

The “blue” side of glutamatergic neurotransmission: NMDA receptor antagonists as possible novel therapeutics for major depression

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In spite of the wide-ranging, continuously expanding arsenal of antidepressants and intensive research on depression, the treatment of severe, recurrent mood disorders as well as antidepressant-resistant refractory mood disturbances has not yet entirely been solved. In this article we attempt to review some data from the growing body of evidence that underlie the presumed implication of the glutamatergic neurotransmission in severe mood disorders and thereby some strategies allowing reinstatement of the normal functioning of the glutamatergic system, particularly through *N*-methyl-D-aspartate (NMDA) receptors. Thus, here we focus on one of the most promising ones, the NMDA receptor-modulating agents including competitive NMDA antagonists, glycine site partial antagonists and channel site antagonists: high- and low-affinity non-competitive NMDA receptor blockers. The glutamate-modulating therapies that specifically affect this system, above all low-affinity non-competitive NMDA receptor antagonists such as amantadine and its derivative memantine which are clinically well tolerated and currently used in other indications hold considerable promise for the development of new, improved antidepressants to treat severe, recurrent and refractory mood disorders.

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INTRODUCTION: CLINICAL FEATURES AND AVAILABLE THERAPEUTICS IN DEPRESSION

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BPD) are overwhelming, often life-threatening psychiatric diseases that affect millions of people worldwide. Patients afflicted with recurrent mood disturbances experience substantial suffering with functional impairment leading to social and occupational disability. For many patients, the long-term outcome is unfavourable, with relapses, incomplete inter-episode syndromal and functional recovery, persistent residual symptoms, progressive wane in psychosocial functioning (Tohen et al., 2000; Fagiolini et al., 2005), and potentially higher risk for suicide. Untreated or ineffectively treated mood disorders and markedly depression are considered, in fact, as principal clinical substrates of suicidality (Angst et al., 1999; Rihmer & Kiss, 2002; Rihmer & Akiskal, 2006; Rihmer et al., 2008).

Recurrent mood disorders, previously regarded as good prognosis conditions, can therefore be chronic, progressive illnesses that have as profound an impact on overall functioning with temporary and/or permanent disability as other serious, chronic medical illnesses, like cerebrovascular disease, HIV/AIDS or chronic obstructive pulmonary disease. Indeed, major depression is ranked as one of the ten leading conditions for global diseases burden considering the number of disability adjusted life years (Lopez et al., 2006). Growing evidence on the underlying etiology and neurobiology indicates that severe mood disorders are associated with impairments of structural and functional plasticity in specific brain areas. Neuroplastic events, impairment of neuroplasticity and cellular resilience are likely involved in the pathophysiology of mood disturbances, corresponding to reduced cortical volume related to reductions in neuronal and glial size and/or density, predominantly in prefrontal cortical regions, amygdala, hippocampal areas and

basal ganglia. Thus, recent evidence and appreciation reshape views about severe mood disorders which are contemporarily conceptualized as complex interactions of various susceptibility genes and environmental factors such as severe and/or prolonged stress, implicating also a constellation of cognitive, motoric, endocrine and vegetative dysfunctions, which finally lead to the phenotypic expression of severe and often progressive mood disturbances (Manji et al., 2003).

In spite of the wide range of pharmacotherapies currently available for the treatment of depression, a relatively small portion of the patients who receive adequate antidepressant therapy will achieve complete recovery. A recent effectiveness study revealed that only about 30% of patients with nonpsychotic MDD achieved full remission with citalopram medication after appropriate duration of treatment (Trivedi et al., 2006). Another study focusing on the outcomes of depressed patients who have not responded adequately to previous, successive treatment trials found low remission rates (<20%) with a third antidepressant monotherapy and the response rates were also below 20% (Fava et al., 2006). Furthermore, there is mounting clinical and literature evidence that approximately 10% to 20% of adequately treated patients will remain persistently depressed in spite of multiple treatment steps and trials. Treatment-resistance and particularly antidepressant-resistance in major depression is still regarded, thereby, as a serious clinical challenge. Nonetheless, it is indispensable to emphasise that one of the causes of antidepressant-resistance in major depression can be the unrecognized bipolar character of the disorder, including patients with “prebipolar” major depression (O’Donovan et al., 2008) as well as MDD patients with subthreshold bipolarity (Keck et al., 2008; Angst et al., 2010). Antidepressant monotherapy in undetected bipolar or bipolar spectrum depression can result in markedly higher treatment-resistance compared to “pure” unipolar major depression (Ghaemi et al., 2004; Woo et al., 2008). Loss of response or inadequate response to usual and often repeated trials of antidepressants in major depression may indicate, therefore, in special clinical conditions, the underlying bipolar diathesis (Rihmer & Gonda, 2011).

