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Novel glutamatergic agents for major depressive disorder and bipolar disorder

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Abstract

Mood disorders such as major depressive disorder (MDD) and bipolar disorder (BPD) are common, chronic, recurrent mental illnesses that affect the lives and functioning of millions of individuals worldwide. Growing evidence suggests 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 the pathophysiology of mood disorders as well as the efficacy of glutamatergic agents as novel therapeutics.

Keywords

bipolar disorder; depression; glutamate; mood disorders; novel treatments; pathophysiology

1. Introduction

Mood disorders—major depressive disorder (MDD) and bipolar disorder (BPD)—are serious, debilitating, life-shortening illnesses that affect millions of individuals worldwide. The World Health Organization (WHO) predicted that, by 2020, MDD would be the second leading cause of disability worldwide (Murray and Lopez, 1996). Although most patients with mood disorders receive some benefit from available treatments (Rush *et al.*, 2006, Trivedi *et al.*, 2006), the largest open label study to date examining the effectiveness of pharmacological treatment of MDD conducted to date (STAR*D) (Trivedi *et al.*, 2006) 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, half of the patients with MDD in the STAR*D study did not achieve remission until they had completed two antidepressant trials and nearly 24 weeks. Similarly, many patients with BPD do not respond

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to existing medications (Judd *et al.*, 2002), particularly during depressive episodes (Nierenberg *et al.*, 2006, Rush *et al.*, 2006).

Thus, therapeutic options for these devastating disorders are still far from adequate for treating acute illness episodes, relapses, and recurrences, as well as for restoring premorbid functioning (Insel and Scolnick, 2006, Machado-Vieira *et al.*, 2008), and the development of new therapies is essential. Such treatments would be expected to be more effective for more patients, be better tolerated, and act more rapidly than currently available therapeutics. In this context, considerable research has taken place over the last decade regarding the role of the glutamatergic system in the pathophysiology of mood disorders. Furthermore, findings from diverse studies suggest the relevance of the glutamatergic system in the development of novel agents to treat mood disorders. In this article, we highlight the promising nature of some of these recent advances, with a special focus on human studies.

2. The Functional Tripartite Glutamatergic System

Glutamate is the most abundant excitatory neurotransmitter in the brain, and acts in three different cell compartments—the pre- and postsynaptic neurons and glia—that together characterize the “tripartite glutamatergic synapse” (Machado-Vieira *et al.*, 2009a). Physiological activity in the glial-neuronal glutamate-glutamine cycle includes the uptake and inactivation of glutamate after its actions as a neurotransmitter have been completed, an effect that aims to prevent toxic effects secondary to overexposure to high glutamate levels (Sanacora *et al.*, 2008).

Glutamate is produced from α -ketoglutarate, an intermediate in the Krebs cycle, and is packaged into secretory vesicles in the presynaptic neuron by glutamate transporters. After release in an activity-dependent process via interactions with soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) proteins and sodium/calcium channels (Takamori *et al.*, 2000), glutamate is taken up by astrocytes and converted to glutamine by the enzyme glutamine synthetase. Glutamine released by astrocytes is transported back to presynaptic neurons, oxidized back into glutamate by the enzyme glutaminase, and repackaged.

Glutamate activates diverse ionotropic and metabotropic receptors involved in synaptic plasticity, learning, behavior, and memory (Collingridge and Bliss, 1995). Diverse types of glutamate ionotropic receptors and their respective subunits have been identified: N-methyl-D-aspartate (NMDA; NR1, NR2, NR2B, NR2C, NR2D, NR3A, and NR3B subunits), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA; GluR1, GluR2, GluR3, GluR4), and kainate (GluR5, GluR6, GluR7, KA1, and KA2). Eight types of G-protein coupled metabotropic (mGluR) receptors have also been identified and characterized based on the signaling transduction pathway that they stimulate: Group I (mGlu1 (a, b, c, d) and mGlu5 (a, b)), Group II (mGlu2 and mGlu3), and Group III (mGlu4, mGlu6, mGlu7, and mGlu8).

The NMDA channel comprises two dissimilar sites: the “s” site and the phencyclidine (PCP) site. A unique property of the NMDA receptor (NMDAR) is its voltage-dependent activation, a result of ion channel block by extracellular magnesium ions. This allows sodium and small amounts of calcium ions to flow into the cell, as well as potassium to flow out of the cell, via a voltage-dependent mechanism. Glutamate’s binding sites are mostly expressed in the NR2A and NR2B subunits, which are both highly expressed in brain areas implicated in mood regulation (Magnusson *et al.*, 2002, Sah and Lopez De Armentia, 2003), whereas the NR1 subunit is placed on the site for its co-agonist, glycine (for a complete overview of the distribution and functional effects of NMDARs see (Cull-Candy *et al.*, 2001)).

AMPA receptors (AMPArs) are activated in the presence of glutamate, thus inducing a fast excitatory synaptic signal involved in early glutamatergic effects in the synapse. These effects play a crucial role in calcium metabolism, synaptic strength, and oxidative stress (Machado-Vieira *et al.*, 2009b, Zarate *et al.*, 2003). Indeed, AMPAR activation opens the pore permitting the inward flow of sodium, which results in the depolarization of the neuronal membrane. This change in intracellular charge liberates the magnesium cation from the NMDAR, which in turn permits the entrance of calcium through that pore. At mature synapses, AMPARs can be co-expressed with NMDARs, thereby contributing to synaptic plasticity and neuroprotection (Barria and Malinow, 2002); it is, however, important to note that AMPARs have a lower affinity for glutamate than NMDARs, which allows for a more rapid dissociation of glutamate and a fast deactivation of the AMPAR (reviewed in (Zarate *et al.*, 2003)).

Kainate receptors (KARs) participate in excitatory neurotransmission by both activating postsynaptic receptors and inhibiting neurotransmission by regulating gamma-aminobutyric acid (GABA) release. KARs have limited distribution in the brain and are believed to affect synaptic signaling and plasticity less than AMPARs (for a review see (Huettner, 2003)).

With regard to mGluRs, Group I mGluRs are coupled to the phospholipase C signal transduction pathway and are located in both pre- and post-synaptic membranes. Both Group II and Group III mGluRs are coupled in an inhibitory manner to the adenylyl cyclase pathway, and are involved in the regulation of glutamate and GABA release (reviewed in (Witkin *et al.*, 2007, Zarate *et al.*, 2003)). Furthermore, the presynaptic mGlu2/3rs limit glutamate release.

In addition to ionotropic receptors and mGluRs, cytoplasmic postsynaptic density (PSD)-enriched molecules, excitatory amino acid transporters (EAATs or GLASTs) and vesicular glutamate transporters (VGLUTs) are also directly involved in synaptic and extra-synaptic glutamate brain levels and may represent potential therapeutic targets. VGLUT1 is the most abundant isoform in the cerebral cortex and hippocampus, selectively located on synaptic vesicles of glutamatergic terminals. Notably, variations in VGLUT1 expression levels critically regulate the efficacy of glutamate synaptic transmission (reviewed in (Machado-Vieira *et al.*, 2009a, Sanacora *et al.*, 2008)). Astrocytes also regulate pre- and post-synaptic activity by directly releasing and taking up glutamate via a number of EAATs (mostly subtypes 1 and 2) (Danbolt, 2001, O'Shea, 2002, Oliet *et al.*, 2001). Decreased EAATs and VGLUTs may, in turn, lead to increased glutamate levels in the synaptic cleft and consequent risk for a hyperglutamatergic state. Meanwhile, cytoplasmic PSD-enriched molecules (such as PSD95) interact with glutamate receptors (particularly NMDARs and AMPARs) to regulate signal transduction (Dingledine *et al.*, 1999, Sheng and Sala, 2001), and also synchronize information from several neurotransmitter systems. For instance, the NR1 subunit interacts with NL-L and Yotiao, while the NR2 subunit acts with several PSD proteins such as PSD95, PSD93, SAP102, CIPP, and Densin-180 (Bleakman and Lodge, 1998, Hollmann and Heinemann, 1994, Nakanishi, 1992).

3. Tripartite Glutamatergic Synapse Dysfunction in Mood Disorders

Synaptic levels of glutamate can rise to excitotoxic concentrations rapidly after an insult (e.g., trauma, ischemia) or when glutamate transporter function is decreased, which may involve direct changes in glutamate packaging, release, and reuptake. Diverse pathophysiological mechanisms have been described. For example, inhibition of astrocytic reuptake of glutamate rapidly decreases glutamate uptake, which can lead to a hyperglutamatergic state and neural toxicity due to increased extrasynaptic glutamate (Jabaudon *et al.*, 1999, Soriano and Hardingham, 2007).

Notably, several pathophysiological findings have been described with regard to glutamatergic neurotransmission in individuals with mood disorders. Broadly, altered glutamate levels have been observed in the plasma, serum, and cerebrospinal fluid (CSF) of individuals with BPD (reviewed in (Sanacora *et al.*, 2008)). Postmortem studies have similarly shown increased glutamate levels in diverse brain areas in individuals with mood disorders (Hashimoto *et al.*, 2007, Scarr *et al.*, 2003). Imaging studies have also found increased levels of glutamate and related metabolites in the occipital cortex (OCC) of individuals with BPD and MDD, and decreased levels in the anterior cingulate cortex (ACC) of these patients (Hasler *et al.*, 2007, Sanacora *et al.*, 2004, Yildiz-Yesiloglu and Ankerst, 2006). In addition, magnetic resonance spectroscopy (MRS) studies performed to date show a consistent pattern of a decreased composite peak formed by glutamate + glutamine (Glx), and GABA in MDD, and increased Glx in BPD, regardless of mood polarity (see (Salvadore *et al.*, 2010, Yuksel and Ongur, 2010)).

