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Role of calcium, glutamate and NMDA in major depression and therapeutic application

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ABSTRACT

Major depression is a common, recurrent mental illness that affects millions of people worldwide. Recently, a unique fast neuroprotective and antidepressant treatment effect has been observed by ketamine, which acts via the glutamatergic system. Hence, a steady accumulation of evidence supporting a role for the excitatory amino acid neurotransmitter (EAA) glutamate in the treatment of depression has been observed in the last years. Emerging evidence indicates that *N*-methyl-D-aspartate (NMDA), group 1 metabotropic glutamate receptor antagonists and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) agonists have antidepressant properties. Indeed, treatment with NMDA receptor antagonists has shown the ability to sprout new synaptic connections and reverse stress-induced neuronal changes. Based on glutamatergic signaling, a number of therapeutic drugs might gain interest in the future. Several compounds such as ketamine, memantine, amantadine, tianeptine, pioglitazone, riluzole, lamotrigine, AZD6765, magnesium, zinc, guanosine, adenosine aniracetam, traxoprodil (CP-101,606), MK-0657, GLYX-13, NRX-1047, Ro25-6981, LY392098, LY341495, D-cycloserine, D-serine, dextromethorphan, sarcosine, scopolamine, pomaglumetad methionil, LY2140023, LY404039, MGS0039, MPEP, 1-aminocyclopropanecarboxylic acid, all of which target this system, have already been brought up, some of them recently. Drugs targeting the glutamatergic system might open up a promising new territory for the development of drugs to meet the needs of patients with major depression.

1. Background

Depression presents with loss of interest, depressed mood, loss of drive and pleasure, feelings of guilt, poor concentration, low self-esteem, sleep disturbances and increased or decreased appetite. Depression can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide, a tragic fatality associated with the loss of about 850,000 lives every year. According to the World Health Organization, depression is the leading cause of disability as measured by disability adjusted live years. In this paper, an attempt is made to overview a glutamatergic concept of the disease and search for perspectives on antidepressant treatment strategies based on glutamatergic neurotransmission.

A paradigm shift from a monoamine hypothesis of depression to a neuroplasticity hypothesis represents a substantial advancement in the working hypothesis that drives research for new therapies of depressive patients. Stress and depression are associated with neuronal atrophy and decreased synaptic connections in the prefrontal cortex, limbic brain regions and hippocampus. Normally, synapses of glutamate terminals are maintained and regulated by circuit activity and function, including activity-dependent release of brain-derived neurotrophic factor (BDNF) and downstream signaling pathways. Stress leads to decreased expression and release of BDNF as well as increased levels of adrenal glucocorticoids. These stress-induced effects are comparable with long-term depression.

Accumulating evidence suggests that the glutamatergic system plays an important role in this process and in the neurobiology and treatment of depression. Excitatory amino acid (EAA) and monoamine neurotransmission are extensively colocalized in brain nuclei relevant for depressive psychopathology such as the locus caeruleus and dorsal raphe. Rapid-acting antidepressants, notably ketamine, cause a burst of glutamate resulting in an increase in synaptogenesis that has been compared with long-term potentiation. The increase in glutamate is thought to occur via blockade of *N*-methyl-D-aspartate (NMDA)

Abbreviations: N-methyl-D-aspartate, (NMDA); gamma-aminobutyric acid, (GABA); brain-derived neurotrophic factor, (BDNF); excitatory amino acid transporters, (EAAT); long-term potentiation, (LTP); calmodulin-dependent protein kinase II, (CaMKII); glycogen synthase kinase, (GSK3); phosphoinositol-dependent kinase 3, (PI3K); NMDA receptor subtype 2B, (NR2B).

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receptors located on inhibitory gamma-aminobutyric acid (GABA)-ergic neurons, resulting in disinhibition of glutamate transmission. The burst of glutamate increases BDNF release and causes the synthesis of synaptic proteins required for new spine synapse formation. These new connections allow for proper circuit activity and normal control of mood and emotion. Indeed, the non-competitive NMDA receptor antagonist ketamine and other glutamatergic drugs are considered as one of the most attractive candidates for an innovative fast antidepressant treatment (Fig. 1).

2. Glutamate

Glutamate is the primary excitatory neurotransmitter in the brain (Kornmeier and Sosic-Vasic, 2012). Glutamate is found in substantially higher concentrations than monoamines and in more than 80% of neurons, cementing its role as a major excitatory synaptic neurotransmitter. Accumulating evidence shows that glutamate plays a key role in regulating neuroplasticity, learning and memory. Indeed, the balance of glutamate with the major inhibitory neurotransmitter GABA is essential for the physiological homeostasis in the CNS (Sanacora et al., 2008). It has been indicated that glutamatergic neurons and synapses by far outnumber all other neurotransmitter systems in the brain with the only exception of the GABAergic system (Sanacora et al., 2012). Whereas glutamate is necessary for the normal development of dendritic branching, excessive glutamatergic neurotransmission, however, causes dendritic retraction and loss of spines. These changes would effectively limit the number of exposed glutamate receptors and as a result, drugs thought to reduce glutamatergic neurotransmission may prevent dendritic retraction and protect brain synapses.