It is important to underline that the available, continuously expanding arsenal of antidepressants still have limitations regarding efficacy, tolerability and side effects. The advantages of antidepressant drugs over another(s) are generally based upon side-effect profiles, but there are no substantial differences and advances in their efficacy and the rapidness of the

antidepressant effect (Sen & Sanacora, 2008). Thus, in spite of the availability of newer antidepressants with ameliorated adverse-effect facets, these medications are widely similar therapies in as much as they have considerable latency in onset of action and they have essentially the same mechanism of action. Following the identification of TCAs and monoamine oxidase inhibitors (MAOIs), the majority of antidepressants, among them the widely used SSRIs and SNRIs, act primarily through monoaminergic mechanisms, modulating principally the serotonergic and noradrenergic systems. Accordingly, neurobiological and clinical studies of mood disorders over the past decade have excessively focused on the monoaminergic systems, attempting to elucidate the underlying pathophysiology and to reveal the specific alterations in these neurotransmitter systems. The monoaminergic pathways abundantly project to the striatal, limbic and prefrontal cortical structures and are widely distributed throughout these neuronal circuits which are thought to be responsible for the behavioural and visceral aspects of mood disorders (Drevets, 2001; Nestler et al., 2002). Depressive symptom clusters are considered, thereby, to be associated with different neurotransmitter systems and neuroanatomic structures, this approach allowing a differential examination of the major symptoms of depression (Faludi et al., 2010). Although dysfunction in the monoaminergic neurotransmitter systems is likely involved in the pathophysiology of mood disorders and it probably mediates certain aspects of the disorder, there has been a growing appreciation that it might represent the sequels of other, more pivotal abnormalities. The majority of antidepressants initially act by enhancing the intrasynaptic levels of biogenic amines via inhibiting monoamine reuptake and/or metabolism but the amelioration of core depressive symptoms is observed only after continuous, chronic administration, suggesting that alterations in downstream cascades, enduring adaptive changes in neuronal processes are finally responsible for their therapeutic effects. This timing, the lag period of onset of action of existing antidepressant agents supports the assumption that dysfunction within the monoaminergic systems is subsequent to other, more incipient abnormalities (Payne et al., 2002). The delayed adaptive and therapeutic effects of classical amine-modulating antidepressants are supposed to be mediated by intracellular signalling pathways as well as the glutamatergic system (Skolnick et al., 2001; Manji et al., 2003). Adaptive processes in the adult central nervous system in response to external and internal stimuli converging

with neurotrophic signalling cascades, outlined as neuroplasticity include alterations in the cytoskeletal network and consequently, in actin-based dendritic spine morphology, maintenance of spine architecture, synaptic structure and function, synaptic remodelling, neurite outgrowth, synapto- and neurogenesis (Matus, 2000; Carlisle & Kennedy, 2005; Tada & Sheng, 2006; Kojima & Shirao, 2007). Several lines of evidence articulate the unequivocal role of the glutamatergic system in neuroplastic events (Mattson, 2008), as well as the relevance of neuroplasticity in mood disorders (Manji et al., 2003). The role of the glutamatergic neurotransmitter system, therefore, should be considered in the biology of mood disorders. Accordingly, increasing preclinical and clinical data suggest that the glutamatergic system is involved in the pathophysiology of mood disorders and mounting evidence appreciate the role of glutamate in the mechanism of antidepressant action (Maeng & Zarate, 2007).

OVERVIEW OF THE GLUTAMATERGIC SYSTEM

Glutamate is the most abundant excitatory neurotransmitter in the mammalian central nervous system, and glutamate receptors, as the principal mediators of excitatory synaptic transmission, are prominently implicated in several, normal and pathological brain functions. Glutamate has been shown to exert a crucial role in the developing and the mature nervous system since it regulates neurogenesis, axonal sprouting, synaptogenesis, programmed cell death (apoptosis) and neuron survival. It is also well-established that glutamate can be excitotoxic under a variety of experimental and pathological conditions, leading to rapid or protracted neuronal cell death. Excessive and prolonged exposition to glutamate, especially when energy availability is impaired and oxidative stress increases, induces distinct cellular phenomena of excitotoxicity, which has exhaustively been proved to be involved in epileptic seizure-induced neuronal death, stroke, traumatic brain injury, as well as in certain neurodegenerative disorders such as Huntington's disease and amyotrophic lateral sclerosis (ALS) (overviewed in Mattson, 2008). A precise regulation of the glutamatergic excitation is thereby indispensable to assure neuroplasticity and to avoid the occurrence of excitotoxicity. Glutamate acts via cell surface receptors which are linked to Ca^{2+} influx and elevation of intracellular Ca^{2+} levels, resulting in kinase- and protease-mediated rapid, as well as transcription-dependent delayed adaptive responses that modify neuronal function and morphology. Glutamate exerts

prompt changes in dendritic membrane excitability, cytoskeletal dynamics and architecture, whereas delayed responses involve transcriptional changes of genes contributing to neuroplastic events. Local, rapid changes in dendritic function and structure, rapid dendritic spine reorganization have recently been shown to be essential for short- and long-term plasticity and to be related to cognition and memory (Kasai et al., 2010). Glutamate also elicits delayed transcriptional changes, including production of neurotrophic factors, which, on the other hand, interact with glutamate to regulate activity-dependent neuroplasticity (Mattson, 2008).

