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Targeting the Glutamatergic System to Develop Novel, Improved Therapeutics for Mood Disorders

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PREFACE

Mood disorders are common, chronic, recurrent mental illnesses that affect the lives of millions of individuals worldwide. To date, the monoaminergic systems (serotonergic, noradrenergic and dopaminergic) in the brain have received the greatest attention in neurobiological studies of mood disorders, and most therapeutics target these systems. However, there is growing evidence that the glutamatergic system is central to the neurobiology and treatment of these disorders. Here, we review data supporting the involvement of the glutamatergic system in mood disorder pathophysiology as well as the efficacy of glutamatergic agents in mood disorders. We also discuss exciting new prospects for the development of improved therapeutics for these devastating disorders.

Keywords

AMPA; antidepressant; bipolar disorder; depression; glutamate; NMDA

Mood disorders (major depressive disorder (MDD) and bipolar disorder (BPD)) are serious, debilitating, life-shortening illnesses that affect millions of people worldwide. The lifetime risk for any mood disorder in the United States is 20.8%, and onset typically begins in childhood or adolescence ¹. Mood disorders are chronic illnesses characterized by multiple episodes of symptom exacerbation, residual symptoms between episodes, and functional impairment ^{2–4}; the World Health Organization's (WHO) Global Burden of Disease project ranked MDD as the fourth leading cause of disability in 1990, and predicts that it will become the second leading cause of disability worldwide by 2020 ⁵.

Although most patients with mood disorders receive some benefit from available treatments ^{6, 7}, the largest open label study examining the effectiveness of pharmacological treatment of MDD conducted to date (STAR*D) ⁷ found that less than one third of patients achieved remission with an adequate trial of a standard antidepressant after up to 14 weeks of treatment. Furthermore, it was not until the completion of two antidepressant trials and nearly 24 weeks of treatment that half of the patients with MDD in the STAR*D study remitted. Similarly, many patients with BPD do not respond to existing medications ⁸, particularly during depressive episodes ^{6, 9}.

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A major obstacle to developing more effective treatments for mood disorders has been our limited understanding of their pathophysiology, and of the mechanisms underlying the efficacy of existing treatments. Mood disorders arise from the complex interaction of multiple genes and environmental factors, and the phenotypic expression of the disease includes not only mood disturbance, but also a constellation of cognitive, motor, autonomic, endocrine and sleep/wake abnormalities. To date, the monoaminergic (i.e., serotonergic, noradrenergic, dopaminergic) systems in the brain have received the greatest attention in neurobiological studies of mood disorders. These systems project widely to limbic, striatal and prefrontal cortical neuronal circuits that are implicated in the behavioral and visceral manifestations of mood disorders (reviewed in ^{10–12}).

However, there are limitations to current monoamine theories related to mood disorders. For example, most antidepressants exert their initial effects by increasing the intrasynaptic levels of serotonin and/or norepinephrine. Nevertheless, meaningful improvement in core depressive symptoms emerges only after several weeks of antidepressant administration, suggesting that downstream neural adaptations rather than the elevation in synaptic monoamine levels itself are responsible for their therapeutic effects. Furthermore, although depletion of monoamines may increase the risk of mood disorders in some individuals under some circumstances, these depletions do not produce widespread clinical depression. Together, these observations suggest that monoaminergic systems do not represent a final common pathway regulating mood, but rather exert a modulatory influence (see ¹³ for review).

Overall, this focus on monoaminergic systems has not yet greatly advanced our understanding of the biology underlying recurrent mood disorders. Any such understanding must include an explanation for the tendency towards episodic and often profound mood disturbance that can become progressive over time. These observations suggest that although monoaminergic neurotransmitter systems play an important role in the pathophysiology and treatment of mood disorders, other systems that regulate synaptic and neural plasticity are more central to the neurobiology and treatment of these disorders ^{14, 15}.

Research on the biological underpinnings of mood disorders has therefore begun to focus less on absolute changes in monoamines, and more on the role of neural circuits and synapses, and the processes controlling their function. Glutamate (Glu) is the major mediator of excitatory synaptic transmission in the mammalian brain ¹⁶. Under normal conditions, Glu plays a prominent role in synaptic plasticity, learning, and memory, but in pathological conditions it is known to be a potent neuronal excitotoxin, triggering either rapid or delayed neurotoxicity. The potential role of the glutamatergic system in the pathophysiology of, and treatment of, mood disorders has recently been investigated in earnest, but the available evidence suggests that abnormal activity of the glutamatergic system is likely to contribute to the impairments in synaptic and neural plasticity that are observed in patients with severe or recurrent mood disorders. Thus, numerous therapeutic strategies are being explored in an attempt to remedy the presumed impairments of Glu-mediated plasticity. Indeed, in preclinical paradigms, several of these treatments exert robust neurotrophic effects ¹⁷. Testing the efficacy and safety of these glutamatergic treatment strategies in patients with MDD and BPD may yield a better understanding of the neurobiological processes involved in these disorders, and lead to the development of improved treatments.

Physiology of the glutamatergic system

Glu can be found throughout the brain. Because tight control over glutamatergic neurotransmission is required to maintain optimal neuronal function and prevent over-activation of the system, multiple levels of regulatory processes have evolved to ensure glutamatergic excitation is maintained within narrow boundaries (Figure 1).

In the brain, Glu can either be synthesized *de novo* from glucose via the Krebs cycle and the transamination of α -oxoglutarate, or it can be recycled through the glutamate/glutamine (Glu/Gln) cycle (see below)¹⁸. Glu is transported into synaptic vesicles by vesicular Glu transporters (VGLUTs)^{19, 20}, where it is stored at high concentrations, and protected from degradation before being released in a Ca²⁺-dependent manner into the synaptic cleft by exocytosis.

