controls. Other studies have shown that anterior cingulate cortex activation predicts improved antidepressant response to electroconvulsive therapy, repetitive transcranial magnetic stimulation, deep brain stimulation, and sleep deprivation. Another study investigating the putative link between brain-derived neurotrophic factor (BDNF) and ketamine found no association between ketamine’s rapid antidepressant effects and plasma BDNF levels, which showed no change from baseline to 230 minutes post-infusion, a time point when antidepressant response is usually present.

Finally, at the cellular level, ketamine’s antidepressant-like effects were found to be selectively abolished using an AMPA antagonist (NBQX) prior to infusion—an effect not observed with imipramine. Thus, in humans, it is possible that ketamine’s antidepressant effects are mediated via AMPAR activation and not critically through NMDAR antagonism. In contrast, the delayed effects induced by standard monoaminergic antidepressants occur via intracellular signaling changes, which might explain their differing time of onset.

FINAL REMARKS

Because monoaminergic antidepressants take weeks to achieve their full effect, patients receiving these medications remain vulnerable to impaired global functioning and are at high risk of self-harm. This long, risky period of latency in MDD, as well as the persistent residual symptoms, low rates of remission, and frequent relapses associated with currently available therapeutics, is a challenge that needs to be better addressed by the next generation of medications to treat this disorder. Available therapeutics for BPD are similarly not always well tolerated or effective—particularly in the treatment of bipolar depression.

While glutamatergic system abnormalities have been associated with mood disorders, the magnitude and extent of these abnormalities require further clarification. An improved understanding of the function, anatomy, and localization of different glutamatergic receptors in the brain would help to develop the subunit-selective agents necessary for producing improved therapeutics. Studies assessing the impact of novel glutamatergic treatments for mood disorders are under way; at least some of these agents are expected to work more quickly, and to be more effective and better tolerated, than current medications. An increasing number of proof-of-principle studies have also attempted to identify relevant therapeutic targets; riluzole and ketamine, for instance, are both being used in such research.

Despite the recent advances in our knowledge, future studies investigating the efficacy, safety, and potential mechanisms involved in the faster and potentially sustained antidepressant actions of new glutamatergic modulators are necessary. The development of such new, safe, and effective agents for the treatment of mood disorders would have an enormous and significant impact on public health worldwide.

Declaration of Interest: Dr Zarate is listed as a coinventor on a patent for the use of ketamine in major depression. He has assigned his patient rights on katamine to the U.S. government.

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