Glutamate is the major excitatory neurotransmitter in the hippocampal formation: the main glutamatergic afferents to the hippocampus are represented by the perforant pathway originating in the entorhinal cortex and terminating in dentate gyrus. The dentate gyrus is the target for the majority of the glutamatergic entorhinal afferents by providing sensory information of multiple modalities about the external world (Freund & Buzsáki, 1996). The dentate gyrus is considered to be the first element in the hippocampal synaptic chain that additionally includes synapses between mossy fibers and CA1-CA3 areas, and synapses of the Schaffer collaterals with CA1 pyramidal cells/subiculum. There is extensive data that the neurotransmitter for members of this hippocampal circuit is glutamate. Glutamate, as the principal excitatory neurotransmitter in the hippocampus, has a key role in long-term potentiation (LTP), memory and learning, synaptic plasticity, but also in excitotoxic and neurodegenerative processes. LTP, the cellular basis of rapid formation of new memories, is a property of certain synapses, including those of the mossy fibers and the Schaffer collaterals of the hippocampus; long-term alteration of synaptic transmission occurs at excitatory synapses, which is thought to be the basis of specific associative memory. Both LTP and long-term depression (LTD) depend on activity-dependent Ca^{2+} increase in the postsynaptic neurons, and enhancement or decrease in the LTP/LTD phenomenon is the cellular substratum of synaptic plasticity. Synaptic plasticity depends, therefore, on the increase of intracellular Ca^{2+} level in the postsynaptic neuron, which occurs principally through the glutamate receptors of the *N*-methyl-D-aspartate (NMDA) subtype and the voltage-dependent Ca^{2+} channels. In particular, glutamate and NMDA receptors play an important role in hippocampal functional changes and synaptic plasticity, including synapse formation in CA1 region (Wooley et al., 1997; McEwen,

2001), regulation of adult neurogenesis of dentate gyrus granule cells (Cameron et al., 1995; Gould & Tanapat, 1999) or remodeling of apical dendrites in CA3 area (McEwen, 2001). Increasing evidence suggests that alterations in the glutamatergic system and particularly in the NMDA receptor function likely contribute to deficiencies in hippocampal synaptic plasticity and, thereby, cell loss and/or atrophy that will lead to morphometric changes demonstrated in patients with severe, recurrent and chronic mood disorders (Sapolsky, 2000; Maeng & Zarate, 2007).

HIPPOCAMPAL GLUTAMATERGIC NEUROTRANSMISSION – RELEVANCE TO MOOD DISORDERS

Recent brain imaging studies and complementary postmortem investigations in patients with severe, prolonged mood disorders have found structural, morphometric changes, indicative of either neuronal or glial cell loss and/or atrophy, preeminently in the hippocampal formation, but also in the amygdala, prefrontal cortical regions and anatomically related parts of the striatum and thalamus (Manji et al., 2003; Sapolsky, 2000). For example, volumetric MRI studies from patients with MDD found about 10% to 20% reduction in left hippocampal volume, and roughly 10% reduction in right hippocampal volume, and there was a correlation between hippocampal atrophy and total lifetime duration of depression. Additionally, large hippocampal low signal foci also correlated with cumulative depression duration, hinting that repeated stress associated with recurrent depressive states leads to hippocampal injury as reflected in volume loss and/or lesions. One of the most consistent findings of brain imaging studies in MDD is the affected left hippocampus either unilaterally (Bremner et al., 2000; Mervaala et al., 2000) or in the context of bilateral hippocampal volume reduction (Sheline et al., 1996, 1999). Another MRI study reported no significant hippocampal atrophy in patients afflicted with MDD compared to control subjects, but a negative correlation was established between the left hippocampal volume in men and the severity of depression determined by Hamilton Depression Rating Scale baseline values (Vakili et al., 2000). Interestingly, responder women showed significantly higher right hippocampal volume than nonresponders in this study providing further support to a conceivable association between structural substrates and biochemical (hormonal) states as well as the severity of disorder, including resistance to