On release, Glu binds to and activates specialized ionotropic and metabotropic receptors found throughout the CNS that have wide-ranging effects on neural excitability (see BOX 1). The post synaptic density (PSD), a large supramolecular complex composed of Glu receptors, anchoring proteins, cytoskeletal proteins, and signaling proteins²¹, also contributes to the regulation of Glu signaling. Glu receptors bind to several receptor-binding proteins in the PSD, including PICK1, stargazin, GRIP, membrane-associated guanylate kinases (MAGUKs), and Homer, via regions on their cytoplasmic domains. These proteins can be regulated by both post-translational splicing and phosphorylation events, and are essential for receptor trafficking, and for coupling the receptors to other scaffolding and signaling proteins.

Glu is cleared from the extracellular space via high-affinity excitatory amino acid transporters (EAATs) in neighboring glial cells, which convert Glu into glutamine (Gln) via the action of glutamine synthetase (GS). Gln is then transported back into the glutamatergic neuron where it is hydrolyzed by glutaminase back into Glu (see Figure 1). Due to the lack of degradative enzymes in the synapse, uptake by the EAATs is the primary mechanism through which the action of extracellular Glu is terminated. Failure of the EAATs to effectively clear Glu from the extracellular space results in various forms of cellular damage^{22, 23} and is believed to be linked with neuropsychiatric disorders²⁴.

Glu in the pathophysiology of mood disorders

Abnormal function of the glutamatergic system has been implicated in the pathophysiology of many different disorders including amyotrophic lateral sclerosis (ALS), Huntington's chorea, epilepsy, Alzheimer's disease, schizophrenia, and anxiety disorders. Thus, dysfunction of glutamatergic neurotransmission may be a common pathophysiological mechanism, aspects of which are shared between several disorders. However, it is beyond the scope of this review to consider this extensive literature, and the reader is referred elsewhere for more information on these other disorders^{25–28}. This review will focus only on the relationship between glutamate neurotransmission and mood disorders.

Changes in Glu levels

Glutamatergic abnormalities have been reported in plasma^{29–31}, serum³², CSF^{33, 34} and brain tissue³⁵ of individuals afflicted with mood disorders. However, these studies are compromised by problems with medication exposure, postmortem effects on metabolism, and the inability to identify the precise source of the Glu in the peripheral tissue, thus rendering the findings difficult to interpret^{36, 37}. A recent postmortem study specifically controlling for the effects of postmortem interval found increased levels of Glu in the frontal cortex of patients with BPD and MDD³⁸.

Fortunately, *in vivo* measures of brain Glu content can now be made with the use of proton magnetic resonance spectroscopy (¹H-MRS). Although it remains extremely difficult to assign unequivocal resonance peaks to the individual Glu resonances, a combined measure termed Glx, which predominantly reflects Glu content but also contains Gln and GABA components, has now been adopted by several groups. A growing collection of ¹H-MRS brain imaging studies suggests that abnormalities do exist within the glutamatergic system of patients with mood disorders. However, the extent and direction of the changes are still to be determined, with reports of elevated Glu levels in the occipital cortex (OCC) of depressed patients, and

decreased Glu levels in the anterior cingulate cortex (ACC) and possibly other frontal regions. In addition, there are reports of increased Glu content in several brain regions of individuals with BPD. While it remains difficult to draw any specific conclusions regarding the pathophysiological significance or etiology of the postmortem and imaging findings related to Glu content to date, the studies do suggest that the glutamatergic system is altered in several brain regions in association with mood disorders. Newer ^{13}C -MRS studies capable of measuring the rate of glutamine/glutamine cycling should provide greater detail on the changes in glutamatergic function associated with mood disorders ³⁹.

Glu receptor alterations

Several studies have found differences related to NMDA receptor expression and binding affinities between individuals with and without mood disorders. An initial report demonstrated differences in the allosteric modulation of glutamate binding through the glycine binding site on the NMDA receptor in the frontal cortex of age- and postmortem interval-matched suicide victims ⁴⁰. Later studies reported decreased binding of Glu receptor antagonists in the hippocampus of eight subjects with BPD ⁴¹. Because these compounds bind to the glutamate binding site and open ion channel of the NMDA receptor, respectively, these data suggest that there is a decrease in the number of open ion channels associated with no significant change in the density of NMDA receptors in regions of the hippocampus from subjects with BPD. Using the same hippocampal tissue, McCullumsmith and colleagues (2007) recently demonstrated a coexistent decrease in NR1 and NR2A transcript expression, but no difference in NR2B expression in BPD subjects ⁴². This finding is consistent with an earlier report of reduced hippocampal NR1 transcript expression in individuals with mood disorders ⁴³. A similar reduction in NMDA receptor binding and NR1 subunit expression was also reported in the superior temporal cortex of individuals with MDD and BPD ⁴⁴. In sum, these studies point to a differential expression of the various NMDA receptor subunits in individuals with mood disorders.

At the genetic level, two polymorphisms of the GRIN1 gene coding for the NR1 subunit have been associated with BPD through a linkage disequilibrium study ⁴⁵. Two polymorphisms in the GRIN2 gene coding for NR2B were also recently reported to be associated with BPD, especially if psychotic features were present, but no coexistent change in NR2B mRNA expression could be associated with the polymorphism in the region of the dorsolateral prefrontal cortex (DLPFC) ⁴⁶. In a related study, the density of GABA interneurons that express the NMDA NR2A subunit appeared to be decreased in the ACC of subjects with BPD ⁴⁷. Fewer postmortem studies have explored the association between AMPA and KA receptors and mood disorders. There is a single report of increased AMPA binding associated with a decreased GluR1 subunit expression in the striatum in BPD ⁴⁸. Although no differences in AMPA or KA binding were detected in hippocampus or DLPFC, decreased levels of GluR2 were found in the DLPFC in individuals with BPD, and GluR2 and GluR3 in individuals with MDD ^{41, 49}.