As regards specific glutamate receptors and subunits, reduced NMDAR binding and expression have also been found in individuals with MDD (Beneyto *et al.*, 2007, Choudary *et al.*, 2005, Law and Deakin, 2001, McCullumsmith *et al.*, 2007, Nudmamud-Thanoi and Reynolds, 2004, Toro and Deakin, 2005). Similar decreases in NR1 and NR2A expression have been observed in individuals with BPD (McCullumsmith *et al.*, 2007). In addition, polymorphisms of the GRIN1, GRIN2A, and GRIN2B genes appear to confer susceptibility to BPD (Itokawa *et al.*, 2003, Martucci *et al.*, 2006, Mundo *et al.*, 2003). These genes have been shown to be involved in long-term potentiation, an activity-dependent increase in the efficiency of synaptic transmission, which is thought to underlie certain kinds of memory and learning. Interestingly, decreased NMDAR expression has been associated with PSD signaling proteins in individuals with BPD (Clinton and Meador-Woodruff, 2004). For instance, decreased PSD95 levels were observed in the dentate of individuals with BPD (Toro and Deakin, 2005). A similar decrease in SAP102 levels was noted in individuals with MDD, and this correlated with decreased NR1 and NR2A subunit expression in the hippocampus, striatum, and thalamus of patients with mood disorders (Clinton and Meador-Woodruff, 2004, Kristiansen and Meador-Woodruff, 2005, McCullumsmith *et al.*, 2007); notably, SAP102 primarily interacts with the NR2B subunit. Recently, NR2A and PSD95 protein levels were found to be significantly increased in the lateral amygdala of individuals with MDD compared to healthy controls (Karolewicz *et al.*, 2009).

Similar findings were described in AMPAR regulation. Decreased GluR2 and GluR3 levels have been reported in the prefrontal cortex (PFC) of subjects with mood disorders (Beneyto and Meador-Woodruff, 2006, Hashimoto *et al.*, 2007, Scarr *et al.*, 2003). Selective decreases in striatal GluR1 expression have also been described in individuals with BPD (Meador-Woodruff *et al.*, 2001). Abnormal mGluR3 expression was also described in suicidal subjects with BPD, but this finding was not subsequently replicated (Devon *et al.*, 2001, Marti *et al.*, 2002).

Fewer studies have explored the association between KARs and mood disorders; however, a recent, large, family-based association study that evaluated the GRIK3 gene (GluR7) described linkage disequilibrium in MDD (Schiffer and Heinemann, 2007). Likewise, elevated GRIK3 DNA-copy number was observed in subjects with BPD (Wilson *et al.*, 2006). In addition, a common variant in the 3'UTR GRIK4 gene was demonstrated to protect against BPD (Pickard *et al.*, 2006). Interestingly, the STAR*D study as well as the Munich Antidepressant Response Signature (MARS) project both described an association between treatment-emergent suicidal ideation and the glutamate system via the involvement of the GRIK3 and GRIK2 genes (Laje *et al.*, 2007, Menke *et al.*, 2008). Another recent study found that GRIK4 polymorphisms may predict antidepressant response (Horstmann *et al.*,

2010). Relatedly, downregulation of the GluK2 kainate receptor was observed in cultured astrocytes after chronic treatment with lithium and valproate (Li *et al.*, 2009).

Finally, reduced expression of EAAT1, EAAT2, EAAT3, EAAT4 and glutamine synthetase have also been observed in postmortem studies of subjects with mood disorders (Choudary *et al.*, 2005, McCullumsmith and Meador-Woodruff, 2002). In MRS studies of glutamate-related abnormalities in MDD, three out of four studies reported results consistent with glutamine reductions, and the fourth reported normal glutamine but elevated glutamate levels (reviewed in (Yuksel and Ongur, 2010)); given that no differences were observed in euthymic subjects, these findings appear to be state-dependent, with potential clinical relevance. Taken together, the evidence reviewed above suggests that increased glutamate levels/expression and normal to reduced glutamine may represent a mechanism involved in the pathophysiology of mood disorders.

4. Mood Disorders: Therapeutic Targets and New Agents That Act Through the Tripartite Glutamatergic Synapse

Many studies have provided important insights regarding the role of the glutamatergic system in the pathophysiology and therapeutics of psychiatric and neurological illnesses. Indeed, glutamatergic system dysfunction 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. Glutamatergic system dysfunction was first proposed to be involved with mood disorders based on seminal preclinical data obtained from NMDA antagonists (Skolnick *et al.*, 2001). Recent studies (reviewed below) suggest that glutamatergic neurotransmission—and its intra- and inter-cellular dynamic cross-talk—may play a promising role in the search for new improved treatments for mood disorders. In this context, diverse glutamatergic agents have been tested in proof-of-concept studies for severe mood disorders.

4.1 Glutamatergic Agents in Mood Disorders

Diverse glutamate-modulating agents have been tested in preclinical models as well as in patients with mood disorders (Sanacora *et al.*, 2008, Zarate *et al.*, 2002). Amongst these, riluzole and ketamine are the prototypical proof-of-concept glutamatergic agents in mood disorders and are discussed in greater detail in Section 5. Here we first describe findings obtained with other agents that target NMDARs, AMPARs, KARs, mGluRs, and the complex dynamics of VGLUTs, EAATs, and PSD. We also describe the effects of currently available antidepressants and mood stabilizers on the glutamatergic system.

NMDA antagonists have been found to produce rapid antidepressant effects in diverse preclinical paradigms (Maeng *et al.*, 2008, Moryl *et al.*, 1993, Papp and Moryl, 1994, Trullas and Skolnick, 1990, Zarate *et al.*, 2007). Furthermore, the prototypical NMDA antagonist ketamine has been increasingly used in preclinical studies as well as in patients with treatment-resistant mood disorders (discussed in greater detail in Section 5.2). However, chronic administration of ketamine is challenging because of the dissociative and perceptual disturbances associated with this agent. These adverse effects, which are believed to be partially due to ketamine's broad effects on most of the subunits of the NMDAR complex, have led investigators to search for more subunit selective NMDA antagonists in the hopes that ketamine's antidepressant effects can be preserved without the adverse effects described above. Initial work from our laboratory showed that a subunit selective NR2B antagonist (Ro25-6981) had antidepressant-like effects similar to those of ketamine in

rodents (Maeng *et al.*, 2008). This finding was recently confirmed (Li *et al.*, 2010). Other brain-penetrant NR2B antagonists currently under development include indole-2-carboxamides, benzimidazole-2-carboxamides, and HON0001 (Borza *et al.*, 2007, Suetake-Koga *et al.*, 2006). Other NR2B antagonists have reached the clinic and one of them—CP-101,606—was reported to have significant and relatively rapid antidepressant effects in patients with treatment-resistant MDD (Preskorn *et al.*, 2008). However, there was also some evidence that this agent induced psychotomimetic effects (Preskorn *et al.*, 2008). Nevertheless, additional clinical studies with subunit NMDR-2A and -2B antagonists are underway or completed, including AZD6765 (AstraZeneca Pharmaceuticals, completed) and EVT 101 (Evotec Neurosciences; ongoing). In addition to determining the efficacy of these agents in treatment-resistant MDD, these studies should also shed some light on the important issue of rapidity of onset of antidepressant action.

AMPA potentiators are a new class of pharmacological agents being tested in mood disorders. They decrease AMPAR insertion rate and/or deactivation in the presence of an agonist (e.g., AMPA and glutamate) (see (Black, 2005, Bleakman and Lodge, 1998)). These compounds are classified based on their effects on the biophysical processes of desensitization and deactivation, and include benzothiazides (e.g., cyclothiazide), benzoyliperidines (e.g., CX-516), and bitylpropylsulfonamides (e.g., LY392098) (Miu *et al.*, 2001, Quiroz *et al.*, 2004). These agents also play a key role in modulating activity-dependent synaptic strength and behavioral plasticity (Sanacora *et al.*, 2008). Several AMPA potentiators showed significant antidepressant-like effects and also improved cognitive function in preclinical paradigms (reviewed in (Black, 2005, Lynch, 2004, Miu *et al.*, 2001, O'Neill *et al.*, 2004)). While AMPA potentiators are associated with antidepressant-like properties, AMPAR antagonists such as talmpanel may have antimanic properties. Talmpanel also has significant anticonvulsant effects; similarly, the competitive AMPAR antagonist NS1209 is currently being evaluated in refractory status epilepticus (reviewed by (Rogawski, 2006)).

To date, no KAR modulators have been tested in the treatment of mood disorders. Notably, however, one recent study found that individuals with MDD who had a GRIK4 gene polymorphism (rs1954787) were more likely to respond to treatment with the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram than those who did not have this allele (Paddock *et al.*, 2007).

Several mGluR-modulating agents have been tested in preclinical and clinical studies in mood disorders. Various agents that target mGluRs have been found to induce anxiolytic, antidepressant, and neuroprotective effects in preclinical models, especially Group II and III mGluR agonists (Chaki *et al.*, 2004, Cosford *et al.*, 2003, Cryan *et al.*, 2003, Gasparini *et al.*, 1999, Maiese *et al.*, 2000, Palucha *et al.*, 2004, Schoepp *et al.*, 2003). The Group II mGluR antagonist MGS-0039 induced antidepressant-like and neuroprotective effects in animal models (Yoshimizu and Chaki, 2004, Yoshimizu *et al.*, 2006). Also, Group III mGluR agonists had antidepressant-like properties in the behavioral despair test (Palucha *et al.*, 2007b, Palucha *et al.*, 2004). The selective Group III mGluR agonists (ACPT-I, [1S,3R,4S]-1-aminocyclopentane-1,3,4-tricarboxylic acid), as well as an mGluR8 agonist (RS-PPG, [RS]-4-phosphonophenylglycine), were also found to have antidepressant-like effects (Gasparini *et al.*, 1999). Interestingly, AMPAR activation critically regulates the antidepressant-like effects of the Group II mGluR antagonist MGS0039 (Karasawa *et al.*, 2005). Finally, Group I mGluR antagonists have shown potential therapeutic effects in mood disorders. The Group I mGluR5 antagonists MPEP (2-methyl-6-[phenylethynyl]-pyridine) and MTEP ([2-methyl-1,3-thiazol-4-yl]ethynyl]pyridine) had antidepressant-like activity in animal models (Li *et al.*, 2006, Wieronska *et al.*, 2002). Also, the potent and selective mGluR5 antagonist fenobam was associated with significant psychostimulant effects (Porter

et al., 2005); this agent showed robust anxiolytic efficacy in a double-blind, placebo-controlled trial (Palucha and Pilc, 2007). Many agents that modulate the mGluRs are under development, but no clinical studies investigating mGluR compounds in patients with mood disorders have yet been published.

