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Review

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.

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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 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

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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 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) and 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) and 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 and Zarate (2010) and 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 were 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 were also described in individuals with BPD (Meador-Woodruff et al., 2001). Abnormal mGluR3 expression was 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 GluR6 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 was also 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 and 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). Among 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 the 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 NR2A and NR2B 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.

AMPAR 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) and 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), benzoylpiperidines (e.g., CX-516), and birylpropylsulfonamides (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), and O'Neill et al. (2004)). While AMPAR potentiators are associated with antidepressant-like properties, AMPAR antagonists such as talampanel may have antimanic properties. Talampanel 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-aminocyclo-pentane-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 (Prica 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 were 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 also reduced 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 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 ^{13}C-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 (Banasr 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 (50 mg/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 (100–200 mg/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 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 h after infusion (Berman et al., 2000). Subsequently, a double-blind, placebo-controlled, crossover study showed a fast (first 2 h 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 h after infusion and 35% showed a sustained response at the end of week one. Notably, response rates with ketamine after 24 h (71%) were similar to those described after six to eight weeks of treatment with traditional monoaminergic-based antidepressants (65%) (Entsuah 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 were 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 min 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 min 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 h 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 min post-infusion. Suicidal ideation scores significantly decreased on the Scale for Suicide Ideation (SSI) and suicidality items of depression rating scales within 40 min after infusion, and this effect remained significant through the first 4 h 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 min 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, Liebrenz 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 with ketamine's initial antidepressant effects. No change was observed in BDNF levels between baseline and up to 230 min 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. Autry and colleagues recently reported that a possible mechanism of action for ketamine was the rapid (30-minute) induction of BDNF, showing that blockade of protein synthesis by pretreatment with anisomycin blocked the induction of both BDNF and the antidepressant-like effects of ketamine in the forced swim test (Autry et al., 2011). 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 BDNF and certain 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 glutamate/glutamine 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 therapeutics 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.

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