Moreover, studies observed abnormalities of the glutamate clearance at the synaptic space and a modulation of astrocytic energy metabolism involving glutamate (John et al., 2012). In this context, significant differences in the methylation patterns specific to astrocytic dysfunction associated with depressive psychopathology have been published recently (Nagy et al., 2014).

Changes in glutamate levels have been noted in plasma (Küçükibrahimoğlu et al., 2009; Mitani et al., 2006), cerebrospinal fluid (Frye et al., 2007; Levine et al., 2000) and brain tissue (Hashimoto et al., 2007) of individuals with mood disorders, as well as in suicide victims (Bernstein et al., 2013). A recent review of the magnetic resonance spectroscopy (MRS) literature in mood disorders found reduced glutamate and glutamine levels in the anterior cingulate cortex, left dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, ventromedial prefrontal cortex, amygdala and hippocampus of major depressive patients (Jun et al., 2007). The deficits of glutamatergic metabolism have been found to be related to the aberrant neuronal activation patterns of the anterior cingulum in depression (Walter et al., 2009).

In bipolar patients, glutamate and glutamine levels have been found elevated in the grey matter areas of the anterior cingulate cortex, medial prefrontal cortex, dorsolateral prefrontal cortex, parieto-occipital cortex, occipital cortex, insula and hippocampus (Jun et al., 2007).

3. The glutamate–glutamine cycle

Glutamate is readily formed in neurons from glutamine synthesized in astrocytes, released into the extracellular space and taken up by neurons (McKenna, 2007). However, the glutamate–glutamine cycle is not a stoichiometric cycle but rather an open pathway that interfaces with many other metabolic pathways to varying extents depending on cellular requirements and priorities (McKenna, 2007). Multiple subcellular compartments of glutamate are located within both neurons and astrocytes, and glutamate can be derived from other amino acids and many energy substrates, including glucose, lactate and 3-hydroxybutyrate (McKenna, 2007). A disruption of glutamate–glutamine cycle significantly impacts on suicidal behavior (Bernstein et al., 2013).

4. Glutamate receptors

Glutamate acts on three key cell compartments: presynaptic neurons, postsynaptic neurons and glia. This “tripartite glutamatergic synapse” functions in the uptake, release and inactivation of glutamate. Glutamate is cleared from the extracellular space by high-affinity excitatory amino acid transporters (EAATs), which are located on neighboring glial cells

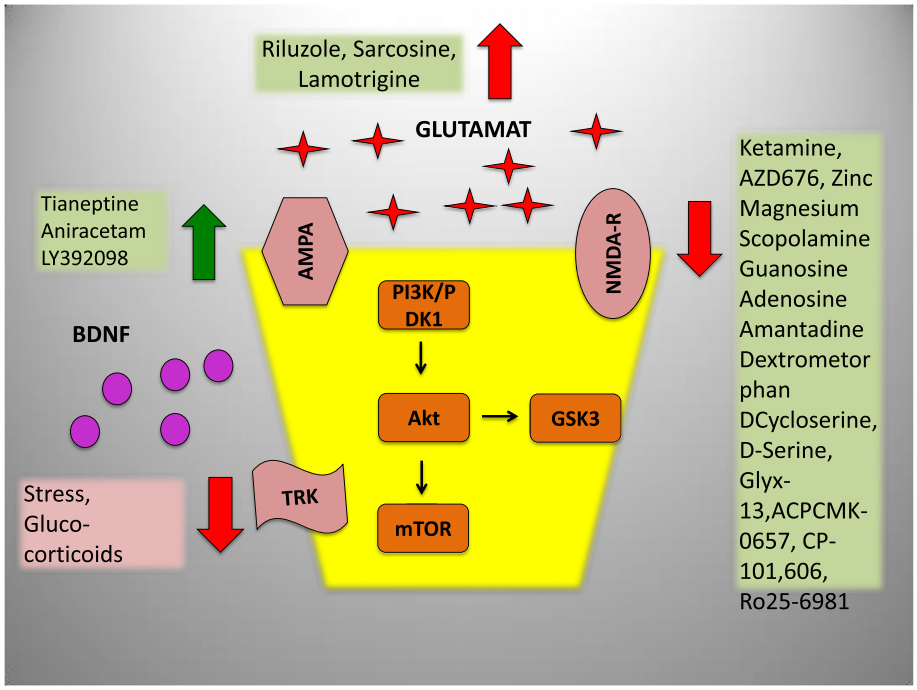

Fig. 1. Different medications targeting the glutamatergic system and their postulated mechanism via AMPA and NMDA receptor and on intracellular relevant signaling cascades.

(EAAT1 and EAAT2) and on neurons (EAAT3 and EAAT4) (O'Shea, 2002). In glial cells, glutamate is converted into glutamine. Glutamine is then transported back into the glutamatergic neuron, where it is hydrolyzed into glutamate (Erecinska and Silver, 1990). Beside the lack of degradative enzymes in the synapse, uptake by EAATs is the main mechanism through which the action of extracellular glutamate is terminated.

Glutamate regulates neuronal migration, neural growth, synaptogenesis and the pruning of neurons by activating ionotropic glutamate receptors and metabotropic glutamate receptors. The number and stability of these receptors at the synaptic membrane is an important factor in determining excitatory synaptic efficacy.