treatment. In addition, there are data indicating correlation between reduction in left hippocampal grey matter density and impairment of verbal performance in treatment-resistant chronic depression (Shah et al., 1998). These results suggest that hippocampal atrophy is a consequence of depression and atrophy will lead to cognitive deficits. Nevertheless, reversed causality seems to be plausible at least in a subpopulation of patients, raising the issue that (cognitive) consequences of a small hippocampus could predispose toward depression. It was found, for example, that pediatric patients with familial MDD displayed bilaterally reduced hippocampal volume, which may be suggestive of a causative factor for developing MDD (MacMaster et al., 2008). The possible mechanisms which might lead to hippocampal atrophy as well as reduced volumes in other limbic and also prefrontal and frontal cortical structures in severe mood disorders (Sheline et al., 1998; Lai et al., 2000; Bremner et al., 2002) include impairments of structural plasticity such as inhibition of neurogenesis, regression of dendritic processes and loss of neurons, likely by an NMDA-receptor mediated glutamatergic pathomechanism (Sapolsky, 2000; McEwen, 2001). In this context, it is noteworthy that prominent reductions in glial cells in the related brain regions, mainly in the amygdala, medial and orbital prefrontal cortex, could be of particular interest in view of the glial functions. Indeed, there is a growing awareness that glia play crucial roles in the regulation of synaptic glutamate concentrations as well as in releasing neurotrophic factors involved in the development and maintenance of synaptic plasticity (Coyle & Schwarcz, 2000; Ullian et al., 2001). Thus, reduced glia and/or glial dysfunction can be interpreted as consistent and integral phenomena of the glutamate-mediated pathophysiology and altered synaptic plasticity in mood disorders.

Considering the presumed pathogenesis of mood disorders leading to changes in synaptic plasticity, impairments of cellular morphology and functioning in response to various stressors have received substantial attention in recent investigations. There is considerable evidence that severe stressful conditions as well as high glucocorticoid (GC) levels influence cellular morphology, resulting in neuronal atrophy and death in the hippocampus and related limbic regions. Consistent with either neuroimaging or postmortem studies in mood disorders demonstrating atrophy in these areas, stress and stress-induced hippocampal changes have therefore been in the focus of neurobiological studies. Moreover, stress has largely been proved to significantly enhance the risk for the