Recent postmortem studies have begun to explore whether alterations in the expression of intracellular anchoring and trafficking proteins associated with the PSD are altered in mood disorders. Decreased expression of SAP102 (a synapse-associated protein that primarily interacts with the NR2B subunit) coincided with a decrease in NR1 and NR2A subunit expression in the hippocampus of subjects with BPD ⁴², and has also been observed in the striatum ⁵⁰ and thalamus ⁵¹ of subjects with MDD and BPD. Additional decreases in NF-L and PSD95 transcripts were observed only in BPD. PSD95 immunoreactivity was also decreased in the hippocampal dentate in BPD, but not in MDD or the orbital frontal cortex or hippocampal hilus in MDD or BPD ⁵². Furthermore, no differences in the expression of AMPA receptor trafficking and signaling molecules (NSF, PICK1, Stargazin, and syntenin) could be found in the DLPFC of individuals with mood disorders ⁴⁹. The key findings are noted in Table 1.

Evidence of glial cell pathology

Recent work has highlighted the importance of glial cells in the function and regulation of the glutamatergic neurotransmitter system. Although some evidence suggests that glial abnormalities are predominantly due to reduced numbers of oligodendrocytes⁵³, other glial cells involved in glutamate neurotransmission are also likely to be involved in glial pathology⁵⁴. Decreased glial cell number and density have been found in several brain regions in individuals with mood disorders^{53, 55–62}. Reduced expression of EAAT1, EAAT2, and GS has been found in two frontal brain regions in postmortem brain samples from individuals with MDD⁶³, and decreased levels of EAAT 3 and EAAT4 mRNA expression were found in the striatum of subjects with mood disorders⁶⁴ (reviewed in^{65–67}). The reduced levels of glial cell number and density in the brains of mood disorder patients are one of the most consistent pathological findings in psychiatric research. If this represents a true decrease in glial cell function it may help to explain the altered Glu content observed in several brain regions of patients with mood disorders.

Effects of mood-disorder therapeutics

Antidepressants

Pursuant to their initial finding showing that NMDA antagonists have antidepressant properties⁶⁸, seminal studies by the Skolnick laboratory demonstrated that chronic antidepressant administration (monoaminergic-based antidepressants, tricyclic antidepressants^{69, 70}, and electroconvulsive therapy) regulates NMDA receptor expression and function^{71–75}. *In situ* hybridization studies^{76, 77} have revealed that repeated electroconvulsive shock (ECS) in rats produced an increase in expression of mRNA for GluR1, a subunit of the AMPA receptor in the dentate gyrus, and in the CA1 and CA3 cell fields of the hippocampus, areas that are believed to be critical for normal affective functioning.

Data also suggest that antidepressants upregulate AMPA receptor function by stimulating AMPA receptor subunit phosphorylation. Acute treatment with fluoxetine increases the phosphorylation of GluR1 at Ser831 and Ser845, whereas chronic dosing (19 days) with fluoxetine selectively increases the phosphorylation of GluR1 at Ser845⁷⁸. Interactions of GluR1 and GluR2/3 with proteins implicated in AMPA receptor trafficking and with scaffolding proteins appear to account for the enhanced membrane expression of AMPA receptors in the hippocampus after antidepressant treatment⁷⁹. Barbon and colleagues (2006) examined the mRNA expression of all subunits of AMPA receptors after antidepressant treatment and found that chronic treatment with fluoxetine and desipramine exerted moderate but selective effects on Glu receptor mRNA expression and RNA editing⁸⁰.

In summary, growing evidence supports the idea that antidepressants, via a cascade of time-dependent signaling changes, ultimately converge to regulate AMPA- and NMDA-mediated synaptic plasticity. Taken together, these preclinical studies suggest that reductions in NMDA receptor function are a consequence of treatment with known antidepressant medications and antidepressants and mood stabilizers regulate AMPA receptor phosphorylation and trafficking (reviewed in⁸¹). The evidence supporting these hypotheses is briefly presented in Table 2.

Mood stabilizers

Patients with BPD are generally treated with a class of medications known as mood stabilizers. Mood stabilizers have antimanic effects, exert prophylactic effects in preventing recurrent manic or depressive episodes, and may also possess some antidepressant properties. The prototypic agent of this class is lithium, a seemingly simple monovalent cation. A variety of anticonvulsant agents, most notably valproic acid (valproate (VPA), a substituted pentanoic acid), are also used as mood stabilizing agents⁸².

In view of the evidence that excessive synaptic Glu may contribute to neuronal atrophy and loss, it is notable that chronic treatment with lithium has been shown to upregulate synaptosomal uptake of Glu in mice ⁸³. Furthermore, chronic treatment with therapeutically relevant concentrations of lithium in cultured rat cerebellar, cortical, and hippocampal neurons protected against glutamate-induced excitotoxicity ⁸⁴. The investigators report that the protection could be attributed, at least in part, to inhibition of NMDA receptor-mediated Ca^{2+} influx ^{84, 85}. Chronic administration of VPA led to a dose-dependent increase in hippocampal Glu uptake capacity, as measured by uptake of [³H]glutamate into proteoliposomes, by increasing the levels of the Glu transporters EAAT1 and EAAT2 in hippocampus. Overall, chronic treatment with VPA or lithium is likely to decrease intrasynaptic Glu levels through a variety of mechanisms.