Ionotropic receptors, i.e., the kainate receptor (GluR5-7, KA-1-2) and the amino-3-hydroxy-5-methyl-isoxa-zoloe-4-proprionic acid (AMPA) (GluR1-4) receptor, play an important role in excitatory neurotransmission by mediating fast postsynaptic potentials.

The NMDA receptor GluN1 (formerly known as NR1), GluN2A-D (formerly known as NR2A-D) and GluN3A-B (formerly known as NR3A-B) (Cull-Candy et al., 2001) is a third ionotropic receptor playing a primary role in long-term potentiation (LTP), which is a major form of use-dependent synaptic plasticity. Each activation of the NMDA receptor leads to easier stimulation of pyramidal neurons. Therefore, the synaptic efficacy increases persistently, resulting in LTP. In LTP preferential routes for impulses develop in the brain. This is the physiological foundation of conditioned reaction and thus learning (Lau et al., 2009). In the hippocampus these neuroplastic effects have been implicated in hippocampal CA3 cell-dependent spatial memory functions that likely rely on dynamic cellular ensemble encoding of space (Hunt et al., 2013). NMDA receptors are activated after binding of the agonist glutamate to the NR2 subunit along with a co-agonist, either L-glycine or D-serine, to the GluN1 subunit.

Several steps are necessary to ensure activation of the NMDA receptor. At resting membrane potential magnesium blocks the NMDA channel, prohibiting calcium influx. Calcium second messenger causes an increased sensitivity of the synapse, resulting in LTP. A brief period of high-intensity excitatory synaptic activity results in a decrease of the membrane potential, which leads to the removement of the magnesium, which blocks the NMDA receptor.

A second mechanism of the activation of the NMDA receptor is the occupation of glutamate at 2 binding sites, which occurs in cases of excessive glutamate release (Goff and Coyle, 2001). After sufficient depolarization of the postsynaptic membrane, magnesium no longer blocks the channel, causing calcium influx. However, excessive glutamate release in the synapse leads to overstimulation of NMDA receptors, an increased calcium influx and elevation of intracellular calcium levels. Thus, toxic metabolic processes are triggered that may lead to neuronal cell death.

Glutamate metabotropic receptors (mGlu1-8) mediate slower neurotransmission and affect intracellular metabolic processes (Harrison et al., 2008). After the activation of mGlu receptors, G-protein is activated, followed by the conversion of ATP to cyclic AMP by adenylyl cyclase. MGlu5 receptors are a potential target for novel drug development because activation of mGlu5 receptors enhances NMDA receptor function (Singh and Singh, 2011). MGlu2 and mGlu3 receptors belong to the subgroup II family of mGluRs. High levels of mGlu2 receptors are found in almost all regions of the limbic system, including the prefrontal cortex, thalamus and amygdala (Fell et al., 2012). The expression of mGlu3 receptors is also seen in other limbic regions, including the hippocampus. The activation of mGlu2 and mGlu3 receptors on presynaptic nerve terminals inhibits presynaptic glutamate release, modulating synaptic plasticity and LTP. Highly selective mGluR2-positive allosteric modulators (PAMs), inhibiting presynaptic glutamate release, are more promising than mixed mGluR2/3 agonists in clinical studies (Adams et al., 2013, 2014; Hopkins, 2013; Trabanco and Cid, 2013).

5. Calcium

Learning and memory is widely believed to result from changes in connectivity within neuronal circuits due to synaptic plasticity. NMDA receptor-dependent synaptic plasticity via LTP and long-term depression is triggered by postsynaptic calcium elevation.

A calcium influx during LTP induction triggers the activation of calcineurin and Calcium/calmodulin-dependent protein kinase II (CaMKII) in dendritic spines (Shonesy et al., 2014). CaMKII activation results in autophosphorylation of the kinase, rendering it constitutively active long after the calcium dissipates within the spine. A diversity of downstream targets can be modulated by CaMKII to exert dynamic control of synaptic structure and function. Recently, a genetic variation in the calcium/calmodulin pathway has been linked to antidepressant response (Shi et al., 2012).

Calcium input can activate at a given frequency, the quantity of CaMKII activated is proportional to the total amount of calcium (Li et al., 2012). Thus, an input of a small amount of calcium at high frequencies can induce the same activation of CaMKII as a larger amount, at lower frequencies (Li et al., 2012). In a recent epidemiological study, the supplementation of vitamin D and calcium in about 36,000 postmenopausal women did not show a significant effect on depressive behavior (Bertone-Johnson et al., 2012).

6. Glutamatergic influence on neurogenesis and plasticity

Decreased hippocampal volumes have been found in a series of studies in humans exposed to chronic stress leading to the hypothesis that chronic stress can inhibit neurogenesis, retract dendritic processes and lead to neuronal loss in the hippocampus (Schmidt and Duman, 2007; Schmidt et al., 2011). The majority of reported volumetric findings agree with reduced hippocampal volumes in depressive subjects (Campbell and MacQueen, 2006).