PSD-enriched molecules, EAATs, and VGLUTs also represent potential therapeutic targets in mood disorders, although few data are currently available. For instance, while PSD regulation by glutamatergic turnover is a key therapeutic target in mood disorders, no agent that targets PSD proteins has yet been developed. The study of VGLUTs is still in its infancy, but diverse compounds that target VGLUTs are in development and may provide insight into the relevance of glutamate transporters in the pathophysiology of mood disorders and their treatment (Thompson *et al.*, 2005). Similarly, increased EAAT2 expression could result in antidepressant-like effects (Mineur *et al.*, 2007). One preclinical study found that chronic blockade of glutamate uptake by a glial/neuronal transporter antagonist decreased social exploratory behavior and altered circadian activity (Lee *et al.*, 2007). Thus, its increased expression may represent a potential target. Notably, this is one of the mechanisms by which riluzole is believed to regulate excess synaptic glutamate (Frizzo *et al.*, 2004).

4.2 Standard Mood Stabilizers and Antidepressants that Target the Glutamatergic System

Several preclinical and clinical studies have shown that currently available mood stabilizers and antidepressants affect the glutamatergic system. For instance, preclinical studies found that chronic treatment with the classic mood stabilizers lithium and valproate decreased hippocampal GluR1 expression in the hippocampus (Du *et al.*, 2004). Chronic lithium treatment also increased glutamate synaptosomal uptake, thus protecting against glutamate-induced excitotoxicity (Hashimoto *et al.*, 2002). Lithium was found to enhance VGLUT1 mRNA expression in neurons of the cerebral cortex (Moutsimilli *et al.*, 2005). Also, chronic valproate increased EAAT1 levels and decreased EAAT2 levels in the hippocampus (Hassel *et al.*, 2001, Ueda and Willmore, 2000). Lamotrigine, which is currently approved by the U.S. Food and Drug Administration (FDA) for relapse prevention in BPD, also had antidepressant-like effects in animal models (Kaster *et al.*, 2007); specifically, it limited glutamate release by blocking voltage-operated sodium channels, thus inducing neuronal membrane stabilization (Pricka *et al.*, 2008). Lamotrigine also increased AMPAR activity by upregulating surface expression and phosphorylation of GluR1 and GluR2 in hippocampal neurons (Bhagwagar and Goodwin, 2005, Du *et al.*, 2007).

Elegant studies conducted with tricyclic antidepressants over a decade ago were among the first to implicate glutamate in the mechanism of action of standard antidepressant agents (Nowak *et al.*, 1993, Paul *et al.*, 1994). The studies demonstrated that the NMDAR represents a final common pathway of antidepressant action and could possibly be involved in a faster onset of antidepressant effects. More recently, chronic treatment with standard antidepressants was found to directly regulate AMPAR expression and phosphorylation (Du *et al.*, 2004, Du *et al.*, 2007, Paul and Skolnick, 2003). Specifically, SSRIs and selective norepinephrine reuptake inhibitors (SNRIs) were found to downregulate NMDA and activate AMPA (Bleakman and Lodge, 1998, Skolnick *et al.*, 1996). For instance, treatment with fluoxetine increased phosphorylation of GluR1 at Ser831 and Ser845 while chronic treatment targeted only GluR1 Ser845 (Svenningsson *et al.*, 2002); these effects may be involved in fluoxetine's antidepressant efficacy. Similarly, chronic treatment with imipramine increased p845 GluR1 (associated with increased GluR1 insertion) (Maeng *et al.*, 2008). These effects are often subtle and delayed after administration.

As noted previously, the GRIK4 gene polymorphism (rs1954787), which codes for the kainic acid-type glutamate receptor KA1, was found to regulate antidepressant response to

citalopram in individuals with MDD (Paddock *et al.*, 2007). Chronic treatment with fluoxetine similarly affected GluR5 and GluR6 levels in the hippocampus (Barbon *et al.*, 2006). Chronic treatment with imipramine was also found to reduce the inhibitory effects of Group II mGluRs (Palucha *et al.*, 2007a).

In preclinical studies, the antidepressants fluoxetine, paroxetine, and desipramine were all found to increase VGLUT mRNA levels in the frontal, orbital, and cingulate cortices, as well as in the hippocampus (Tordera *et al.*, 2005, Tordera *et al.*, 2007). Recent studies also found that specific compounds enhanced EAAT levels, especially beta-lactam antibiotics (Miller and Cleveland, 2005, Mineur *et al.*, 2007, Rothstein *et al.*, 2005). In addition, in the postsynaptic density (PSD), paroxetine enhanced the interaction of GluR1 with Rab4A, and desipramine markedly increased the interaction of GluR1 with SAP97 (Song *et al.*, 1998). Chronic treatment with fluoxetine also affected GluR2, GluR5, and GluR6 expression in the hippocampus (GluR5 and GluR6 are kainate subunits). Finally, the atypical antidepressant tianeptine prevented or reversed stress-associated structural and cellular brain changes related to normalizing increased glutamatergic neurotransmission (Kasper and McEwen, 2008, Svenningsson *et al.*, 2007).

5. Riluzole and Ketamine: Prototypes for New and Improved Treatment of Mood Disorders Through the Glutamatergic System

5.1 Riluzole

Riluzole (2-amino-6-trifluoromethoxy benzothiazole), which has both neuroprotective and anticonvulsant properties, is a glutamatergic modulator approved by the FDA for the treatment of ALS. Although riluzole induces no known direct effects on NMDARs or KARs (Debono *et al.*, 1993), it inhibits glutamate release by inhibiting voltage-dependent sodium channels in neurons, its best known mechanism; riluzole also enhances AMPA trafficking and membrane insertion of GluR1 and GluR2 and increases glutamate reuptake (Du *et al.*, 2007; Frizzo *et al.*, 2004). Other potential effects include stimulation of nerve growth factor, brain derived growth factor (BDNF), and synthesis of other neurotrophic factors in cultured astrocytes (Mizuta *et al.*, 2001). Repeated injections of riluzole induced prolonged elevation of hippocampal BDNF and neurogenesis (Katoh-Semba *et al.*, 2002).

Riluzole was shown to protect astrocytes against glutamate excitotoxicity (Dagci *et al.*, 2007). It also prevented the overstimulation of extrasynaptic glutamate receptors and consequent excitotoxicity, potentially through EAATs (Azbill *et al.*, 2000, Frizzo *et al.*, 2004, Fumagalli *et al.*, 2008, Hardingham, 2006). In preclinical models, increased ¹³C-glucose metabolism was observed in the hippocampus and PFC after 21 days of treatment with riluzole; this suggests increased glutamatergic metabolism rather than decreased glutamate release in these areas (Chowdhury *et al.*, 2008). Long-term administration of riluzole in behavioral studies has also been found to generate antidepressant- and antimanic-like effects (Banasz and Duman, 2008, Lourenco Da Silva *et al.*, 2003).

In clinical studies, riluzole demonstrated antidepressant effects in patients with both MDD and BPD. In the first open-label study, 13 patients with treatment-resistant MDD (68%) completed the trial and all had significantly improved at week six (Zarate *et al.*, 2004). A similar result was obtained with riluzole as add-on therapy for MDD; riluzole (50mg/twice daily) induced antidepressant effects after one week of treatment, with a significant decrease (36%) in Hamilton Depression Rating Scale (HAM-D) scores observed among completers (Sanacora *et al.*, 2007).

In an open-label trial of 14 patients with bipolar depression, riluzole was used adjunctively to lithium; patients experienced a 60% overall decrease in Montgomery Asberg Depression

Rating Scale (MADRS) scores across the eight weeks of treatment and a significant improvement on the MADRS by week five. A recent open-label study that evaluated the adjunctive use of riluzole (100–200mg/day for six weeks) in 14 patients with bipolar depression found a significant reduction in HAM-D scores (Brennan *et al.*, 2010). Riluzole was also found to have significant therapeutic effects in two open-label trials of generalized anxiety disorder (GAD) and compulsive disorder (OCD) (Coric *et al.*, 2005, Mathew *et al.*, 2005).

A small pilot study (n=14) of patients with treatment-resistant MDD who had responded to ketamine evaluated the potential role of riluzole in preventing relapses in the first month. The authors reported that riluzole was not more effective than placebo in preventing relapses in this group of patients (Mathew *et al.*, 2010). However, this lack of response may in part have been due to the small number of subjects randomized; ultimately, larger studies will be needed to support or refute these preliminary findings. Regarding potential biomarkers of response, riluzole seems to rapidly increase Glutamine/Glutamate (Glu/Gln) ratios, suggesting increased Glu/Gln cycling; Gln/Glu was significantly enhanced by Day 2 of riluzole treatment (Brennan *et al.*, 2010). Overall, these promising findings suggest that double-blind, placebo-controlled trials with riluzole are warranted. Despite its efficacy in MDD and bipolar depression, there is no indication that riluzole acts more rapidly than existing antidepressants; however, it may represent an important therapeutic option in treatment-resistant cases.

5.2 Ketamine

The non-competitive, high-affinity NMDA receptor antagonist ketamine is a phencyclidine (PCP) derivative. By antagonizing NMDARs, ketamine prevents excessive calcium influx and cellular damage. In vitro, ketamine enhances the firing rate of glutamatergic neurons as well as the presynaptic release of glutamate (Moghaddam *et al.*, 1997). Some of these properties are believed to be involved in ketamine's antidepressant effects. Interestingly, AMPAR activation critically regulates ketamine's antidepressant-like effects (described below) (Maeng *et al.*, 2008); this suggests that enhanced AMPA transmission may represent a common mechanism for the antidepressant action of this agent, and may ultimately result in increased synaptic potentiation.