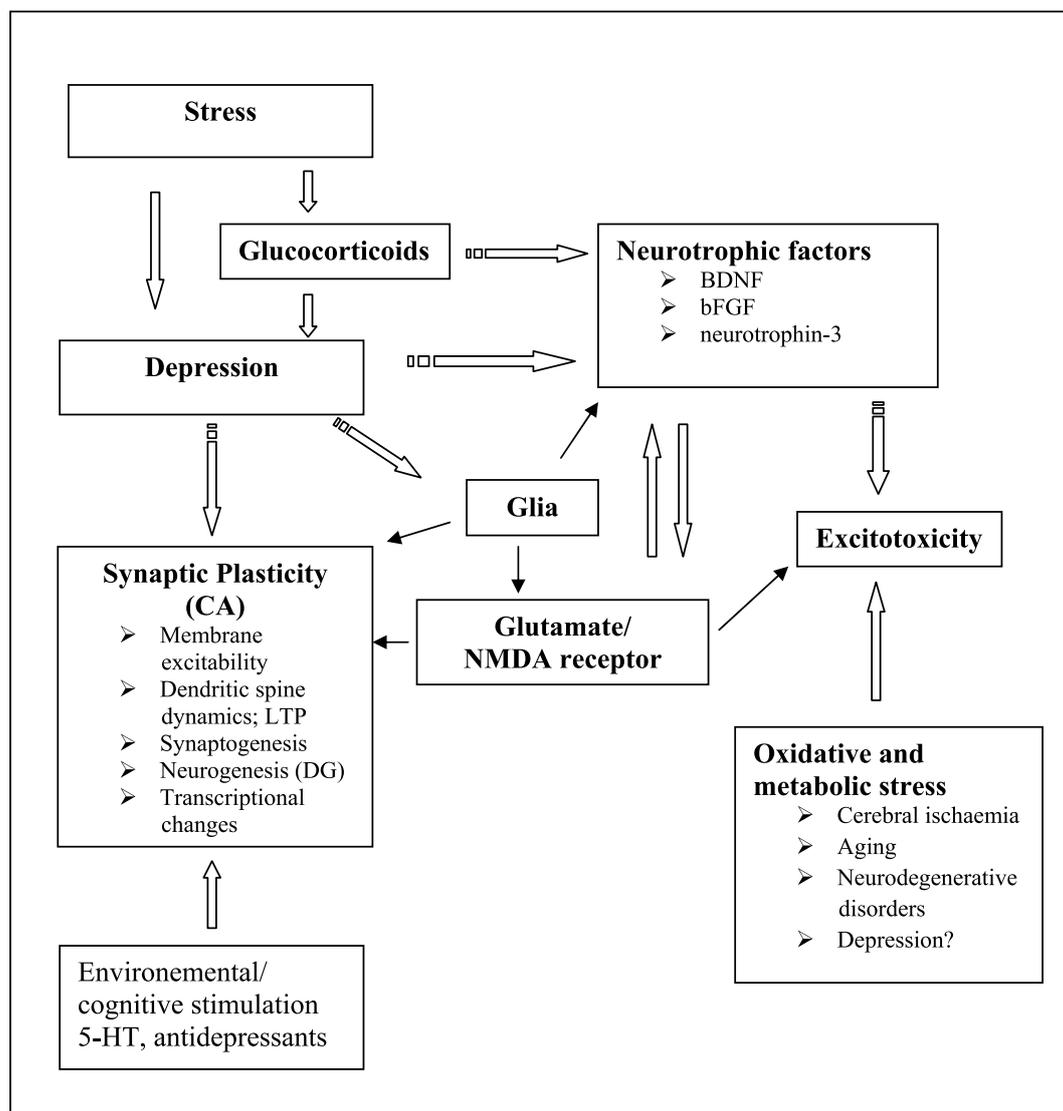


Figure 1 Interactions of glutamate via NMDA receptors with distinct mechanisms of normal and pathological brain functioning with focus on the hippocampus, presumed to be relevant to depression. Arrows show involvement of glutamate/NMDA receptors and glia in prominent CNS processes, thick arrows indicate stimulation/facilitation, whereas striped arrows denote inhibitory effects. BDNF: brain-derived neurotrophic factor, bFGF: basic fibroblast growth factor, CA: Cornu Ammonis, DG: dentate gyrus, 5-HT: 5-hydroxytryptamine (serotonin), LTP: long-term potentiation, NMDA: *N*-methyl-D-aspartate.

onset of mood disorders in individuals predisposed, however, by a genetic vulnerability as mood disorders have definitely a marked genetic background. These appreciations fully support the contention that stress is an influential element in mood disorders. Stress, actually considered as the major precipitating factor of depression and depression are often associated with elevated GC levels. Stress and GCs have been shown to cause atrophy and death of the CA3 pyramidal neurons and to decrease neurogenesis of dentate granule cells, these adverse effects being pre-

eminently mediated by increased glutamate release, through an NMDA-receptor mediated excitatory pathway, and by decreased expression of the brain-derived neurotrophic factor (BDNF) (Duman et al., 1999). Accordingly, blockade of NMDA receptors enhance granule cell proliferation, whereas activation of NMDA receptors inhibits this process (Gould & Tanapat, 1999). Conversely to the stress-induced decrease of neurogenesis, serotonin (5-HT) stimulates granule cell proliferation, at least in part, via up-regulation of BDNF. Therapeutic interventions

that increase serotonergic neurotransmission (antidepressants) may prevent the down-regulation of BDNF and augment neurogenesis and consequently block or reverse hippocampal atrophy (Figure 1).

Given the potential role of glutamate, and particularly, the role of NMDA receptors in neuroplasticity deficiency that may lie behind the pathophysiology of mood disorders, it is of great interest to assess novel treatment strategies in order to reduce glutamate-mediated impairments and to modulate glutamatergic neurotransmission.

The glutamatergic system, and predominantly the different antiglutamatergic agents that modulate different parts of this system have, therefore, received great attention in an effort to diminish glutamate-mediated excitotoxicity and to better regulate glutamate levels in these disorders. Various glutamatergic modulators, including antagonists of glutamate receptors proved to exert important neuroprotective effects in several preclinical paradigms and methodological issues as well as in humans afflicted with these disorders. The neuroprotective properties of glutamate receptor antagonist drugs might be of rising interest also in severe, recurrent, chronic mood disorders, particularly since structural brain imaging studies have revealed morphometric alterations in mood disturbances denotative of cell damage and/or loss. Thus, different antagonists of the NMDA subtype of the ionotropic glutamate receptors as well as other modulators of the glutamatergic system have already been evaluated and are currently being investigated for therapeutic purposes in depression. Existing preclinical and clinical data suggest that NMDA receptor antagonists, apart from and/or in association with their neuroprotective effects, have notable antidepressant properties.