In view of the critical role of AMPA receptor trafficking in regulating various forms of plasticity, recent studies have sought to determine whether these two structurally highly dissimilar antimanic agents—lithium and VPA—affect AMPA receptor trafficking. Both have the common effect of downregulating AMPA GluR1 synaptic expression in hippocampus after prolonged treatment with therapeutically relevant concentrations, both *in vitro* and *in vivo* ⁸⁶. The key findings are highlighted in Table 3.

Additional support for the therapeutic relevance of these data is provided by recent studies indicating that AMPA receptor antagonists attenuate several “manic-like” behaviors produced by amphetamine administration ⁸⁷.

Lamotrigine is an anticonvulsant that also has mood stabilizing properties in patients with BPD. Of all the medications currently used in the treatment of mood disorders, lamotrigine probably has the most direct effects on the Glu system. There is evidence that it inhibits the release of Glu in the hippocampus of rats ⁸⁸, and that it increases AMPA subunit receptor expression ⁸⁹.

Glutamatergic agents in mood disorders

Several therapeutic agents that act on the glutamatergic system can be explored as potential treatments for mood disorders.

Inhibitors of glutamate release

In addition to lamotrigine, the US Food and Drug Administration-approved drug riluzole (2-amino-6-(trifluoromethoxy) benzothiazole), which is used for the treatment of ALS, has also been shown to inhibit Glu release. However, riluzole exerts a range of effects on the glutamatergic system, including AMPA receptor trafficking ⁸⁹, stimulation of neurotrophic factor synthesis ⁹⁰, and enhancement of Glu reuptake ⁹¹. It does not appear to directly affect NMDA or KA receptors ⁹². Riluzole has also been found to strongly attenuate the electrically evoked release of dopamine and norepinephrine but not serotonin; as mentioned previously, such neurotransmitters have long been implicated in the mechanism of antidepressant action ⁹³.

Both preclinical and clinical studies indicate that riluzole has antidepressant properties ^{94–96}. The first open label study, undertaken in depressed patients who had failed to respond to adequate trials of at least two antidepressants, found riluzole had significant antidepressant effects with 46% of trial completers meeting response criteria ⁹⁴. In a subsequent study of patients with bipolar depression, augmentation of lithium with open label riluzole for eight weeks significantly improved depressive symptoms with the average total Montgomery-Asberg Depression Rating Scale scores dropping by more than 15 points by the eighth week of the study ⁹⁵. Finally, in another open label study where riluzole was added to ongoing

antidepressant therapy in patients with treatment-resistant MDD, patients experienced a significant improvement in depressive symptoms reflected by a nearly 10 point reduction in Hamilton depression rating scale scores after six to 12 weeks⁹⁶. Overall, riluzole was well-tolerated in these trials, and interestingly, the patients who responded to riluzole tended to be in remission (i.e., almost symptom-free), suggesting that there may be a subgroup of patients for whom glutamatergic strategies have considerable value.

Although the mechanisms of lamotrigine and riluzole appear to be similar, preliminary data have also shown that patients who had previously failed to respond to lamotrigine subsequently responded to riluzole. This may be due in part to riluzole's additional effects on Glu neurotransmission, such as enhanced Glu uptake, that are not seen with lamotrigine⁹¹. The studies that highlight riluzole's efficacy in subjects who were previously medication resistant are encouraging, especially because these patients usually have markedly reduced rates of response to medication. However, it will be important to confirm these findings in randomized placebo controlled trials before any firm conclusions can be drawn about the true efficacy of riluzole in the treatment of MDD.

Partial NMDA receptor agonists

D-Cycloserine (4-amino-isoxazolidin-3, DCS) is a broad spectrum antibiotic with some antidepressant properties in rodent models of depression. Early reports based on clinical observation indicated that DCS had positive effects on mood, insomnia, and appetite in depressed tuberculosis patients^{97, 98}. A subsequent double-blind, placebo-controlled, six-week crossover study involving 22 patients with treatment-resistant MDD found the addition of DCS at 250 mg/day to other antidepressants to be ineffective⁹⁹. However, it is possible that the doses studied were too low. It wasn't until 1997 that it was shown that doses higher than 500 mg/day of DCS are required to elicit a neuroendocrine response (measured as an increase in plasma levels of luteinizing hormone); such a response is indicative of NMDA antagonism^{100, 101}. Interestingly, based on animal work showing that DCS facilitated extinction of fear when given either before or shortly after exposure to fearful cues¹⁰², several recent clinical studies have shown that lower doses of DCS are effective in enhancing the efficacy of exposure-based therapies for anxiety disorders; no significant effect was seen when the higher dose of 500 mg/day was used^{103–105}.

NMDA antagonists

Memantine (1-amino-3, 5-dimethyl-adamantane) is a derivative of amantadine, a low-affinity, uncompetitive, open-channel NMDA antagonist. Memantine is well-tolerated¹⁰⁶, and is approved for the treatment of moderate to severe Alzheimer's disease, where it has been shown to enhance cognition and minimize clinical deterioration in patients with Alzheimer's disease, vascular dementia, and mixed dementia¹⁰⁷.

Preclinical studies have described a dose-dependent decrease in immobility time in the forced swim test (FST) in rats following administration of memantine. A synergistic effect was seen when imipramine and fluoxetine were given jointly with memantine in the FST in rats (reviewed in^{65, 81}). One recent paper reported that two patients with treatment-resistant BPD had improved cognition and mood stabilization with memantine¹⁰⁸, but an eight-week, double-blind, placebo-controlled trial of memantine in 32 patients with MDD found no significant antidepressant or anti-anxiety effects¹⁰⁹. It is possible, however, that antidepressant effects might have occurred with much higher doses of memantine, as suggested by another recent open-label flexible dosing study of memantine in MDD¹¹⁰. Another possibility is that memantine may evince antidepressant properties by augmenting the effects of other agents.