Diverse animal models have noted that ketamine has significant antidepressant and anxiolytic effects (Aguado *et al.*, 1994, Garcia *et al.*, 2008, Maeng *et al.*, 2008, Mickley *et al.*, 1998, Silvestre *et al.*, 1997). In clinical studies, an initial trial in seven subjects with treatment-resistant MDD found that ketamine improved depressive symptoms within 72 hours after infusion (Berman *et al.*, 2000). Subsequently, a double-blind, placebo-controlled, crossover study showed a fast (first two hours after infusion) and relatively sustained antidepressant effect (1–2 weeks) after a single ketamine injection in patients with treatment-resistant MDD (Zarate *et al.*, 2006a). More than 70% of patients responded 24 hours after infusion and 35% showed a sustained response at the end of week one. Notably, response rates with ketamine after 24 hours (71%) were similar to those described after six to eight weeks of treatment with traditional monoaminergic-based antidepressants (65%) (Entsuhah *et al.*, 2001, Thase *et al.*, 2005). This finding has since been replicated in several other, albeit uncontrolled, studies (aan het Rot *et al.*, 2010, Machado-Vieira *et al.*, 2009c, Phelps *et al.*, 2009); the magnitude and time-frame of response to ketamine in these studies was similar to the previous controlled studies.

Ketamine's antidepressant effects were also recently assessed in subjects with bipolar depression (Diazgranados *et al.*, 2010a). In that study, a significant improvement in depressive symptoms was noted in subjects who received ketamine compared to those who received placebo within 40 minutes after infusion; these effects remained significant through

Day 3, and up to Day 7 in those who completed both phases of the study. Seventy-one percent of all subjects responded to ketamine at some point during the study. Of the 17 subjects treated with ketamine, 56% met response criteria at 40 minutes post-infusion, and 44% met response criteria and 31% met remission criteria the day after ketamine infusion.

Ketamine was also found to have significant antisuicidal effects (Diazgranados *et al.*, 2010b, Price *et al.*, 2009). In the study by Price and colleagues, 26 patients with treatment-resistant MDD had significant reductions on the suicidality item of the MADRS 24 hours after a single ketamine infusion. In the study by Diazgranados and colleagues, 33 subjects with treatment-resistant MDD received a single open-label infusion of ketamine and were rated at baseline and at 40, 80, 120, and 230 minutes post-infusion. Suicidal ideation scores significantly decreased on the Scale for Suicide Ideation (SSI) and suicidality items of depression rating scales within 40 minutes after infusion, and this effect remained significant through the first four hours post-infusion. Measures of depression, anxiety, and hopelessness were significantly improved at all time points. The second study confirmed the findings of the first study, and further demonstrated that suicidal ideation was improved as soon as 40 minutes post-infusion, a finding with enormous public health implications.

Ketamine infusion has also been demonstrated to induce rapid antidepressant effects in subjects with depressive symptoms during pre- and post-operative states, as well as in MDD comorbid with pain syndrome and/or alcohol dependence (Goforth and Holsinger, 2007, Kudoh *et al.*, 2002, Liebreiz *et al.*, 2007, Ostroff *et al.*, 2005). Because of the aforementioned inherent propensity of ketamine to produce cognitive deficits and psychotomimetic effects, its use at this time remains limited to research settings. Repeated exposure to ketamine infusion also appears to increase the risk of severe psychosis and more dissociative and psychotomimetic effects in patients and healthy subjects, which could potentially limit its long-term use (Carpenter, 1999, Perry *et al.*, 2007). However, another small, recent trial evaluated 10 patients with treatment-resistant MDD who received repeated ketamine infusions—six infusions over 12 days (aan het Rot *et al.*, 2010). Response criteria were met by nine patients after the first through sixth infusions with corresponding decreases in psychotomimetic symptoms with each subsequent infusion, suggesting that repeated NMDA blocking is a feasible approach for treating acute, treatment-resistant MDD. However, it is important to emphasize that the long-term effects on brain anatomy and function—that is, long-term safety—of ketamine use remain unknown. It is also interesting to note that several variables (reviewed below) have been found to predict initial antidepressant response to ketamine.

5.2.1 Biological correlates of ketamine antidepressant response: Alcohol dependence

—Previous studies found that alcohol-dependent individuals showed marked reductions to the subjective intoxicating effects of ketamine compared with healthy controls (Krystal *et al.*, 2003), and that healthy individuals with a positive family history of alcohol dependence had fewer perceptual alterations and lower dysphoric mood after receiving ketamine (Petrakis *et al.*, 2004). Echoing these findings, a recent study by our group found that family history of alcohol dependence in MDD subjects was associated with better short-term outcome after ketamine infusion (Phelps *et al.*, 2009). The precise reasons underlying the more favorable response of patients with treatment-resistant MDD with a positive family history of alcohol dependence to ketamine remain unknown. However, emerging data suggest that genetically determined alterations in NMDAR subunits may be associated with alcohol dependence. Ketamine acts as a partial NR2A receptor antagonist (Petrenko *et al.*, 2004), and NR2A expression is regulated by alcohol in the amygdala and hippocampus (Boyce-Rustay and Holmes, 2006). As a result, differences in NR2A sensitivity may account for ketamine's differential antidepressant effects in individuals with MDD with or without a family history of alcohol dependence.

5.2.2 Biological correlates of ketamine antidepressant response: ACC activity

—Studies have shown that ACC activity can predict improved antidepressant response to standard antidepressants, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS) (Chen *et al.*, 2007, Langguth *et al.*, 2007, Mayberg *et al.*, 1997, McCormick *et al.*, 2007, Pizzagalli *et al.*, 2001). Similar effects have been also associated with other antidepressants and sleep deprivation (Saxena *et al.*, 2003, Wu *et al.*, 1999). One recent study investigated whether ACC activity could act as a neurophysiologic biomarker for ketamine's rapid antidepressant effects. Using magnetoencephalography (MEG) recordings, the investigators found that increased pretreatment rostral ACC activity positively correlated with rapid antidepressant response to ketamine infusion in 11 individuals with MDD versus healthy controls (Salvadore *et al.*, 2009). Relatedly, anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task was also found to predict antidepressant response to ketamine (Salvadore *et al.*, 2010). It is also interesting to note that another study observed that orbitofrontal and subgenual ACC blood oxygenation level dependent (BOLD) activity was directly regulated by ketamine in healthy individuals (Deakin *et al.*, 2008). Specifically, that study found an unexpected decrease in the ventromedial frontal cortex, including the orbitofrontal cortex and the subgenual cingulate; this decrease was associated with dissociative effects and enhanced activity in the mid-posterior cingulate, the thalamus, and temporal cortical regions (Deakin *et al.*, 2008).

5.2.3 Biological correlates of ketamine antidepressant response: BDNF—A

recent study from our laboratory investigated whether changes in BDNF levels were associated ketamine's initial antidepressant effects. No change was observed in BDNF levels between baseline and up to 230 minutes post-infusion (a time point when antidepressant effects and response were present) (Machado-Vieira *et al.*, 2009c). However, it is important to emphasize that BDNF obtained in this study was peripheral, which may not necessarily correspond to CNS function. It is also interesting to note that a recent study found that a single nucleotide polymorphism (SNP) for BDNF conferred a differential response to ketamine in animal models (Aghajanian, 2010). Clearly, human studies are needed to determine whether such SNPs are important to antidepressant response to ketamine.

5.2.4 AMPA relative to NMDA throughput—On a cellular level, the net effect of ketamine's antidepressant effects is increased glutamatergic throughput. One study observed that ketamine's antidepressant-like effects were selectively abolished by using an AMPA antagonist (NBQX) prior to infusion (Maeng *et al.*, 2008). This finding suggests that ketamine's effects occur mostly via AMPAR activation, not critically through NMDAR antagonism, thus inducing a rapid AMPA-mediated synaptic potentiation; in contrast, traditional antidepressants induce delayed effects via intracellular signaling changes (Sanacora *et al.*, 2008), which might explain why it takes longer for their antidepressant effects to manifest. Ketamine seems to enhance synaptic efficacy in the amygdala-accumbens pathway (Kessal *et al.*, 2005). Therefore, it is possible that increased glutamatergic throughput of AMPARs relative to NMDARs after ketamine treatment may enhance synaptic potentiation and activate early neuroplastic genes.

In an extension of this work, a recent study found that mammalian target of rapamycin (mTOR)-dependent synapse formation underlies ketamine's rapid antidepressant properties (Li *et al.*, 2010). This elegant series of studies demonstrated that ketamine rapidly activates the mTOR pathway, leading to increased synaptic signaling proteins and increased number and function of new spine synapses in the rat PFC.

5.3 Other Glutamate Modulators: Cytidine and Memantine

Cytidine, a pyrimidine component of RNA that regulates dysfunctional neuronal-glial glutamate cycling has been clinically evaluated in bipolar depression. A recent, double-blind, placebo-controlled study evaluated 35 subjects with bipolar depression who received valproate plus either cytidine or placebo for 12 weeks (Yoon *et al.*, 2009). Cytidine plus valproate improved depressive symptoms earlier than valproate plus placebo; the antidepressant effects observed in the cytidine group were positively associated with lower midfrontal glutamate/glutamine levels, suggesting that the therapeutic effects of cytidine supplementation in bipolar depression occur by lowering brain Glu/Gln levels (Yoon *et al.*, 2009).