One mechanism by which ketamine might function is a deactivated eukaryotic elongation factor 2 kinase, resulting in reduced phosphorylation and desuppression of rapid dendritic protein translation, including BDNF (Gideons et al., 2014; Autry et al., 2011). BDNF regulates synaptic plasticity in neuronal networks and is involved in depressive behaviors (Pittenger and Duman, 2007; Schinder and Poo, 2000). Upregulation of BDNF may reverse stress-induced deficits in structural and synaptic plasticity in the adult brain, resulting in cognitive flexibility and an increased ability to adapt with environmental challenges that may precipitate or exacerbate depressive episodes. Recent studies demonstrate that BDNF levels are decreased in the blood of depressed patients and its levels are increased with antidepressant treatment (Aydemir et al., 2005; Brunoni et al., 2008; Deuschle et al., 2013; Gervasoni et al., 2005; Karege et al., 2002; Kim et al., 2007; Lee et al., 2006, 2011; Ricken et al., 2013; Sen et al., 2008; Shimizu et al., 2003). Moreover, human BDNF polymorphism and serum levels have been connected with anxiety, risk of depression, neuroticism and serotonergic neurotransmission (Lang et al., 2002; 2004, 2005a, 2005b, 2007, 2009a, 2009b).

It has been discussed recently that BDNF might well signal through phosphoinositol-dependent kinase 3, Akt and glycogen synthase kinase (GSK3) pathways to cause depressive and anxiety symptoms (Beaulieu, 2010), which has been supported also by our own data (Ackermann et al., 2008, 2010; Lang, 2010; Lang and Borgwardt, 2013).

7. Mammalian target of rapamycin (mTOR) signaling

Recent studies investigating the medial prefrontal cortex show that the synaptogenic and antidepressant-like effects of a single standard dose of ketamine in rodents are dependent upon the activation of the mTOR complex 1 signaling pathway together with inhibitory phosphorylation of GSK-3, which relieves its inhibitory influence on mTOR (Liu et al., 2013). Indeed, one of the pathways required for the NMDA actions is the mTOR signaling pathway. The mTOR signaling pathway is disturbed in the prefrontal cortex from subjects diagnosed with major depressive disorder (Chandran et al., 2013). Chronic unpredictable stress decreases the phosphorylation levels of mTOR and its downstream

signaling components, i.e., ERK-1/2, Akt-1 and GluR1 (Chandran et al., 2013). However, in an own study, we observed mood changes in patients using the mTOR inhibitor everolimus (Lang et al., 2009a, 2009b; Lang and Borgwardt, 2013). It is of interest to note that some antidepressants, including 5-HT2C receptor antagonists, citalopram and electroconvulsive seizures increase mTOR levels (Elfving et al., 2013; Opal et al., 2014). Sertraline, a serotonin reuptake inhibitor, and imipramine, a tricyclic antidepressant both have antiproliferative effects that are mediated by inhibition of mTOR (Jeon et al., 2011; Lin et al., 2010).

Furthermore, there is evidence that suggests rapamycin administration alone and the subsequent inhibition of mTOR signaling is capable of inducing antidepressant-like effects in the rat forced swim test (Cleary et al., 2008; Lang and Borgwardt, 2013) and in humans (Lang et al., 2009a, 2009b).

Interestingly, it was found recently that the synaptogenic and antidepressant-like effects of ketamine were potentiated when given together with a single dose of lithium chloride or a preferential GSK-3β inhibitor (Liu et al., 2013). Effects, exerted by ketamine and an additional GSK-3β inhibitor, include the rapid activation of the mTOR signaling pathway, an increased inhibition of the phosphorylation of GSK-3β, an increased synaptic spine density, an increased excitatory postsynaptic currents in mPFC layer V pyramidal neurons and an antidepressant responses that persist for up to 1 week in the forced swim test model of depression (Liu et al., 2013). However, the possible risks involved in the stimulation of a pathway, which is implicated in disease states where growth is deregulated and homeostasis is compromised, such as cancer, metabolic diseases and aging, should not be underevaluated (Zoncu et al., 2011).

8. Antidepressant strategies based on interaction with the glutamatergic system

8.1. NMDA receptor antagonists

Ketamine overcomes glutamate synaptic depression by stimulating synaptic glutamate release and enhancing synaptic AMPA receptor signaling and blocking extrasynaptic NMDA receptors (Krystal et al., 2013). The hypothesis that ketamine might increase synaptic release is supported by a number of observations related to the effects of NMDA receptor antagonists: they reduce the activation of GABA neurons in hippocampus and prefrontal cortex, they increase neuronal firing and raise extracellular glutamate levels in prefrontal cortex and they increase cortical glutamate levels and activation (Krystal et al., 2013).

A single subanesthetic dose (0.5 mg/kg) of the NMDA receptor antagonist ketamine causes a rapid antidepressant effect within hours in treatment-resistant patients with major depressive disorder (Diazgranados et al., 2010). The rapid antidepressant response after ketamine administration in treatment-resistant depressed patients suggests a possible new approach for treating mood disorders compared to the weeks or months required for standard medications (Li et al., 2010). Indeed, the described effect intensity of ketamine on clinical psychopathology scores is not comparable to any other known glutamatergic substance, and in several studies, it reaches effects over 70% response in clinical studies: Wang et al. (2012) (79%), Okamoto et al. (2010) (78%), Jarventausta et al. (2013) (71%), Kranaster et al. (2011) (76%). After a single infusion, ketamine demonstrated rapid antidepressant effects in a two-site, parallel-arm, randomized controlled trial compared to an active placebo control condition (Murrough et al., 2013). In detail, patients with treatment-resistant major depression ($N = 73$) had greater improvement in the ketamine group than a midazolam treated group 24 h after treatment (Murrough et al., 2013). In a further study of Berman et al. (2000), subjects with depression evidenced significant improvement in depressive symptoms within 72 h after ketamine but not placebo infusion (Berman et al., 2000).