Ketamine (dl2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride) is another NMDA antagonist¹¹¹ and a derivative of phencyclidine (PCP). Its use in humans is associated with psychotomimetic and cognitive effects that possibly preclude its chronic use in treatment¹¹².

Ketamine's primary mechanism of action is blocking the NMDA receptor at the PCP site within the ionotropic channel. Simultaneously, ketamine, presumably by producing a disinhibition of GABAergic inputs and thereby enhancing the firing rate of glutamatergic neurons, increases the presynaptic release of Glu, resulting in increased extracellular levels of Glu¹¹³. This increase in Glu 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. The ability to block ketamine's antidepressant-like effects with an AMPA antagonist suggests that enhanced AMPA throughput may be critical in producing these effects¹¹⁴.

Clinically, ketamine is a popular agent for emergency department procedural sedation in children, with ample evidence to support its safety and efficacy¹¹⁵. Although its psychotomimetic side effects have led to its misuse and abuse, there is no evidence that ketamine causes physical dependence in humans¹¹⁶, and recent studies found no evidence that repeated, albeit limited (mostly less than four exposures), exposure to ketamine increases the risk of more severe or more protracted psychosis, perceptual changes resembling dissociation, severe emotional distress, or euphoria in healthy subjects¹¹⁷ or patient populations¹¹⁸.

Ketamine and related NMDA antagonists have been shown to have anxiolytic and antidepressant effects in animal models (reviewed in^{65, 81}) as well as antidepressant effects in humans^{109, 119}. One study found that seven subjects with treatment-resistant MDD showed significant improvement in depressive symptoms within 72 hours of treatment with ketamine¹¹⁹. Furthermore, a double-blind placebo-controlled crossover study found that a single intravenous dose of ketamine (0.5 mg/kg over 40 minutes) resulted in rapid and significant antidepressant effects in patients with treatment-resistant MDD within two hours, an effect that remained significant for seven days. Seventy-one percent of subjects met response criteria, and 29% achieved remission at 24 hours following the infusion of ketamine. Thirty-five percent of subjects maintained response to ketamine for at least one week; two of these maintained response at least two weeks. By contrast, no subject on placebo responded at one or seven days. Mild perceptual disturbances occurred in most patients, but in all cases lasted less than one hour. No serious adverse events occurred¹⁰⁹.

Emerging promise of novel therapeutics

AMPA potentiators

Positive modulators of AMPA receptors do not activate AMPA receptors themselves but slow the rate of receptor desensitization and/or deactivation in the presence of an agonist (see^{120, 121} for review). Several modulators from various structural classes have been synthesized, including benzothiazides (e.g., cyclothiazide), the benzoylperidines (e.g., CX-516), and the bitylpropylsulfonamides (e.g., LY392098). They are being studied in cognition, anxiety, stroke, Parkinson's disease, and MDD (reviewed in¹²²). In preclinical studies, Aniracetam¹²², Ampalex¹²³, LY392098¹²⁴, LY 451616^{124, 125}, and S18986^{126, 127} have all been found to have some antidepressant properties, such as reduction of submissive behavior. Some of these compounds have entered clinical trials but proof of their antidepressant efficacy is pending.

Subunit selective NR2B antagonists

The first generation NMDA receptor complex antagonists include ketamine, MK-801, and PCP. These blockers are potent neuroprotectants in vitro and in vivo, but are likely to produce psychotomimetic effects when used acutely. However, other more selective NMDA antagonists, especially those that act on the NR2B receptor subtype (e.g., Ifenprodil), appear to have a low liability for this outcome, particularly when used at lower doses. Unfortunately, some of these compounds also have a high affinity to α 1-adrenoreceptors and other ion channels.

More recently, a series of oral, brain-penetrant NR2B antagonists with more selective effects are being developed. These include indole-2-carboxamides, benzimidazole-2-carboxamides, and HON0001^{128–130}. A recent double-blind, randomized, placebo-controlled study indicated that CP-101–606, another NR2B-specific NMDA antagonist, had statistically significant antidepressant effects in patients with treatment-resistant MDD¹³¹. The average reduction in symptom severity was approximately two times greater in active versus placebo-treated patients. Dissociative symptoms produced by the active infusion were generally modest and resolved within eight hours.

Glial Glu transporter enhancers

Recently, there has been considerable enthusiasm in the scientific community for studying the effects of β -lactam antibiotics in neurodegenerative diseases because, unlike other classes of antibiotics, they selectively induce transcription of the gene encoding the EAAT2 (GLT1) Glu transporter^{132–134}. One of the β -lactam antibiotics — ceftriaxone — was found to increase expression of the gene encoding for the GLT1 receptor within a few days of its administration, and therefore might selectively modulate the glutamatergic system. Ceftriaxone has been found to have antidepressant-like effects in several animal models of depression¹³⁵. The data from this study are also consistent with the hypothesis that excessive Glu transmission might be involved in the pathophysiology of MDD.