Memantine is a moderately selective noncompetitive NMDA antagonist approved for the treatment of Alzheimer's disease. Memantine had antidepressant-like effects when used as monotherapy or synergistically with imipramine in preclinical studies. However, a double-blind study of patients with MDD found that it had no significant antidepressant effects compared to placebo (Zarate *et al.*, 2006b). In a case series of two patients with bipolar depression, memantine improved depressive symptoms and cognitive performance as add-on therapy to mood stabilizers (Teng and Demetrio, 2006). More recently, and unexpectedly given recent theories of NMDA and mood disorders, an open-label pilot study found that memantine had significant antimanic effects (Keck *et al.*, 2009); this finding highlights the complexity of the role of NMDARs in mood disorders.

6. Conclusions

Glutamate is the main excitatory neurotransmitter in the human brain. Based on this fact alone, one might expect agents that act on the glutamatergic system to have therapeutic efficacy in some psychiatric disorders. Glutamate controls synaptic excitability and plasticity in most brain circuits, including limbic pathways involved in plasticity and mood disorders. Thus, drugs that target glutamate neuronal transmission offer significant novel approaches for the treatment of mood disorders. Biological parameters and biomarkers are needed to determine the clinical relevance of glutamatergic modulators that target particular receptors/subunits, particularly those that may have a more subtle side-effect profile.

As this paper has highlighted, clear glutamatergic system abnormalities exist in individuals with mood disorders, but the magnitude and extent of these abnormalities require further clarification. Existing effective antidepressants and mood stabilizers also modulate different components of the glutamate neurotransmitter system, and these effects may also be relevant to the development of improved therapeutic for mood disorders. While an increasing number of proof-of-principle studies have attempted to identify relevant therapeutic targets within the glutamatergic system, for now riluzole and ketamine still represent the definitive proof of concept agents and indeed, initial forays with riluzole-like or ketamine-like drugs, while still very preliminary, provide powerful incentive for further study of the role of glutamate in mood disorders.

Continued exploration of the antidepressant-like effects of glutamatergic agents holds considerable promise for developing new treatments for mood disorders, and such treatments are urgently needed. The fact that currently available antidepressants and mood stabilizers 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.

Highlights

Mood disorders affect the lives and functioning of millions of individuals worldwide. The glutamatergic system is central to the pathophysiology of mood disorders. We review the efficacy of glutamatergic agents as novel therapeutics for mood disorders.

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References

- aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney D, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry*. 2010; 67:139–145. [PubMed: 19897179]
- Aghajanian, G. BDNF/mTOR pathway mediates ketamine stimulation of synaptogenesis in medical prefrontal cortex. Annual meeting of the American College of Neuropsychopharmacology (ACNP); Miami Beach, Florida, USA. 2010.
- Aguado L, San Antonio A, Perez L, del Valle R, Gomez J. Effects of the NMDA receptor antagonist ketamine on flavor memory: conditioned aversion, latent inhibition, and habituation of neophobia. *Behav Neural Biol*. 1994; 61:271–281. [PubMed: 8067982]
- Azbill RD, Mu X, Springer JE. Riluzole increases high-affinity glutamate uptake in rat spinal cord synaptosomes. *Brain Res*. 2000; 871:175–180. [PubMed: 10899284]
- Banasr M, Duman RS. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. *Biol Psychiatry*. 2008; 64:863–870. [PubMed: 18639237]
- Barbon A, Popoli M, La Via L, Moraschi S, Vallini I, Tardito D, et al. Regulation of editing and expression of glutamate alpha-amino-propionic-acid (AMPA)/kainate receptors by antidepressant drugs. *Biol Psychiatry*. 2006; 59:713–720. [PubMed: 16460696]
- Barria A, Malinow R. Subunit-specific NMDA receptor trafficking to synapses. *Neuron*. 2002; 35:345–353. [PubMed: 12160751]
- Beneyto M, Kristiansen LV, Oni-Orisan A, McCullumsmith RE, Meador-Woodruff JH. Abnormal glutamate receptor expression in the medial temporal lobe in schizophrenia and mood disorders. *Neuropsychopharmacology*. 2007; 32:1888–1902. [PubMed: 17299517]
- Beneyto M, Meador-Woodruff JH. Lamina-specific abnormalities of AMPA receptor trafficking and signaling molecule transcripts in the prefrontal cortex in schizophrenia. *Synapse*. 2006; 60:585–598. [PubMed: 16983646]
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000; 47:351–354. [PubMed: 10686270]
- Bhagwagar Z, Goodwin GM. Lamotrigine in the treatment of bipolar disorder. *Expert Opin Pharmacother*. 2005; 6:1401–1408. [PubMed: 16013989]
- Black MD. Therapeutic potential of positive AMPA modulators and their relationship to AMPA receptor subunits. A review of preclinical data. *Psychopharmacology (Berl)*. 2005; 179:154–163. [PubMed: 15672275]
- Bleakman D, Lodge D. Neuropharmacology of AMPA and kainate receptors. *Neuropharmacology*. 1998; 37:1187–1204. [PubMed: 9849657]
- Borza I, Bozo E, Barta-Szalai G, Kiss C, Tarkanyi G, Demeter A, et al. Selective NR1/2B N-methyl-D-aspartate receptor antagonists among indole-2-carboxamides and benzimidazole-2-carboxamides. *J Med Chem*. 2007; 50:901–914. [PubMed: 17290978]

- Boyce-Rustay JM, Holmes A. Genetic inactivation of the NMDA receptor NR2A subunit has anxiolytic- and antidepressant-like effects in mice. *Neuropsychopharmacology*. 2006; 31:2405–2414. [PubMed: 16482087]
- Brennan BP, Hudson JI, Jensen JE, McCarthy J, Roberts JL, Prescott AP, et al. Rapid enhancement of glutamatergic neurotransmission in bipolar depression following treatment with riluzole. *Neuropsychopharmacology*. 2010; 35:834–846. [PubMed: 19956089]
- Carpenter WT Jr. The schizophrenia ketamine challenge study debate. *Biol Psychiatry*. 1999; 46:1081–1091. [PubMed: 10536744]
- Chaki S, Yoshikawa R, Hirota S, Shimazaki T, Maeda M, Kawashima N, et al. MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. *Neuropharmacology*. 2004; 46:457–467. [PubMed: 14975669]
- Chen CH, Ridler K, Suckling J, Williams S, Fu CH, Merlo-Pich E, et al. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol Psychiatry*. 2007; 62:407–414. [PubMed: 17217921]
- Choudary PV, Molnar M, Evans SJ, Tomita H, Li JZ, Vawter MP, et al. Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. *Proc Natl Acad Sci U S A*. 2005; 102:15653–15658. [PubMed: 16230605]
- Chowdhury GM, Banasr M, de Graaf RA, Rothman DL, Behar KL, Sanacora G. Chronic riluzole treatment increases glucose metabolism in rat prefrontal cortex and hippocampus. *J Cereb Blood Flow Metab*. 2008; 28:1892–1897. [PubMed: 18628780]
- Clinton SM, Meador-Woodruff JH. Abnormalities of the NMDA Receptor and Associated Intracellular Molecules in the Thalamus in Schizophrenia and Bipolar Disorder. *Neuropsychopharmacology*. 2004; 29:1353–1362. [PubMed: 15054476]
- Collingridge GL, Bliss TV. Memories of NMDA receptors and LTP. *Trends Neurosci*. 1995; 18:54–56. [PubMed: 7537406]
- Coric V, Taskiran S, Pittenger C, Wasyluk S, Mathalon DH, Valentine G, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Biol Psychiatry*. 2005; 58:424–428. [PubMed: 15993857]
- Cosford ND, Tehrani L, Roppe J, Schweiger E, Smith ND, Anderson J, et al. 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-pyridine: a potent and highly selective metabotropic glutamate subtype 5 receptor antagonist with anxiolytic activity. *J Med Chem*. 2003; 46:204–206. [PubMed: 12519057]
- Cryan JF, Kelly PH, Neijt HC, Sansig G, Flor PJ, van Der Putten H. Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. *Eur J Neurosci*. 2003; 17:2409–2417. [PubMed: 12814372]
- Cull-Candy S, Brickley S, Farrant M. NMDA receptor subunits: diversity, development and disease. *Curr Opin Neurobiol*. 2001; 11:327–335. [PubMed: 11399431]
- Dagci T, Yilmaz O, Taskiran D, Peker G. Neuroprotective agents: is effective on toxicity in glial cells? *Cell Mol Neurobiol*. 2007; 27:171–177. [PubMed: 16758318]
- Danbolt NC. Glutamate uptake. *Prog Neurobiol*. 2001; 65:1–105. [PubMed: 11369436]
- Deakin JF, Lees J, McKie S, Hallak JE, Williams SR, Dursun SM. Glutamate and the neural basis of the subjective effects of ketamine: a pharmacological-magnetic resonance imaging study. *Arch Gen Psychiatry*. 2008; 65:154–164. [PubMed: 18250253]
- Debono MW, Le Guern J, Canton T, Doble A, Pradier L. Inhibition by riluzole of electrophysiological responses mediated by rat kainate and NMDA receptors expressed in *Xenopus* oocytes. *Eur J Pharmacol*. 1993; 235:283–289. [PubMed: 7685290]
- Devon RS, Anderson S, Teague PW, Burgess P, Kipari TM, Semple CA, et al. Identification of polymorphisms within Disrupted in Schizophrenia 1 and Disrupted in Schizophrenia 2, and an investigation of their association with schizophrenia and bipolar affective disorder. *Psychiatr Genet*. 2001; 11:71–78. [PubMed: 11525420]
- Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010a; 67:793–802. [PubMed: 20679587]

- Diazgranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2010b
- Dingledine R, Borges K, Bowie D, Traynelis SF. The glutamate receptor ion channels. *Pharmacol Rev*. 1999; 51:7–61. [PubMed: 10049997]
- Du J, Gray NA, Falke CA, Chen W, Yuan P, Szabo ST, et al. Modulation of synaptic plasticity by antimanic agents: the role of AMPA glutamate receptor subunit 1 synaptic expression. *J Neurosci*. 2004; 24:6578–6589. [PubMed: 15269270]
- Du J, Suzuki K, Wei Y, Wang Y, Blumenthal R, Chen Z, et al. The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorders. *Neuropsychopharmacology*. 2007; 32:793–802. [PubMed: 16936714]
- Entsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. *J Clin Psychiatry*. 2001; 62:869–877. [PubMed: 11775046]
- Frizzo ME, Dall'Onder LP, Dalcin KB, Souza DO. Riluzole enhances glutamate uptake in rat astrocyte cultures. *Cell Mol Neurobiol*. 2004; 24:123–128. [PubMed: 15049516]
- Fumagalli E, Funicello M, Rauen T, Gobbi M, Mennini T. Riluzole enhances the activity of glutamate transporters GLAST, GLT1 and EAAC1. *Eur J Pharmacol*. 2008; 578:171–176. [PubMed: 18036519]
- Garcia LS, Comim CM, Valvassori SS, Reus GZ, Barbosa LM, Andreazza AC, et al. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; 32:140–144. [PubMed: 17884272]
- Gasparini F, Bruno V, Battaglia G, Lukic S, Leonhardt T, Inderbitzin W, et al. (R,S)-4-phosphonophenylglycine, a potent and selective group III metabotropic glutamate receptor agonist, is anticonvulsive and neuroprotective in vivo. *J Pharmacol Exp Ther*. 1999; 289:1678–1687. [PubMed: 10336568]
- Goforth HW, Holsinger T. Rapid relief of severe major depressive disorder by use of preoperative ketamine and electroconvulsive therapy. *J Ect*. 2007; 23:23–25. [PubMed: 17435569]
- Hardingham GE. Pro-survival signalling from the NMDA receptor. *Biochem Soc Trans*. 2006; 34:936–938. [PubMed: 17052231]
- Hashimoto K, Sawa A, Iyo M. Increased levels of glutamate in brains from patients with mood disorders. *Biol Psychiatry*. 2007; 62:1310–1316. [PubMed: 17574216]
- Hashimoto R, Hough C, Nakazawa T, Yamamoto T, Chuang DM. Lithium protection against glutamate excitotoxicity in rat cerebral cortical neurons: involvement of NMDA receptor inhibition possibly by decreasing NR2B tyrosine phosphorylation. *J Neurochem*. 2002; 80:589–597. [PubMed: 11841566]
- Hasler G, van der Veen JW, Tumonis T, Meyers N, Shen J, Drevets WC. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch Gen Psychiatry*. 2007; 64:193–200. [PubMed: 17283286]
- Hassel B, Iversen EG, Gjerstad L, Tauboll E. Up-regulation of hippocampal glutamate transport during chronic treatment with sodium valproate. *J Neurochem*. 2001; 77:1285–1292. [PubMed: 11389179]
- Hollmann M, Heinemann S. Cloned glutamate receptors. *Annu Rev Neurosci*. 1994; 17:31–108. [PubMed: 8210177]
- Horstmann S, Lucae S, Menke A, Hennings JM, Ising M, Roeske D, et al. polymorphisms in GRIK4, HTR2A, and FKBP5 show interactive effects in predicting remission to antidepressant treatment. *Neuropsychopharmacology*. 2010; 35:727–740. [PubMed: 19924111]
- Huettner JE. Kainate receptors and synaptic transmission. *Prog Neurobiol*. 2003; 70:387–407. [PubMed: 14511698]
- Insel TR, Scolnick EM. Cure therapeutics and strategic prevention: raising the bar for mental health research. *Mol Psychiatry*. 2006; 11:11–17. [PubMed: 16355250]

- Itokawa M, Yamada K, Iwayama-Shigeno Y, Ishitsuka Y, Detera-Wadleigh S, Yoshikawa T. Genetic analysis of a functional GRIN2A promoter (GT)_n repeat in bipolar disorder pedigrees in humans. *Neurosci Lett*. 2003; 345:53–56. [PubMed: 12809987]
- Jabaudon D, Shimamoto K, Yasuda-Kamatani Y, Scanziani M, Gahwiler BH, Gerber U. Inhibition of uptake unmasks rapid extracellular turnover of glutamate of nonvesicular origin. *Proc Natl Acad Sci U S A*. 1999; 96:8733–8738. [PubMed: 10411944]
- Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002; 59:530–537. [PubMed: 12044195]
- Karasawa J, Shimazaki T, Kawashima N, Chaki S. AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist. *Brain Res*. 2005; 1042:92–98. [PubMed: 15823257]
- Karolewicz B, Szebeni K, Gilmore T, Maciag D, Stockmeier CA, Ordway GA. Elevated levels of NR2A and PSD-95 in the lateral amygdala in depression. *Int J Neuropsychopharmacol*. 2009; 12:143–153. [PubMed: 18570704]
- Kasper S, McEwen BS. Neurobiological and clinical effects of the antidepressant tianeptine. *CNS Drugs*. 2008; 22:15–26. [PubMed: 18072812]
- Kaster MP, Raupp I, Binfare RW, Andreatini R, Rodrigues AL. Antidepressant-like effect of lamotrigine in the mouse forced swimming test: evidence for the involvement of the noradrenergic system. *Eur J Pharmacol*. 2007; 565:119–124. [PubMed: 17433291]
- Katoh-Semba R, Asano T, Ueda H, Morishita R, Takeuchi IK, Inaguma Y, et al. Riluzole enhances expression of brain-derived neurotrophic factor with consequent proliferation of granule precursor cells in the rat hippocampus. *FASEB J*. 2002; 16:1328–1330. [PubMed: 12154010]
- Keck PE Jr, Hsu KS, Papadakis K, Russo J Jr. Memantine efficacy and safety in patients with acute mania associated with bipolar I disorder: a pilot evaluation. *Clin Neuropharmacol*. 2009; 32:199–204. [PubMed: 19620854]
- Kessal K, Chessel A, Spennato G, Garcia R. Ketamine and amphetamine both enhance synaptic transmission in the amygdala-nucleus accumbens pathway but with different time-courses. *Synapse*. 2005; 57:61–65. [PubMed: 15858833]
- Kristiansen LV, Meador-Woodruff JH. Abnormal striatal expression of transcripts encoding NMDA interacting PSD proteins in schizophrenia, bipolar disorder and major depression. *Schizophr Res*. 2005; 78:87–93. [PubMed: 16023328]
- Krystal JH, Petrakis IL, Krupitsky E, Schutz C, Trevisan L, D'Souza DC. NMDA receptor antagonism and the ethanol intoxication signal: from alcoholism risk to pharmacotherapy. *Ann N Y Acad Sci*. 2003; 1003:176–184. [PubMed: 14684445]
- Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. *Anesth Analg*. 2002; 95:114–118. table of contents. [PubMed: 12088953]
- Laje G, Paddock S, Manji H, Rush AJ, Wilson AF, Charney D, et al. Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. *Am J Psychiatry*. 2007; 164:1530–1538. [PubMed: 17898344]
- Langguth B, Wiegand R, Kharraz A, Landgrebe M, Marienhagen J, Frick U, et al. Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). *Neuro Endocrinol Lett*. 2007; 28:633–638. [PubMed: 17984932]
- Law AJ, Deakin JF. Asymmetrical reductions of hippocampal NMDAR1 glutamate receptor mRNA in the psychoses. *Neuroreport*. 2001; 12:2971–2974. [PubMed: 11588613]
- Lee Y, Gaskins D, Anand A, Shekhar A. Glia mechanisms in mood regulation: a novel model of mood disorders. *Psychopharmacology (Berl)*. 2007; 191:55–65. [PubMed: 17225169]
- Li B, Zhang S, Li M, Zhang H, Hertz L, Peng L. Down-regulation of GluK2 kainate receptor expression by chronic treatment with mood-stabilizing anti-convulsants or lithium in cultured astrocytes and brain, but not in neurons. *Neuropharmacology*. 2009; 57:375–385. [PubMed: 19596362]
- Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010; 329:959–964. [PubMed: 20724638]

- Li X, Need AB, Baez M, Witkin JM. Metabotropic glutamate 5 receptor antagonism is associated with antidepressant-like effects in mice. *J Pharmacol Exp Ther*. 2006; 319:254–259. [PubMed: 16803860]
- Liebreinz M, Borgeat A, Leisinger R, Stohler R. Intravenous ketamine therapy in a patient with a treatment-resistant major depression. *Swiss Med Wkly*. 2007; 137:234–236. [PubMed: 17525879]
- Lourenco Da Silva A, Hoffmann A, Dietrich MO, Dall'Igna OP, Souza DO, Lara DR. Effect of riluzole on MK-801 and amphetamine-induced hyperlocomotion. *Neuropsychobiology*. 2003; 48:27–30. [PubMed: 12886037]
- Lynch G. AMPA receptor modulators as cognitive enhancers. *Curr Opin Pharmacol*. 2004; 4:4–11. [PubMed: 15018832]
- Machado-Vieira R, Manji HK, Zarate CA. The role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders. *Neuroscientist*. 2009a; 15:525–539. [PubMed: 19471044]
- Machado-Vieira R, Salvatore G, Ibrahim LA, Diaz-Granados N, Zarate CA Jr. Targeting glutamatergic signaling for the development of novel therapeutics for mood disorders. *Curr Pharm Des*. 2009b; 15:1595–1611. [PubMed: 19442176]
- Machado-Vieira R, Salvatore G, Luckenbaugh DA, Manji HK, Zarate CA Jr. Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. *J Clin Psychiatry*. 2008; 69:946–958. [PubMed: 18435563]
- Machado-Vieira R, Yuan P, Brutsche N, Diazgranados N, Luckenbaugh D, Manji HK. Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist. *J Clin Psychiatry*. 2009c; 70:1662–1666. [PubMed: 19744406]
- Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, Chen G. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino 3-hydroxy 5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry*. 2008; 63:349–352. [PubMed: 17643398]
- Magnusson KR, Nelson SE, Young AB. Age-related changes in the protein expression of subunits of the NMDA receptor. *Brain Res Mol Brain Res*. 2002; 99:40–45. [PubMed: 11869807]
- Maiese K, Vincent A, Lin SH, Shaw T. Group I and group III metabotropic glutamate receptor subtypes provide enhanced neuroprotection. *J Neurosci Res*. 2000; 62:257–272. [PubMed: 11020218]
- Marti SB, Cichon S, Propping P, Nothen M. Metabotropic glutamate receptor 3 (GRM3) gene variation is not associated with schizophrenia or bipolar affective disorder in the German population. *Am J Med Genet*. 2002; 114:46–50. [PubMed: 11840505]
- Martucci L, Wong AH, De Luca V, Likhodi O, Wong GW, King N. N-methyl-D-aspartate receptor NR2B subunit gene GRIN2B in schizophrenia and bipolar disorder: Polymorphisms and mRNA levels. *Schizophr Res*. 2006; 84:214–221. [PubMed: 16549338]
- Mathew SJ, Amiel JM, Coplan JD, Fitterling HA, Sackeim HA, Gorman JM. Open-label trial of riluzole in generalized anxiety disorder. *Am J Psychiatry*. 2005; 162:2379–2381. [PubMed: 16330605]
- Mathew SJ, Murrough JW, van den Heuvel M, Collins KA, Reich DL, Charney D. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. *Int J Neuropsychopharmacol*. 2010; 13:71–82. [PubMed: 19288975]
- Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport*. 1997; 8:1057–1061. [PubMed: 9141092]
- McCormick LM, Boles Ponto LL, Pierson RK, Johnson HJ, Magnotta V, Brumm MC. Metabolic correlates of antidepressant and antipsychotic response in patients with psychotic depression undergoing electroconvulsive therapy. *J ECT*. 2007; 23:265–273. [PubMed: 18090701]
- McCullumsmith RE, Kristiansen LV, Beneyto M, Scarr E, Dean B, Meador-Woodruff JH. Decreased NR1, NR2A, and SAP102 transcript expression in the hippocampus in bipolar disorder. *Brain Res*. 2007; 1127:108–118. [PubMed: 17113057]