THE NMDA RECEPTOR AS A THERAPEUTIC TARGET

The glutamatergic synaptic connections are based upon the concerted action of α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), *N*-methyl-D-aspartate (NMDA), and kainate (KA) type ionotropic glutamate receptors as well as G-protein-coupled metabotropic receptors. The ionotropic glutamate receptors are ligand-gated ion channels, named for the agonists that selectively activate them: NMDA, AMPA and KA, the latter two groups often referred to together as non-NMDA receptors (Wenthold & Roche, 1998; Molnar & Isaac, 2002). NMDA and AMPA receptors are co-localized in about 70% of

adult excitatory synapses and are densely expressed in the cerebral cortex, hippocampal formation, amygdala, striatum and septum (Bekkers & Stevens, 1989). AMPA receptors are stimulated directly by the presence of glutamate, and their activation opens the channel allowing the inflow of Na^+ ions resulting in fast depolarization of the postsynaptic neuron. Unlike AMPA receptors, activation of NMDA receptors requires the binding of glutamate and the presence of the coagonist glycine or D-serine, as well as depolarization of the membrane to liberate Mg^{2+} from the NMDA receptor channel. The NMDA receptor pore is blocked by Mg^{2+} ion in a voltage-dependent manner and only activation of AMPA receptors at the same synapse, resulting in membrane depolarization can relieve the voltage-dependent Mg^{2+} block, permitting the inflow of Na^+ and Ca^{2+} ions through the pore. It has been argued, thereby, that AMPA receptors are implicated in rapid, moment-to-moment neuronal information transfer, whereas NMDA receptors act primarily as detectors of specific activity patterns that lead to long-term synaptic changes (Molnar & Isaac, 2002).

Under a variety of pathological conditions (e.g. hypoxia, neurodegenerative disorders) the concentration of glutamate in the synaptic spaces excessively increases leading to activation of glutamate receptors and finally to massive, uncontrolled Ca^{2+} influx via NMDA receptor channels which is thought to be responsible for excitotoxicity. NMDA receptors, therefore, play a key role in the integration of intra- and extracellular signalling.

The NMDA receptor channel complex consists of the combination of NR1, NR2 (NR2A-NR2D) and NR3 (NR3A and NR3B) subunits. Glutamate's binding site is localized to the NR2 subunit and the site for the coagonist glycine has been found in the NR1 subunit. It is noteworthy that the polyamine site is also localized to NR1/NR2B and compounds acting on polyamine site can modulate NMDA mediated responses. Inside the ion channel, it has been identified the "s" site and the phencyclidine (PCP) binding site, and the latter is the binding site also for ketamine and dizocilpine (MK-801). As mentioned, Mg^{2+} permanently blocks the receptor channel when the membrane is in the resting state.

Competitive NMDA antagonists

2-amino-5-phosphonovaleric acid (AP5) and 2-amino-7-phosphonoheptanoic acid (AP7) were identified as competitive, selective NMDA antagonists, followed

by a series of other competitive NMDA antagonists, such as D-CPP and D-CPPene. Competitive NMDA antagonists as modulators of the glutamatergic system are experimental drugs used in preclinical studies and their toxicity and/or side effects strongly limit the possible clinical utility. Nevertheless, preclinical investigations with competitive NMDA antagonists provided further evidence for glutamate's involvement in the mechanism of antidepressant action. For example, AP-7 (among other NMDA antagonists) has been shown to imitate the effects of clinically effective antidepressants in inescapable stress models in rats (Trullas & Skolnick, 1990). Another study found that intrahippocampal administration of AP-7 had antidepressant-like properties in forced swim test in rats (Padovan & Guimarães, 2004), indicating that NMDA-antagonism in the hippocampus has stress-attenuating effect. This suggests that NMDA receptors located in the hippocampus are involved in behavioural changes emerging from exposure to uncontrollable stressors, these behavioural changes being related to depressive states in humans.

Glycine site partial antagonists: cycloserine

D-cycloserine is a broad spectrum antibiotic that acts at the glycine site of the NMDA receptor as partial agonist. At low doses D-cycloserine behaves as an agonist, whilst at high doses it has antagonist properties. Preclinical studies with cycloserine found antidepressant-like effects in animal models of depression (Papp & Moryl, 1996; Lopes et al., 1997). Clinical studies heretofore failed to show that this partial antagonist of the NMDA receptor has antidepressant effects in MDD, although it was formerly registered that D-cycloserine (500–1000 mg/day dose) had mood elevating effects in tuberculosis patients (Crane, 1959, 1961). A recent controlled study of D-cycloserine for treatment-resistant MDD did not find it effective as adjuvant therapy, although the drug was well-tolerated and resulted in symptom reduction (Heresco-Levy et al., 2006). However, it has to be considered that the 250 mg/day dose of D-cycloserine employed in this study was probably too low.