Group I metabotropic receptor modulators

As noted above, the group I mGlu receptors play a major role in regulating postsynaptic excitability through interactions with NMDA receptors. mGluR5 receptors are an attractive target for modulating Glu neurotransmission because, in addition to being present on postsynaptic neurons, they are also present on glial cells where they appear to regulate the release of excitatory transmitters from glia; this, in turn, leads to selective stimulation of extrasynaptic NMDA receptors^{136–138}. Group I metabotropic receptor modulating agents, especially mGluR1/5 antagonists such as 2-methyl-6-(phenylethynyl) pyridine (MPEP) and 3-[(2-Methyl-1,3-thiazol-4-ylethynyl)pyridine (METP), have strong anxiolytic effects in preclinical animal models. More recent studies suggest that they may also possess antidepressant-like properties (see^{139, 140}); however, to date there are no published clinical studies demonstrating the effectiveness of this class of drug.

Group II metabotropic receptors (mGluR 2 and 3) are largely present on presynaptic membranes and on glial cells where they are believed to modulate glutamatergic neurotransmission by sensing Glu spillover and regulating transmitter release. The function of these mGluR2/3 receptors in modulating Glu neurotransmission make them extremely interesting targets for antidepressant drug development, and there is evidence suggesting that mGluR2/3-targeted drugs possess both antidepressant and anxiolytic properties (see^{139, 140} for reviews).

However, whereas mGluR2/3 receptor antagonists (e.g. LY341495, MSG0039) appear to have antidepressant-like properties, mGluR2/3 receptor agonists (i.e. LY404039, LY354740) have

a profile consistent with anxiolytic and antipsychotic drugs. As with the NMDA antagonists, many of the antidepressant-like effects of the mGluR2/3 receptor antagonists can be prevented by co-administration of an AMPA receptor antagonist ¹⁴¹, suggesting that activation of synaptic AMPA receptors may be a common pathway through which the antidepressant effects are transduced. No clinical studies have yet been conducted to explore the antidepressant efficacy of mGluR2/3 receptor antagonists ^{139 140}.

Early phase clinical trials have recently supported the efficacy of mGluR2/3 receptor agonists in the treatment of schizophrenia ¹⁴², though some safety concerns for this class of drugs have been raised ¹⁴³. If replicated in larger clinical trials, mGluR2/3 receptor agonists would represent completely novel class of therapeutics for schizophrenia.

Presynaptic packaging and Glu release inhibitors

Increasing evidence suggests that chronic antidepressant treatment results in modulation of presynaptic Glu release ¹⁴⁴. Some evidence suggests this is the result of effects on the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) complex that controls the structural and biochemical aspects of synaptic vesicle exocytosis ¹⁴⁵; therefore, targeting the expression and function of these proteins has been suggested as a useful tool in the development of novel biomarkers and therapies for neuropsychiatric disorders ¹⁴⁶.

As mentioned previously, an essential step in Glu neurotransmission is the concentration of Glu into synaptic vesicles before release from the presynaptic terminal. As a result, a series of inhibitors of Glu vesicular transporters are being developed and include amino acids and amino acid analogs, fatty acids, azo dyes, quinolines, and alkaloids. The potency with which these agents inhibit VGLUT varies considerably ¹⁴⁷.

Recent studies have also shown the importance of the cystine-glutamate antiporter in controlling extracellular Glu content ¹⁴⁸ and vesicular Glu release ¹⁴⁹. N-Acetyl Cystine, an agent known to modulate the function of the cystine-glutamate antiporter has recently gained attention as a potential treatment for various neuropsychiatric disorders ^{150, 151}, and several clinical trials are currently underway.

Conclusions

A considerable body of evidence supports the role of the Glu system in mediating synaptic plasticity as well as long-term cell growth/atrophy. Mounting evidence now also suggests that disturbances of brain and synaptic plasticity contribute to the pathological processes associated with mood disorders ¹⁵², thus providing a potential link between the glutamatergic neurotransmitter system and the pathophysiology of mood disorders. The data reviewed here suggest mood disorders are in fact associated with abnormal function and regulation of the glutamatergic neurotransmitter system. Further, emerging studies suggest that targeting glutamatergically-mediated synaptic plasticity could be an effective strategy for treating these devastating disorders.

There has, unfortunately, been little progress in developing truly novel medications for mood disorders. Although a relationship between the glutamatergic system and mood disorders was originally proposed nearly two decades ago ⁶⁸, interest in the field has grown rapidly in recent years. Today, several therapies targeting this system show substantial promise for the treatment of mood disorders. Most notably, ketamine and riluzole merit continued study as putative archetypes for improved therapeutics. Ketamine is of particular interest because it has been shown to bring about rapid and relatively sustained antidepressant effects. Its rapid, robust, and consistently reproducible antidepressant effects offer a unique opportunity to better delineate the precise cellular mechanisms involved ¹¹⁴.

AMPA receptor stimulation appears to mediate the antidepressant-like effects of both ketamine and the group II metabotropic Glu receptor antagonist MGS0039¹⁴¹, suggesting that enhanced transmission through glutamatergic AMPA receptors may provide a common mechanism of antidepressant action. In agreement with this hypothesis, chronic administration of antidepressants also enhances AMPA receptor surface levels^{89, 153}, and AMPA potentiators have shown antidepressant-like effects in animal models¹²⁴. We postulate that the therapeutic effects of both monoaminergic antidepressants and glutamatergic agents may be mediated by increased AMPA to NMDA throughput in critical neuronal circuits (Figure 2).

Although the results obtained with riluzole-like or ketamine-like drugs are still very preliminary, they provide incentive for further study of the role of Glu in mood disorders. Continued exploration of the antidepressant-like effects of glutamatergic drugs holds considerable promise for the development of new treatments for mood disorders. The fact that currently available antidepressants take weeks to achieve their full effects leaves patients particularly vulnerable to devastating symptoms and elevated risk of self-harm. Thus, any pharmacological strategy that could exert a rapid and sustained antidepressant effect within hours or even days could have a substantial beneficial impact on patients' quality of life as well as public health.