- McCullumsmith RE, Meador-Woodruff JH. Striatal excitatory amino acid transporter transcript expression in schizophrenia, bipolar disorder, and major depressive disorder. *Neuropsychopharmacology*. 2002; 26:368–375. [PubMed: 11850151]
- Meador-Woodruff JH, Hogg AJ Jr, Smith RE. Striatal ionotropic glutamate receptor expression in schizophrenia, bipolar disorder, and major depressive disorder. *Brain Res Bull*. 2001; 55:631–640. [PubMed: 11576760]
- Menke A, Lucae S, Kloiber S, Horstmann S, Bettecken T, Uhr M. Genetic markers within glutamate receptors associated with antidepressant treatment-emergent suicidal ideation. *Am J Psychiatry*. 2008; 165:917–918. [PubMed: 18593792]
- Mickley GA, Schaldach MA, Snyder KJ, Balogh SA, Len T, Neimanis K. Ketamine blocks a conditioned taste aversion (CTA) in neonatal rats. *Physiol Behav*. 1998; 64:381–390. [PubMed: 9748108]
- Miller TM, Cleveland DW. Medicine. Treating neurodegenerative diseases with antibiotics. *Science*. 2005; 307:361–362. [PubMed: 15661995]
- Mineur YS, Picciotto MR, Sanacora G. Antidepressant-like effects of ceftriaxone in male C57BL/6J mice. *Biol Psychiatry*. 2007; 61:250–252. [PubMed: 16860779]
- Miu P, Jarvie KR, Radhakrishnan V, Gates MR, Ogden A, Ornstein PL. Novel AMPA receptor potentiators LY392098 and LY404187: effects on recombinant human AMPA receptors in vitro. *Neuropharmacology*. 2001; 40:976–983. [PubMed: 11406188]
- Mizuta I, Ohta M, Ohta K, Nishimura M, Mizuta E, Kuno S. Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes. *Neurosci Lett*. 2001; 310:117–120. [PubMed: 11585581]
- Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci*. 1997; 17:2921–2927. [PubMed: 9092613]
- Moryl E, Danysz W, Quack G. Potential antidepressive properties of amantadine, memantine and bifemelane. *Pharmacol Toxicol*. 1993; 72:394–397. [PubMed: 8361950]
- Moutsimilli L, Farley S, Dumas S, El Mestikawy S, Giros B, Tzavara ET. Selective cortical VGLUT1 increase as a marker for antidepressant activity. *Neuropharmacology*. 2005; 49:890–900. [PubMed: 16111724]
- Mundo E, Tharmalingham S, Neves-Pereira M, Dalton EJ, Macciardi F, Parikh SV. Evidence that the N-methyl-D-aspartate subunit 1 receptor gene (GRIN1) confers susceptibility to bipolar disorder. *Mol Psychiatry*. 2003; 8:241–245. [PubMed: 12610658]
- Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science*. 1996; 274:740–743. [PubMed: 8966556]
- Nakanishi S. Molecular diversity of glutamate receptors and implications for brain function. *Science*. 1992; 258:597–603. [PubMed: 1329206]
- Nierenberg AA, Ostacher MJ, Calabrese JR, Ketter TA, Marangell LB, Miklowitz DJ. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry*. 2006; 163:210–216. [PubMed: 16449473]
- Nowak G, Trullas R, Layer RT, Skolnick P, Paul IA. Adaptive changes in the N-methyl-D-aspartate receptor complex after chronic treatment with imipramine and 1-aminocyclopropanecarboxylic acid. *J Pharmacol Exp Ther*. 1993; 265:1380–1386. [PubMed: 8099620]
- Nudmamud-Thanoi S, Reynolds GP. The NR1 subunit of the glutamate/NMDA receptor in the superior temporal cortex in schizophrenia and affective disorders. *Neurosci Lett*. 2004; 372:173–177. [PubMed: 15531111]
- O'Neill MJ, Bleakman D, Zimmerman DM, Nisenbaum ES. AMPA receptor potentiators for the treatment of CNS disorders. *Curr Drug Targets CNS Neurol Disord*. 2004; 3:181–194. [PubMed: 15180479]
- O'Shea RD. Roles and regulation of glutamate transporters in the central nervous system. *Clin Exp Pharmacol Physiol*. 2002; 29:1018–1023. [PubMed: 12366395]

- Oliet SH, Piet R, Poulain DA. Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. *Science*. 2001; 292:923–926. [PubMed: 11340204]
- Ostroff R, Gonzales M, Sanacora G. Antidepressant effect of ketamine during ECT. *Am J Psychiatry*. 2005; 162:1385–1386. [PubMed: 15994728]
- Paddock S, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJ. Association of GRIK4 with outcome of antidepressant treatment in the STAR*D cohort. *Am J Psychiatry*. 2007; 164:1181–1188. [PubMed: 17671280]
- Palucha A, Branski P, Klak K, Sowa M. Chronic imipramine treatment reduces inhibitory properties of group II mGlu receptors without affecting their density or affinity. *Pharmacol Rep*. 2007a; 59:525–530. [PubMed: 18048952]
- Palucha A, Klak K, Branski P, van der Putten H, Flor PJ, Pilc A. Activation of the mGlu7 receptor elicits antidepressant-like effects in mice. *Psychopharmacology (Berl)*. 2007b; 194:555–562. [PubMed: 17622518]
- Palucha A, Pilc A. Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. *Pharmacol Ther*. 2007; 115:116–147. [PubMed: 17582504]
- Palucha A, Tatarczynska E, Branski P, Szewczyk B, Wieronska JM, Klak K. Group III mGlu receptor agonists produce anxiolytic- and antidepressant-like effects after central administration in rats. *Neuropharmacology*. 2004; 46:151–159. [PubMed: 14680755]
- Papp M, Moryl E. Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. *Eur J Pharmacol*. 1994; 263:1–7. [PubMed: 7821340]
- Paul IA, Nowak G, Lamer RT, Popik P, Skolnick P. Adaptation of the N-methyl-D-aspartate receptor complex following chronic antidepressant treatments. *J Pharmacol Exp Ther*. 1994; 269:95–102. [PubMed: 8169857]
- Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci*. 2003; 1003:250–272. [PubMed: 14684451]
- Perry EB Jr, Cramer JA, Cho HS, Petrakis IL, Karper LP, Genovese A. Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology (Berl)*. 2007; 192:253–260. [PubMed: 17458544]
- Petrakis IL, Limoncelli D, Gueorguieva R, Jatlow P, Boutros NN, Trevisan L. Altered NMDA glutamate receptor antagonist response in individuals with a family vulnerability to alcoholism. *Am J Psychiatry*. 2004; 161:1776–1782. [PubMed: 15465973]
- Petrenko AB, Yamakura T, Fujiwara N, Askalany AR, Baba H, Sakimura K. Reduced sensitivity to ketamine and pentobarbital in mice lacking the N-methyl-D-aspartate receptor GluR5 subunit. *Anesth Analg*. 2004; 99:1136–1140. table of contents. [PubMed: 15385364]
- Phelps LE, Brutsche N, Moril JR, Luckenbaugh DA, Manji HK, Zarate CA Jr. Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. *Biol Psychiatry*. 2009; 65:181–184. [PubMed: 18996507]
- Pickard BS, Malloy MP, Christoforou A, Thomson PA, Evans KL, Morris SW. Cytogenetic and genetic evidence supports a role for the kainate-type glutamate receptor gene, GRIK4, in schizophrenia and bipolar disorder. *Mol Psychiatry*. 2006; 11:847–857. [PubMed: 16819533]
- Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *Am J Psychiatry*. 2001; 158:405–415. [PubMed: 11229981]
- Porter RH, Jaeschke G, Spooren W, Ballard TM, Buttelmann B, Kolczewski S. Fenobam: a clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity. *J Pharmacol Exp Ther*. 2005; 315:711–721. [PubMed: 16040814]
- Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J Clin Psychopharmacol*. 2008; 28:631–637. [PubMed: 19011431]