However, the widespread use of ketamine as a fast-acting antidepressant in routine clinical settings is curtailed by its abuse potential as well as possible psychotomimetic and cognitive side effects. Also, the fading of ketamine's antidepressant effects is a clinical problem, which has been hypothesized to be mitigated by additional treatment with GSK-3 inhibitors (Liu et al., 2013).

However, the fast and high efficacy of ketamine raises the question of whether other clinically better tolerated NMDA receptor antagonists might possess similar antidepressant properties and provides a unique opportunity for the investigation of mechanisms that mediate clinically relevant behavioral effects and to produce a rapid and long-lasting antidepressant response in patients with depression. However, several agents that increase synaptic levels of glutamate or act at postsynaptic sites to enhance glutamate receptor signaling have been investigated but the clinical antidepressant effect of ketamine has not been reached so far and seems to require a burst of glutamate transmission.

The NMDA receptor antagonist dextromethorphan has also been discussed as a potential rapid-acting antidepressant (Lauterbach, 2011).

AZD6765, an NMDA channel blocker, was assessed for its antidepressant-like qualities in a double-blind crossover study involving 22 subjects. Although no psychotomimetic effects of this compound were reported, depressive symptoms were alleviated only for the first 2 h following infusion (Zarate et al., 2013).

Zinc and magnesium are potent antagonists of the NMDA receptor complex and the deficiency of both of them may lead to functional NMDA receptor hyperactivity. Magnesium gates the activity of NMDA receptors and indeed magnesium restriction is associated with reduced amygdala-hypothalamic protein levels of GluN1-containing NMDA complexes (Ghafari et al., 2014). In suicide victims, the potency of zinc and magnesium to inhibit MK-801 binding to NMDA receptors was decreased and lower concentrations of magnesium have been found in suicide tissue (Sowa-Kućma et al., 2013).

In a double-blind, randomized and placebo-controlled study, zinc supplementation was shown to improve mood states, reduce anger-hostility score and depression-dejection score (Sawada and Yokoi, 2010). A preclinical study investigated the effect of magnesium treatment in the chronic mild stress model of depression in rats. In this study, magnesium reduced depressive symptoms and increased the level of GluN2B and PSD-95 in the prefrontal cortex (Pochwat et al., 2014). High doses of magnesium in animal models can lead to synaptic sprouting and synaptic strengthening (Murck, 2013).

A randomized clinical trial showed that magnesium was as effective as the tricyclic antidepressant imipramine in treating depression (Barragan-Rodríguez et al., 2008). Oral administration of magnesium leads to a strong antidepressant effect in animals and in humans (Eby and Eby, 2010). Also, ketamine acts to increase brain magnesium levels (Murck, 2013), and ketamine action has been hypothesized to be associated with magnesium levels (Murck, 2013). In conclusion, it has been hypothesized that magnesium should be prescribed at least for treatment-resistant depression (Eby and Eby, 2010).

Other neurotransmitter systems that indirectly increase glutamate via regulation of tonic firing of GABAergic interneurons may also produce ketamine-like effects. For example, the roles of glutamate, synaptogenesis, and mTOR signaling in the rapid antidepressant actions of scopolamine, a muscarinic receptor antagonist (Drevets et al., 2013), are currently under investigation. Recently, it has been reported that the antimuscarinic agent, scopolamine, produces a rapid and robust antidepressant effect in currently depressed male and female patients with major depressive disorder or bipolar disorder (Drevets and Furey, 2010a, 2010b; Furey and Drevets, 2006). In a recent review, data from a series of randomized, double-blind, placebo-controlled studies involving subjects with unipolar or bipolar depression treated with parenteral doses of scopolamine show robust antidepressant effects versus placebo, which were evident within 3 days after the initial infusion (Drevets et al., 2013). The onset and duration of the antidepressant response of scopolamine has been led back to involve

neurobiological systems beyond the cholinergic system (Drevets et al., 2013). In a recent double-blind randomized controlled crossover study cholinergic and visual processing dysfunction in the pathophysiology of major depression measured via Blood-Oxygen-Level-Dependent (BOLD) response (scopolamine versus placebo) suggested to provide a useful biomarker for identifying depressive patients who will respond favorably to scopolamine (Furey et al., 2013).

Interestingly, memantine as an NMDA antagonist seems to lack substantial efficacy as an augmentation treatment for major depressive disorder. In a randomized, double-blind, placebo-controlled trial of memantine as an augmentation treatment for patients with DSM-IV major depressive disorder, participants receiving memantine did not show a statistically or clinically significant change in depressive symptoms when compared to placebo (Smith et al., 2013). Although ketamine and memantine effectively block NMDA-receptor-mediated excitatory postsynaptic currents, key functional differences between ketamine and memantine have been found. In contrast to ketamine, memantine does not inhibit the phosphorylation of eukaryotic elongation factor 2 or augment subsequent expression of BDNF, which are critical determinants of ketamine-mediated antidepressant efficacy (Gideons et al., 2014). These results demonstrate significant differences between the efficacies of ketamine and memantine on NMDA-receptor-mediated neurotransmission that have impacts on downstream intracellular signaling.