Channel site antagonists: high-affinity non-competitive NMDA receptor blockers

Phencyclidine (PCP), ketamine and dizocilpine as channel site antagonists are high-affinity non-competitive NMDA receptor blockers and proved to have

neuroprotective properties against anoxia and seizure-related brain damage (Szakács et al., 2003). The experimental drug dizocilpine (MK-801) was found to have antidepressant properties in preclinical investigations, either alone or in combination with traditional antidepressants of different classes (Maj et al., 1996; Papp & Moryl, 1993; Redmond et al., 1997; Berman et al., 2000). It is of interest that chronic administration of dizocilpine displays antidepressant-like activity in an animal model of depression, but unlike conventional antidepressants, it does not restore the 5-HT and NA neurotransmitter deficits (Redmond et al., 1997), suggesting that the mechanism of antidepressant action of NMDA-antagonism involves other signalling pathways and steps. Ketamine, a derivative of the hallucinogenic drug phencyclidine, clinically used for procedural sedation in emergency medicine and for the induction and maintenance of general anaesthesia, demonstrated also notable antidepressant activity. Thus, administration of ketamine has been shown to exert antidepressant effects in animal models of depression, as well as in humans. Berman et al. (2000) reported that depressed patients experienced significant, rapid (within 72 hours) and relatively sustained improvement in depressive symptoms following ketamine treatment. Similarly, it was shown in a recent study (Zarate et al., 2006) that a single intravenous, subanaesthetic dose of ketamine (0.5 mg/kg) resulted in robust, prompt (within 2 hours), maintained antidepressant effect in treatment-resistant MDD patients. However, treatment with ketamine was associated with side effects, such as dissociation, perceptual disturbances, transient cognitive deficits, euphoria, increased blood pressure and increased libido (Berman et al., 2000; Zarate et al., 2006). The psychotomimetic and euphoric properties of ketamine, therefore, strongly limit its clinical utility.

Low-affinity non-competitive NMDA receptor antagonists

Alike high-affinity open-channel blockers, low-affinity non-competitive NMDA antagonists such as amantadine (1-aminoadamantane), memantine (1-amino-3,5-dimethyladamantane), dextrometorphan ((+)-3-methoxy-N-methylmorphinan) display anticonvulsant and neuroprotective activities (reviewed in Heresco-Levy et al., 2006). Some preclinical and clinical investigations suggest that amantadine and its derivative memantine might have antidepressant properties. Amantadine, a well-tolerated NMDA antagonist, clinically is used as an antiparkinsonian

Table 1 Related NMDA antagonists acting at different sites of the receptor channel complex, supporting the involvement of glutamate in the mechanisms of antidepressant action as well as their potential therapeutic effects

I.	Competitive NMDA antagonists
	2-amino-5-phosphonovaleric acid (AP5)
	2-amino-7-phosphonoheptanoic acid (AP7)
II.	Glycine site partial antagonists
	D-cycloserine
III.	High-affinity non-competitive NMDA receptor blockers
	Phencyclidine (PCP)
	Ketamine
	Dizocilpine (MK-801)
IV.	Low-affinity non-competitive NMDA receptor antagonists
	Amantadine (1-aminoadamantane)
	Memantine (1-amino-3,5-dimethyladamantane)
	Dextrometorphan ((+)-3-methoxy-N-methylmorphinan)

drug due to its dopaminergic properties and it is also applied as an antiviral agent in the treatment and prophylaxis of influenza infection. At high doses, amantadine decreases NMDA receptor function by approximately 50%, an effect attributed to the instability of the drug in the NMDA receptor channel (Parsons et al., 1996; Danysz et al., 1997). Amantadine has been shown to exert antidepressant action in patients with Parkinson's disease as well as in depressed patients (reviewed in Zarate et al., 2002). It is noteworthy, that the prevalence of comorbid depression in Parkinson's disease is substantial, approximates 40% (Reijnders et al., 2008). The antidepressant properties of amantadine in Parkinson's disease, however, are supposed to be related to NMDA antagonism, rather than to its dopaminergic effects. Furthermore, apart from NMDA antagonism and dopaminergic properties, amantadine acts through some other mechanisms as it has serotonergic and noradrenergic activity, blocks monoamine oxidase A and appears to increase beta endorphin levels (reviewed in Huber et al., 1999). A novel aspect of amantadine's action is the antiviral effect on neurotropic Borna disease virus (BDV), which virus is suspected to be associ-

ated with certain forms of depression. Accordingly, amantadine proved to have notable antidepressive efficacy in BDV-infected depressive patients, this effect likely being related to its antiviral property against BDV, a potential etiopathogenetic factor of depressive disorders (Dietrich et al., 2000). These multiple pharmacological effects and modes of action, including that of the NMDA antagonism, could constitute the base of antidepressant activity. Preclinical and clinical studies point to antidepressant properties of amantadine, but heretofore only a limited body of evidence is available and further investigations are necessary to support the possible efficacy of amantadine in MDD.