- Prca C, Hascoet M, Bourin M. Antidepressant-like effect of lamotrigine is reversed by veratrine: a possible role of sodium channels in bipolar depression. *Behav Brain Res*. 2008; 191:49–54. [PubMed: 18433891]
- Price RB, Nock MK, Charney D, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry*. 2009; 66:522–529. [PubMed: 19545857]
- Quiroz JA, Singh J, Gould TD, Denicoff KD, Zarate CA, Manji HK. Emerging experimental therapeutics for bipolar disorder: clues from the molecular pathophysiology. *Mol Psychiatry*. 2004; 9:756–776. [PubMed: 15136795]
- Rogawski MA. Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Res*. 2006; 69:273–294. [PubMed: 16621450]
- Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature*. 2005; 433:73–77. [PubMed: 15635412]
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006; 163:1905–1917. [PubMed: 17074942]
- Sah P, Lopez De Armentia M. Excitatory synaptic transmission in the lateral and central amygdala. *Ann N Y Acad Sci*. 2003; 985:67–77. [PubMed: 12724149]
- Salvadore G, Cornwell BR, Colon-Rosario V, Coppola R, Grillon C, Zarate CA Jr. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. *Biol Psychiatry*. 2009; 65:289–295. [PubMed: 18822408]
- Salvadore G, Cornwell BR, Sambataro F, Latov D, Colon-Rosario V, Carver F. Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. *Neuropsychopharmacology*. 2010; 35:1415–1422. [PubMed: 20393460]
- Sanacora G, Gueorguieva R, Epperson CN, Wu YT, Appel M, Rothman DL. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry*. 2004; 61:705–713. [PubMed: 15237082]
- Sanacora G, Kendell SF, Levin Y, Simen AA, Fenton LR, Coric V. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry*. 2007; 61:822–825. [PubMed: 17141740]
- Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov*. 2008; 7:426–437. [PubMed: 18425072]
- Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *Am J Psychiatry*. 2003; 160:522–532. [PubMed: 12611834]
- Scarr E, Pavey G, Sundram S, MacKinnon A, Dean B. Decreased hippocampal NMDA, but not kainate or AMPA receptors in bipolar disorder. *Bipolar Disord*. 2003; 5:257–264. [PubMed: 12895203]
- Schiffer HH, Heinemann SF. Association of the human kainate receptor GluR7 gene (GRIK3) with recurrent major depressive disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B:20–26. [PubMed: 16958029]
- Schoepp DD, Wright RA, Levine LR, Gaydos B, Potter WZ. LY354740, an mGlu2/3 receptor agonist as a novel approach to treat anxiety/stress. *Stress*. 2003; 6:189–197. [PubMed: 13129812]
- Sheng M, Sala C. PDZ domains and the organization of supramolecular complexes. *Annu Rev Neurosci*. 2001; 24:1–29. [PubMed: 11283303]
- Silvestre JS, Nadal R, Pallares M, Ferre N. Acute effects of ketamine in the holeboard, the elevated-plus maze, and the social interaction test in Wistar rats. *Depress Anxiety*. 1997; 5:29–33. [PubMed: 9250438]

- Skolnick P, Layer RT, Popik P, Nowak G, Paul IA, Trullas R. Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. *Pharmacopsychiatry*. 1996; 29:23–26. [PubMed: 8852530]
- Skolnick P, Legutko B, Li X, Bymaster FP. Current perspectives on the development of non-biogenic amine-based antidepressants. *Pharmacol Res*. 2001; 43:411–423. [PubMed: 11394932]
- Song I, Kamboj S, Xia J, Dong H, Liao D, Haganir RL. Interaction of the N-ethylmaleimide-sensitive factor with AMPA receptors. *Neuron*. 1998; 21:393–400. [PubMed: 9728920]
- Soriano FX, Hardingham GE. Compartmentalized NMDA receptor signalling to survival and death. *J Physiol*. 2007; 584:381–387. [PubMed: 17690142]
- Suetake-Koga S, Shimazaki T, Takamori K, Chaki S, Kanuma K, Sekiguchi Y. In vitro and antinociceptive profile of HON0001, an orally active NMDA receptor NR2B subunit antagonist. *Pharmacol Biochem Behav*. 2006; 84:134–141. [PubMed: 16764916]
- Svenningsson P, Bateup H, Qi H, Takamiya K, Haganir RL, Spedding M. Involvement of AMPA receptor phosphorylation in antidepressant actions with special reference to tianeptine. *Eur J Neurosci*. 2007; 26:3509–3517. [PubMed: 18088278]
- Svenningsson P, Tzavara ET, Witkin JM, Fienberg AA, Nomikos GG, Greengard P. Involvement of striatal and extrastriatal DARPP 32 in biochemical and behavioral effects of fluoxetine (Prozac). *Proc Natl Acad Sci U S A*. 2002; 99:3182–3187. [PubMed: 11880651]
- Takamori S, Rhee JS, Rosenmund C, Jahn R. Identification of a vesicular glutamate transporter that defines a glutamatergic phenotype in neurons. *Nature*. 2000; 407:189–194. [PubMed: 11001057]
- Teng CT, Demetrio FN. Memantine may acutely improve cognition and have a mood stabilizing effect in treatment-resistant bipolar disorder. *Rev Bras Psiquiatr*. 2006; 28:252–254. [PubMed: 17063225]
- Thase ME, Haight BR, Richard N, Rockett CB, Mitton M, Modell JG. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J Clin Psychiatry*. 2005; 66:974–981. [PubMed: 16086611]
- Thompson CM, Davis E, Carrigan CN, Cox HD, Bridges RJ, Gerdes JM. Inhibitor of the glutamate vesicular transporter (VGLUT). *Curr Med Chem*. 2005; 12:2041–2056. [PubMed: 16101493]
- Tordera RM, Pei Q, Sharp T. Evidence for increased expression of the vesicular glutamate transporter, VGLUT1, by a course of antidepressant treatment. *J Neurochem*. 2005; 94:875–883. [PubMed: 15992385]
- Tordera RM, Totterdell S, Wojcik SM, Brose N, Elizalde N, Lasheras B. Enhanced anxiety, depressive-like behaviour and impaired recognition memory in mice with reduced expression of the vesicular glutamate transporter 1 (VGLUT1). *Eur J Neurosci*. 2007; 25:281–290. [PubMed: 17241289]
- Toro C, Deakin JF. NMDA receptor subunit NRI and postsynaptic protein PSD 95 in hippocampus and orbitofrontal cortex in schizophrenia and mood disorder. *Schizophr Res*. 2005; 80:323–330. [PubMed: 16140506]
- Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006; 163:28–40. [PubMed: 16390886]
- Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. *Eur J Pharmacol*. 1990; 185:1–10. [PubMed: 2171955]
- Ueda Y, Willmore LJ. Molecular regulation of glutamate and GABA transporter proteins by valproic acid in rat hippocampus during epileptogenesis. *Exp Brain Res*. 2000; 133:334–339. [PubMed: 10958523]
- Wieronska JM, Szewczyk B, Branski P, Palucha A, Pilc A. Antidepressant-like effect of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist in the olfactory bulbectomized rats. *Amino Acids*. 2002; 23:213–216. [PubMed: 12373540]
- Wilson GM, Flibotte S, Chopra V, Melnyk BL, Honer WG, Holt RA. DNA copy-number analysis in bipolar disorder and schizophrenia reveals aberrations in genes involved in glutamate signaling. *Hum Mol Genet*. 2006; 15:743–749. [PubMed: 16434481]

- Witkin JM, Marek GJ, Johnson BG, Schoepp DD. Metabotropic glutamate receptors in the control of mood disorders. *CNS Neurol Disord Drug Targets*. 2007; 6:87–100. [PubMed: 17430147]
- Wu J, Buchsbaum MS, Gillin JC, Tang C, Cadwell S, Wiegand M. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am J Psychiatry*. 1999; 156:1149–1158. [PubMed: 10450253]
- Yildiz-Yesiloglu A, Ankerst DP. Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: a systematic review of the in vivo proton magnetic resonance spectroscopy findings. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30:969–995. [PubMed: 16677749]
- Yoon SJ, Lyoo IK, Haws C, Kim TS, Cohen BM, Renshaw PF. Decreased glutamate/glutamine levels may mediate cytidine's efficacy in treating bipolar depression: a longitudinal proton magnetic resonance spectroscopy study. *Neuropsychopharmacology*. 2009; 34:1810–1818. [PubMed: 19194376]
- Yoshimizu T, Chaki S. Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039. *Biochem Biophys Res Commun*. 2004; 315:493–496. [PubMed: 14766235]
- Yoshimizu T, Shimazaki T, Ito A, Chaki S. An mGluR2/3 antagonist, MGS0039, exerts antidepressant and anxiolytic effects in behavioral models in rats. *Psychopharmacology (Berl)*. 2006; 186:587–593. [PubMed: 16612616]
- Yuksel C, Ongur D. Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biol Psychiatry*. 2010; 68:785–794. [PubMed: 20728076]
- Zarate CA Jr, Charney DS, Manji HK. Searching for rational anti-N-methyl-D-aspartate treatment for depression. *Arch Gen Psychiatry*. 2007; 64:1100–1101.
- Zarate CA Jr, Du J, Quiroz J, Gray NA, Denicoff KD, Singh J. Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: role of the glutamatergic system. *Ann N Y Acad Sci*. 2003; 1003:273–291. [PubMed: 14684452]
- Zarate CA Jr, Payne JL, Quiroz J, Sporn J, Denicoff KK, Luckenbaugh D. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry*. 2004; 161:171–174. [PubMed: 14702270]
- Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006a; 63:856–864. [PubMed: 16894061]
- Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KK, Luckenbaugh DA. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am J Psychiatry*. 2006b; 163:153–155. [PubMed: 16390905]
- Zarate CA, Quiroz J, Payne J, Manji HK. Modulators of the glutamatergic system: implications for the development of improved therapeutics in mood disorders. *Psychopharmacol Bull*. 2002; 36:35–83. [PubMed: 12858143]