Guanosine is an extracellular signaling molecule, which has been implicated in antidepressant-like activity via the modulation of glutamatergic neurotransmission (Bettio et al., 2012). Indeed, its effect seems to be mediated through an interaction with NMDA receptors and mTOR pathways (Bettio et al., 2012). Also, the antidepressant effect of adenosine is likely dependent on the inhibition of NMDA receptors mediated by the activation of adenosine A1 receptors (Kaster et al., 2012).

Pioglitazone seems to exert antidepressant-like effects in the forced swimming test in mice by a reduction of NMDA-mediated calcium currents in hippocampal neurons (Salehi-Sadaghiani et al., 2012). Also, in humans pioglitazone monotherapy or adjunctive therapy decreased depression symptom severity, reduced insulin resistance and reduced inflammation in a 12-week, open-label, flexible-dose study (Kemp et al., 2012). In a recent 6-week double-blind study, pioglitazone was superior to metformin in reducing Hamilton Depression Rating Scores at the end of the study while homeostatic model assessment of insulin resistance did not differ between the two groups (Kashani et al., 2012). This study might suggest that pioglitazone improves depression with mechanisms largely unrelated to its insulin-sensitizing action (Kashani et al., 2012).

Amantadine inhibits NMDA receptors by accelerating channel closure during channel block (Blanpied et al., 2005). It has been discussed to exert antidepressant properties firstly by Vale (Vale et al., 1971). However, the only randomized placebo-controlled trials on amantadine showed a significant effect in treating fatigue in multiple sclerosis patients but this benefit was not due to changes in sleep, depression or neurologic disability (Krupp et al., 1995).

9. Partial NMDA receptor agonists

D-Cycloserine is a partial agonist at the glycine B co-agonist site of NMDA receptors (GluN2A and GluN2B subunits) and an agonist of NMDA receptors containing the GluN2C and GluN2D subunits (Dravid et al., 2010). D-Cycloserine was firstly described as a tuberculosis antibiotic in 1959, where it produced mood improvement predominately within 2 weeks in 30 of 37 tuberculosis patients suffering from depression (Crane, 1959, 1961). Recently, the first placebo-controlled replication of this finding reported progressive improvement with D-cycloserine over 6 weeks of treatment (Heresco-Levy et al., 2013). In light of the antidepressant efficacy of NMDA receptor antagonists, D-cycloserine may have reduced symptoms of depression by attenuating the function of NMDA receptors bearing GluN2A or GluN2B subunits.

D-Serine is produced through isomerization of L-serine by serine racemase, either in neurons or in astrocytes. It is released by astrocytes by an activity-dependent mechanism. D-Serine interacts with the GluN1 NMDA receptor unit. Mice lacking GluN1 expression in the forebrain exhibit a depression-like phenotype and do not respond to D-serine treatment (Malkesman et al., 2012).

The behavioral effects of a single, acute D-serine administration reduced immobility in the forced swim test, rescued sexual reward-seeking deficits caused by serotonin depletion and reversed learned helplessness behavior, as measured by escape latency, number of escapes and percentage of mice developing learned helplessness behavior (Malkesman et al., 2012). Elevated brain D-serine levels in serine racemase transgenic mice seem to reduce the proneness towards depression-related behavior (Otte et al., 2013). Chronic dietary D-serine supplement might improve mood disorders (Otte et al., 2013).

Glyx-13 is another promising NMDA receptor glycine-site functional partial agonist. In rats, it induced antidepressant-like effects in the Porsolt, novelty induced hypophagia and learned helplessness tests (Burgdorf et al., 2013).

1-Aminocyclopropanecarboxylic acid (ACPC) is a high-affinity partial agonist at the glycine B site of the NMDA glutamate receptor. Parenterally and orally administered ACPC was equipotent in reducing immobility in the forced swim test (Trullas et al., 1991). In the elevated plus maze, ACPC was active for 1-2 h after parenteral administration. These findings suggest that ACPC may constitute a novel class of antidepressant agents (Trullas et al., 1991).

10. Selective NMDA receptor subtype 2B (NR2B) antagonists

Non-competitive NMDA receptor antagonists like ketamine and PCP can produce psychotomimetic effects; therefore, it has been discussed that subtypeselective, rather than pan blockers of the NMDA receptor, could maintain an efficacious profile and minimize the adverse effects associated with blocking this receptor. In this regard, NR2B receptors are of particular interest. Selective NMDA receptor subtype 2B (NR2B) antagonists produce antidepressant behavioral and synaptogenic actions, but they are not as rapid and not as effective as the effect of ketamine (Li et al., 2010).

In a small, randomized, double-blind, placebo-controlled, crossover pilot study an oral formulation of the selective NMDA NR2B antagonist MK-0657 in patients with treatment-resistant depression has been evaluated (Ibrahim et al., 2012a, 2012b). Because of recruitment challenges and the discontinuation of the compound's development by the manufacturer, only 5 of the planned 21 patients completed both periods of the crossover administration of MK-0657 and placebo. Significant antidepressant effects were observed as early as day 5 in patients receiving MK-0657 compared with those receiving placebo, as assessed by the Hamilton Depression Rating Scale and Beck Depression Inventory (Ibrahim et al., 2012a, 2012b). However, no improvement was noted when symptoms were assessed with the Montgomery–Asberg Depression Rating Scale, the primary efficacy measure (Ibrahim et al., 2012a, 2012b).