Box 1 | Glutamate receptors

There are two major subtypes of glutamatergic receptors in the CNS: ionotropic and metabotropic. Metabotropic Glu receptors (mGluRs) are G protein-coupled receptors. Eight types have been cloned and they can be organized into three different subgroups based upon the signaling transduction pathways that they activate. Group I (mGluR1 a-d, mGluR5 a-b) act primarily through PLC β and the activation of the IP3 and DAG second messenger systems¹⁵⁴. Groups II (mGluR 2 and 3) and III (mGluR4, mGluR6-8) are negatively coupled to adenylyl cyclase. Ionotropic Glu receptors are ligand-gated ion channels that open when activated by the binding of an agonist. There are three different subgroups:

AMPA Receptors

AMPA receptors mediate the fast, rapidly desensitizing excitation at most synapses, and are responsible for the initial reaction to Glu in the synapse. Their activation opens the pore permitting the inward flow of sodium, resulting in the depolarization of the neuronal membrane. The AMPA receptors comprise a homo or heteromeric complex of four subunits (GluR1-4). Because of differences in individual subunit expression, posttranscriptional modifications, and alternative splicing modifications they are functionally diverse. At mature synapses, AMPA receptors are usually co-expressed with NMDA receptors.

Kainate (KA) Receptors

KA receptors are coded by two gene families coding for the low affinity GluR5-7 subunits and the high affinity KA1 and KA2 subunits. These subunits are also subject to extensive posttranscriptional and posttranslational modification. Like AMPA receptors, KA receptors are associated with voltage-dependent channels that primarily allow for the influx of Na⁺ ions that mediate fast excitatory neurotransmission, but they appear to have a distinct distribution.

NMDA Receptors

NMDA receptors are believed to exist primarily as tetrameric complexes comprising two obligatory NR1 subunits and two NR2 subunits. There are at least eight splice variants of the NR1 subunit, four NR2 genes (NR2 A-D), and two NR3 subunits (NR3A and NR3B). The binding site for Glu has been found in the NR2 subunit and the site for the co-agonist glycine has been localized to the NR1 subunit.

NMDA receptors are normally blocked under resting conditions by the obstructing effects of Mg⁺. However, once the surrounding membrane is depolarized, these receptors may be activated by the combined binding of two molecules of Glu and two molecules of glycine or D-serine¹⁵⁵. Thus, NMDA receptor activation serves as a functional marker of converging excitatory input and produces excitation over longer periods of time. Synaptic NMDA receptors activate MAPK and the transcription factor cAMP- Ca²⁺ response element-binding protein (CREB), induce expression of the gene that encodes brain-derived neurotrophic factor (BDNF), and promote neuronal survival, whereas extrasynaptic NMDA receptors propagate opposing signals that promote cell death^{156, 157}.

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GLOSSARY TERMS

Synaptic plasticity, The cellular processes that result in lasting changes in the efficacy of neurotransmission. Changes in neurotransmitter levels, receptor subunit phosphorylation, surface/cellular levels of receptors, and conductance changes all regulate the strength of signal transmission at the synapse.; Neural plasticity, Changes in intracellular signalling cascades and gene regulation that lead to modifications of synapse number and strength, variations in neurotransmitter release, remodelling of axonal and dendritic architecture and, in some areas of the CNS, the generation of new neurons. These modifications can be of short duration or long lasting.; Major depressive disorder (MDD), A chronic mood disorder characterized by a long-lasting depressed mood or marked loss of interest or pleasure in all or nearly all activities. MDD often affects mental efficiency, memory, appetite, and sleep habits.; Bipolar disorder (BPD), A mood disorder in which affected individuals alternate between states of deep depression and mania. While depression is characterized by persistent and long-term sadness or despair, mania is a mental state characterized by great excitement, flight of ideas, a decreased need for sleep, and, sometimes, uncontrollable behavior, hallucinations, or delusions.; Glutamate/glutamine (Glu/Gln) cycle, Process through which most brain Glu is recycled. Glu released by neurons is converted to Gln in astrocytes. Gln is then transported out for re-uptake by neurons, which convert it back into Glu via the action of glutaminase.; Psychotomimetic, Refers to a drug or substance that produces psychological or behavioral changes that resemble those of a psychotic state.; RNA editing, Molecular processes in which the information content is altered in a RNA molecule through a chemical change in the base makeup.; Montgomery-Asberg Depression Rating Scale, An eleven-item clinician-administered questionnaire used to rate the severity of a patient's depression.; Hamilton Depression Rating Scale, A 21-question, multiple-choice, clinician-administered questionnaire used to rate the severity of a patient's depression..

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Figure 1. Glutamatergic neurotransmission and potential targets for drug development

Tight physiological control is maintained over glutamatergic neurotransmission. Glutamine (Gln) is converted to glutamate (Glu) by glutaminase, though it can also be derived from the TCA cycle (not shown). Glu is packaged into presynaptic vesicles by the vesicular Glu transporter (VGLUT) proteins and released from the neuron in an activity-dependent manner through interactions with SNARE proteins. Glu is cleared from the extracellular space by excitatory amino acid transporters (EAATs) present predominantly on glia. In glial cells Glu is converted to Gln by Gln synthetase (GS). A variety of Glu receptors are present on presynaptic and postsynaptic neurons as well as on glial cells. These include both ionotropic receptors (AMPA, NMDA, and KA), as well as metabotropic receptors (mGluRs). The effect of Glu is determined by the receptor subtype, localization, and interactions with various scaffolding and signaling proteins in the postsynaptic density (PSD). Activation of Glu receptors results not only in rapid ionotropic effects, but also in long-term synaptic plasticity.