Memantine, a dimethyl derivative of amantadine, is a clinically well-tolerated non-competitive low-affinity NMDA receptor blocker that easily crosses the blood-brain barrier (Parsons et al., 1999). Memantine has been applied over decades as a treatment for Parkinson's disease and spasticity with minimal side effects and is currently used in the treatment of Alzheimer's dementia since it has been shown to improve cognitive function (Reisberg et al., 2003; Kovács, 2009). It is also being explored as possible treatment for a variety of indications that are supposed to be

related to/results of glutamatergic dysfunction such as different types of dementia, Parkinson's disease, multiple sclerosis, spasticity, tinnitus, neuropathic and chronic pain, epilepsy, alcohol dependency, drug addiction, head trauma. Considering the role of glutamatergic dysfunction in depression, as well as the favourable pharmacological profile, the tolerability and safety of memantine, this NMDA antagonist can be a novel and attractive candidate for the treatment of depression. Moreover, preliminary clinical observations report promising antimanic and mood-stabilizing effects of memantine also in treatment-resistant bipolar disorder, presumably via blockade of NMDA-receptor mediated phenomenon of the sensitization of dopamine D2 receptors (Koukopoulos et al, 2010). Preclinical investigations have described that memantine possesses antidepressant-like properties in animal models of depression. In the forced swim test, memantine (and also amantadine) produced antidepressant-like activity as it decreased immobility time (Moryl & Danysz, 1993). A synergistic (hyper-additive) antidepressant-like effect was observed when imipramine and fluoxetine were administered in combination with memantine in the forced swim test. Interestingly, fluoxetine, which was inactive when given alone, displayed a positive effect when coadministered with aminoadamantanes, such as amantadine and memantine, suggesting that the combination of traditional antidepressants and NMDA antagonists may produce enhanced antidepressant effect (Rogóz et al., 2002). This assumption could be of particular relevance for treatment-resistant depressive patients. A recent double-blind, placebo-controlled clinical trial of memantine found no significant antidepressant effect in subjects with MDD (Zarate et al., 2006), although it is possible that higher doses of memantine or combination of memantine with traditional antidepressants may be effective in the treatment of depression.

CONCLUDING REMARKS

Preclinical and clinical investigations of the glutamatergic neurotransmission recently provide further insight into the etiology and pathophysiology of mood disorders. Thereby, the therapies that specifically affect and modulate this system, and particularly *N*-methyl-*D*-aspartate receptor-modulating agents (Table 1) hold considerable promise for the development of new, improved antidepressants to treat severe, recurrent and either refractory mood disorders. Might a subpopulation of patients afflicted

with severe and difficult-to-treat mood disturbances respond better and/or preferentially to glutamatergic agents? Can NMDA receptor modulators enhance and/or accelerate antidepressant effects of currently available traditional antidepressant drugs? Further and continuing research is indispensable to explore the detailed involvement of the glutamatergic system in mood disorders and to open new perspectives in drug development.

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A glutamáterg neurotranszmisszió „szomorú” vetülete: az NMDA-receptor antagonisták mint új terápiás lehetőségek a major depresszió kezelésében

A széleskörű és folyamatosan bővülő antidepresszívum „fegyvertár”, valamint a depresszió intenzív kutatása ellenére a súlyos, rekurrens hangulatzavarok, illetve az antidepresszívum-rezisztens hangulatbetegségek kezelése nem kellőképpen megoldott. Jelen összefoglalóban megkísérelünk áttekintést nyújtani azon eredményekről, melyek alátámasztják a glutamáterg neurotranszmisszió súlyos hangulatzavarokban feltételezett szerepét, és ezáltal olyan terápiás lehetőségek számára nyitnak utat, melyek a glutamáterg rendszer normális működésének helyreállítását célozzák, mindenekelőtt az *N*-metil-D-aszpartát (NMDA) receptorok révén. A hangsúlyt tehát az egyik legígéretesebb terápiás lehetőségre, az NMDA-receptorok modulátoraira helyezzük, beleértve a kompetitív NMDA-antagonistákat, a glicin kötőhely parciális antagonistáit és az ioncsatorna blokkolókat: a nagy és kis affinitású nem kompetitív NMDA-receptor antagonistákat. A glutamáterg rendszert specifikusan moduláló terápiák, főként a kis affinitású nem kompetitív NMDA-antagonisták, így az amantadin, vagy annak származéka, a memantin, melyek klinikailag jól tolerálható, más kórképekben és indikációkban már alkalmazott készítmények, igen ígéretesnek tűnnek a súlyos, rekurrens, illetve refrakter hangulatzavarok kezelésében, mint új típusú és hatékony(abb) antidepresszívumok.

Kulcsszavak: hangulatzavarok, depresszió, glutamáterg neurotranszmisszió, NMDA-antagonisták, antidepresszívum