Another NR2B subunit-selective NMDA receptor antagonist, CP-101,606 (traxoprodil), has been evaluated in a randomized, placebo-controlled, double-blind study. On the main outcome measure (Montgomery–Asberg Depression Rating Scale total score at day 5), CP-101,606 produced a greater decrease than did placebo. The Hamilton Depression Rating Scale response rate was 60% for CP-101,606 versus 20% for placebo. Seventy-eight percent of the CP-101,606-treated responders maintained response status for at least 1 week after the infusion. CP-101,606 was generally well tolerated and capable of producing an antidepressant response (Preskorn et al., 2008). However, CP-101,606 also produced dissociative effects in 6 of 15 patients (Preskorn et al., 2008).

In preclinical models, the GluN2B specific antagonist Ro25-6981 evoked robust antidepressant-like effects (Lima-Ojeda et al., 2013). Moreover, Ro25-6981 did not cause hyperactivity as displayed after treatment with unspecific NMDA receptor antagonists, a correlate of psychosis-like effects in rodents. The NR2B antagonist Ro25-6981 reversed stress-induced hippocampal LTP and had behavioral antidepressant-like effects in the forced swim test.

11. Glutamate release inhibitors

Studies have shown that drugs, which increase glutamate clearance, can prevent or reverse the effects of chronic stress and chronic glucocorticoid exposure and exert antidepressant effects in animal models of depression (Banasr et al., 2010; Gourley et al., 2011; Mineur et al., 2007).

Riluzole increases glutamate uptake by increasing the expression of glutamate transporters (Sanacora et al., 2004; Zarate et al., 2004). In a randomized placebo-controlled and double-blind study in treatment-resistant depressive patients, the efficacy of the glutamate-modulating agent riluzole in preventing post-ketamine relapse has been tested recently (Mathew et al., 2010). However, riluzole did not prevent relapse in the first month following ketamine, i.e., an interim analysis found no significant differences in time to relapse between riluzole and placebo groups with 80% of patients relapsing on riluzole vs. 50% on placebo (Mathew et al., 2010). Another randomized placebo-controlled double-blind study examined riluzole as add on to ketamine treatment but again suggested that the combination of riluzole with ketamine treatment did not significantly alter the course of antidepressant response in comparison to ketamine alone (Ibrahim et al., 2012a, 2012b). However, in an open-label study, riluzole appeared to be an effective, well-tolerated and rapidly acting anxiolytic medication for some patients with generalized anxiety disorder (Mathew et al., 2005).

Sarcosine is a glycine I transporter inhibitor which enhances NMDA function. In a preclinical study, sarcosine decreased the time to immobility in the forced swim test and tail suspension test and reduced the latency to feed, which are classical antidepressant-like properties (Huang et al., 2013). In a recent clinical study, patients were randomly assigned to citalopram or sarcosine. Patients who received sarcosine were more likely to stay in the study and more likely to remit, and sarcosine treatment produced a more rapid and greater improvement than treatment with citalopram and was connected with less side effects (Huang et al., 2013).

Lamotrigine is a presynaptic glutamate release inhibitor (Normann et al., 2002; Obrocea et al., 2002), approved for maintenance treatment of bipolar type I disorder and as an antiepileptic for seizure disorders (Geddes et al., 2009; Goodnick, 2007). Trials have demonstrated that lamotrigine has beneficial effects on depressive symptoms in the depressed phase of bipolar disorder (Geddes et al., 2009).

12. AMPA receptor enhancers

Positive AMPA receptor potentiating agents produce antidepressant behavioral responses in rodents and stimulate mTOR signaling in cultured cells (Jourdi et al., 2009; Sanacora et al., 2008). A relative increase in AMPA receptor activation may be critical to the antidepressant effects also of NMDA antagonists like ketamine and others, which additionally enhance AMPA receptor activation (Autry et al., 2011; Koike et al., 2011; Li et al., 2010).

Enhancement of AMPA receptor function by the AMPA receptor potentiator LY392098 functioned like classic antidepressants by reducing weight loss, deterioration and immobility in the tail suspension test in mice. However, this substance did not restore sucrose preference and did not reduce anxiety in stressed mice (Farley et al., 2010). The same substance reduced immobility in the forced swim test and in the tail suspension test in a dose-dependent manner (Li et al., 2001). Also, the AMPA receptor potentiating drug LY451646 has been hypothesized to exert antidepressant effects at least in BDNF heterozygous mice (Lindholm et al., 2012).

Tianeptine increases phosphorylation of glutamate receptor subtypes in circumscribed brain regions (Qi et al., 2009; Svenningsson et al., 2007), normalizes the glutamatergic tone in the amygdala and the hippocampus, normalizes the stress-induced changes in the amplitude ratio of NMDA receptor to AMPA/kainate receptor-mediated currents (Kole et al., 2002) and increases the phosphorylation of the CaMK II-PKC site of the GluR1 subunit of AMPA receptors (Svenningsson et al., 2007). It provides rapid relief of depressive symptoms in mild to severe major depression, where it alleviates anxious symptoms (Guelfi et al., 1989; Invernizzi et al., 1994; Lepine et al., 2001). When administered several hours after stress exposure, tianeptine overcomes the block of hippocampal LTP induction by inescapable stress (Shakesby et al., 2002).