Potential Targets for Drug Development numbered in the figure:

1) AMPA receptor modulation; **2)** NMDA receptor modulation (a) extrasynaptic, (b) synaptic; **3)** Group I metabotropic receptor modulation; **4)** Voltage dependent Na⁺ channel modulation that regulates Glu release; **5)** Group II metabotropic receptor modulation (mGluR2/3 receptor antagonists have demonstrated antidepressant activity, mGluR2/3 agonists have demonstrated

axiolytic activity); **6)** Facilitation of Glu clearance by EAATs; **7)** Modulation of extrasynaptic Glu release. **8)** PSD proteins. Theoretically, it is possible that agents capable of modifying the expression or function of PSD proteins could be used to treat mood disorders; **9)** Modulation of presynaptic vesicular Glu release; **10)** Modulation of presynaptic vesicular loading of Glu. Gln=glutamine; Glu=glutamate; VGLUT=vesicular glutamate transporter; mGlu metabotropic glutamate transporter; EAAT=excitatory amino acid transporter; Ca=calcium; Na=sodium; NMDA=N-methyl-D-aspartate receptor; AMPA= α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptor; BDNF=brain derived neurotrophic factor; TCA=tricarboxylic acid cycle; Ac-CoA=acetyl-CoA; α -KG= α -ketoglutarate; SNARE=soluble N-ethylmaleimide sensitive factor attachment receptor complex.

Figure 2. Antidepressants converge to regulate AMPA- and NMDA-mediated synaptic plasticity in critical neuronal circuits

This figure depicts the complex, time-dependent regulation of intracellular signaling cascades by traditional antidepressants (green). Via their initial effects on intrasynaptic serotonin and/or norepinephrine, these agents ultimately converge to regulate AMPA and NMDA receptor trafficking, synaptic plasticity, and information processing in critical circuits. Targeting AMPA/NMDA-mediated synaptic throughput more directly may result in improved and faster-acting antidepressants. NE=norepinephrine; 5-HT=5-hydroxytryptamine (serotonin); α_2 -AR= α_2 adrenergic autoreceptor; AMPAR=AMPA receptor; NMDAR=NMDA receptor; Gs=G protein stimulating adenylyl cyclase; AC=adenylyl cyclase; Gi or Gq=G proteins coupled to phosphoinositide turnover; PKC=protein kinase C; PKA=protein kinase A;

DARPP-32= dopamine and cAMP-regulated phosphoprotein of 32 kD; PP1=protein phosphatase 1.

Table 1

Evidence for alterations in NMDA and AMPA/KA receptor function in mood disorders

Target	Mood Disorder	Brain Region	Effect	Ref
NMDA receptor	MDD	Frontal cortex	Reduced [³ H]CGP-39653 binding	75
NMDA receptor	MDD	Superior temporal cortex	NMDA receptor binding and NR1 subunit expression	44
NMDA receptor	BPD	Hippocampus	Reduced CGP-39653 and MK-801 binding and levels of NR1 and NR2A transcript	41–43
NMDA receptor	BPD	Superior temporal cortex	NMDA receptor binding and NR1 subunit expression	44
NMDA receptor	BPD	ACC	NR2A subunit decreased in GABA interneurons	47
NMDA receptor	BPD		polymorphisms in genes coding NR1 and NR2B	46
AMPA receptor	MDD	DLPFC	Decreased levels of GluR2 and GluR3	41
AMPA receptor	MDD	Thalamus and Striatum	Decreased expression of SAP102	50, 51
AMPA receptor	BPD	Striatum	Increased AMPA binding is associated with decreased GluR1 subunit expression	48
AMPA receptor	BPD	DLPFC	Decreased levels of GluR2	49
AMPA receptor	BPD	Thalamus and Striatum	Decreased expression of SAP102	50, 51
NMDA and AMPA receptors	BPD	Hippocampus	Decrease in PSD95 immunoreactivity	52

Reviewed in: 65, 66, 81

Abbreviations: BPD: bipolar disorder; DLPFC: dorsolateral prefrontal cortex; MDD: major depressive disorder; ACC: anterior cingulate cortex.

Table 2

Effects of antidepressants on the glutamatergic system

Effect	Drug	Brain region	References
Reduced depolarizationstimulated Glu release and overflow	Several classes of antidepressants	Hippocampus and PFC	144, 158
Reduced expression or function of NMDA receptors	Several classes of antidepressants	Several brain regions	69, 70, 72–75, 159, 160
Altered expression and activation of AMPA receptors	Various antidepressants	Prefrontal cortex and hippocampus	78–80, 114, 161, 162
Increased expression of the vesicular glutamate transporter	Several antidepressant agents	Cerebral cortex	163, 164

Reviewed in 65, 66, 81

Abbreviations: Glu: glutamate; PFC: prefrontal cortex;

Table 3
Effects of lithium or VPA on the glutamatergic system

Drug	Effect	Reference
Lithium	Alters VGLUT1 expression and presynaptic Glu release	83, 163, 165
Lithium	Alters Glu uptake	166
Lithium	Alters Glu receptor expression and function	84, 85, 153, 167, 168
VPA	Alters VGLUT1 expression and presynaptic Glu release	169, 170
VPA	Increases EAAT expression	171, 172
VPA	Alters Glu receptor expression and function	89, 153, 173–178

Reviewed in 65, 81, 114, 153, 163, 179

Abbreviations: EAAT: excitatory amino acid transporter; VGLUT: vesicular glutamate transporter; mRNA: mitochondrial RNA; VPA: valproate.