Aniracetam is a pyrrolidinone-containing nootropic compound, which behaves as a dual allosteric positive modulator of AMPA-sensitive and metabotropic glutamate receptors in a variety of systems, including intact brain tissue and cultured neurons (Nicoletti et al., 1992). Indeed, this experimentally observed potentiation of glutamatergic activity by aniracetam provides the molecular explanation for its clinical efficacy as cognition enhancer (Knapp et al., 2002; O'Neill et al., 2004). Aniracetam seems to exert certain long-term effects on geriatric depression (Koliaki et al., 2012). However, a significant effect of aniracetam on severe clinical depression has to be proven in future clinical studies.

13. Regulators of metabotropic glutamate receptors

Adaptive upregulation of metabotropic mGlu5 receptors may be a common change induced by several antidepressant drugs, such as escitalopram, reboxetine, milnacipran, moclobemide and imipramine as been suggested recently (Nowak et al., 2014).

Several lines of evidence suggest an antidepressant-like activity for 3-((methyl-1,3-thiazol-4-yl)ethynyl)-pyridine, a highly selective, non-competitive antagonist of metabotropic glutamate receptors subtype 5 (Palucha et al., 2007). Antidepressant-like activity of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), which blocks mGlu5 receptors was found in rats (Wieronska et al., 2002) and mice (Belozertseva et al., 2007).

Blockade of mGluR2/3 receptors, which are located presynaptically and regulate the release of glutamate, produces rapid behavioral responses that require mTOR signaling (Dwyer et al., 2012; Koike et al., 2011).

Pomaglumetad methionil (LY2140023 monohydrate) is a methionine amide prodrug of the active compound LY404039, acting as a selective and potent orthosteric agonist at both mGluR2 and mGluR3 (Conn et al., 2009; Harrison et al., 2008). Initially, this mixed mGluR2/3 agonist showed promise as potential monotherapy for schizophrenia in the proof-of-concept study, consistent with the predictions from preclinical animal studies (Patil et al., 2007).

LY341495 is a mGluR2/3 antagonist and showed preclinical antidepressant-like effects, i.e., reduced immobility in the mouse forced swim test and in the marble burying test. Further, LY341495 had no effects in the elevated plus maze and stress-induced hyperthermia tests in mice but enhanced spatial memory (Bespalov et al., 2008).

MGS0039 is a potent and selective group II metabotropic glutamate receptor antagonist (Chaki et al., 2004). It exerts dose-dependent antidepressant-like effects in the rat forced swim test and in the mouse tail suspension test, however, without apparent effects in the rat social interaction test and in the rat elevated plus maze.

14. Glutamatergic action of 5-HT-Receptors

Indirect modulation of glutamate neurotransmission through the serotonin (5-HT) system may be a viable alternative treatment effect.

Based on localization and function, 5-HT can modulate glutamate neurotransmission at least through the 5-HT1A, 5-HT1B, 5-HT3 and 5-HT7 receptors, which present a rational pharmacological opportunity for modulating glutamatergic transmission without the direct use of glutamatergic compounds (Pehrson and Sanchez, 2014). 5-HT1B receptor agonism increases hippocampal excitatory field potentials through a CaM kinase-dependent pathway (Cai et al., 2013). 5-HT3 receptors are localized in GABAergic interneurons in cortical and hippocampal regions and mediate excitation of GABA neurons (Puig et al., 2004; Reznic and Staubli, 1997). Ondansetron significantly suppresses the firing rate of CA1 hippocampal GABAergic interneurons and concomitantly increases the firing rate of glutamatergic pyramidal cells by disinhibition (Puig et al., 2004; Reznic and Staubli, 1997).

15. Glutamatergic action of corticosteroids and noradrenaline

Exposure to stress rapidly elicits the release of noradrenaline and corticosteroids in the brain (Joels and Baram, 2009). The induction of LTP is greatly impaired after a prolonged period of mild stress or chronic corticosteroid exposure. This exposure inhibits glutamatergic synaptic transmission in the prefrontal cortex and reduces the surface expression of glutamate receptors (GluN1 and GluA1). Synaptic NMDA receptors and AMPA receptors are lost (Yuen et al., 2011) and levels of GluN2B and GluA2/3 are decreased (Gourley et al., 2009). Brief exposure to corticosterone and/or noradrenaline may underlie the enhanced memory formation of emotionally arousing events (Krugers et al., 2012), where excitatory synaptic transmission and synaptic insertion of AMPA receptors is enhance thereby leading to consolidation and expression of fearful memories. In contrast, chronic stress and low maternal care can determine processing of emotional information later in life via a persistent regulation of excitatory synaptic function and persistently enhance hippocampal NMDA receptor function (Bagot et al., 2012) via enhancing GluN2B-containing NMDA receptors. This is accompanied by suppressed synaptic plasticity (Bagot et al., 2009).

16. Future perspective

Drugs targeting the glutamatergic system might open up a promising new territory for the development of drugs to meet the needs of patients with major depression. Based on glutamatergic signaling, a number of therapeutic drugs have been studied in animal research and might gain interest in the future. Hopefully, more clinical (human) studies will be performed in future to translate this already gained preclinical knowledge successfully in clinical practice.

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