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REVIEW ARTICLE

GLUTAMATERGIC NMDA RECEPTORS AS TARGETS FOR THE THERAPY OF DEPRESSION

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ABSTRACT

Glutamate is the major central nervous system excitatory neurotransmitter found in approximately 60% of synapses. While monoamines have been historically emphasized as causal factors in depression, there is growing evidence that glutamate neurotransmission plays a major role. This new evidence has significant implications for the etiopathogenesis and treatment of major depressive disorder. The exact mechanism by which glutamate may contribute towards depressive symptoms is unclear, but recent research suggests that glutamatergic dysregulation is mediated via glutamate NMDA receptors. Preclinical data, as well as several clinical studies, have indicated that NMDA receptor antagonists have an antidepressant effect. Specifically, agents such as ketamine and riluzole have been shown to have antidepressant properties and may point to potential new targets for antidepressant research. Larger controlled studies with these pharmacological agents in the treatment of depression are warranted.

INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability and is the fourth largest contributor to the global burden of disease. By the year 2020, depression is projected to become the second most disabling illness in the world, as measured by disability-adjusted life years (DALYs) calculated for all ages and in both sexes (1). Consequently, research must continue to aggressively seek new avenues for the treatment of this burdensome disease. Over the years, pharmacological treatment of MDD has centered on the monoamine hypothesis of depression. Based on this hypothesis, various antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), have been developed and many more are in the pipeline. While these medications have contributed enormously to understanding the etiopathogenesis and treatment of depression, their efficacy rates and adverse effects are significant limiting factors. In fact, the largest efficacy study in depression, the STAR*D trial, found that antidepressants may be effective in only 50% of individuals suffering from depression (2). Furthermore, a delayed onset of action and adverse effects, including sexual side effects, limit their utility as well (3).

These limitations have led to a renewed focus on elucidating the broader pathophysiology of depression and identifying potential new targets for antidepressant activity. Given its ubiquitous presence in the central nervous system (CNS), glutamate, the leading excitatory amino acid, has emerged as the major target for elucidating the final common pathway of depression (4). Recent research, notably clinical trials with the NMDA antagonist ketamine, indicates that this compound has a rapid, sustained and reproducible antidepressant effect. This clinical finding together with similar preclinical data has indicated that the glutamatergic NMDA receptors have a significant role in the etiology and treatment of depression (5, 6).

Here we review the evidence illustrating the central role of NMDA receptors in the pathophysiology of depression and highlight the role of these receptors as potential targets for the therapy of depression.

GLUTAMATE

Glutamate is the principal excitatory neurotransmitter and is found in 60-80% of synapses in the brain (7). Glutamatergic neurons are postulated to play a role in the encoding of information, the formation and retrieval of memories and the maintenance of consciousness (8). Control of the glutamate system is also extremely important since glutamatergic excitotoxicity has been associated with the pathophysiology of hypoxic injury, hypoglycemia, stroke and epilepsy (9). Likewise, in bipolar depression, lamotrigine, and possibly lithium, may directly or indirectly modulate glutamatergic neurotransmission. Apart from various intracortical connections, projections from the cortex and the thalamus to the ventral tegmental area, the locus coeruleus and the dorsal raphe nuclei abound in glutamatergic neurons (10).

In the brain, glutamate can either be synthesized de novo from glucose via the Krebs cycle or recycled through the glutamate/glutamine cycle (11). Glutamate is stored in synaptic vesicles. Upon its release, it binds to and activates specialized ionotropic and metabotropic receptors found throughout the CNS. Ionotropic receptors are named after the agonists that were used to identify them in initial pharmacological studies and include the amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors ($GluR_{1-4}$), the kainate receptors ($GluR_{5-7}$ and KA1-2) and the *N*-methyl-D-aspartate (NMDA) receptors (12-14). All three classes of ionotropic receptors are also found in glia, where they may contribute substantially to glutamate homeostasis (15).

Following an action potential, glutamate is released into the extracellular space by glutamatergic neurons. Thereafter, synaptic glutamate is rapidly cleared by excitatory amino acid transporters (EAATs). There are five of these EAATs and the majority of synaptic glutamate is cleared by the glial glutamate transporters EAAT1 (GLAST-1) and EAAT2 (4, 7). Glutamate is converted to glutamine in glial cells and is transported back into neurons, where it is hydrolyzed back to glutamate. Although glutamate is the key excitatory neurotransmitter, research in various neuropsychiatric disorders, including neurodegenerative disorders and Alzheimer's disease, suggests that excess glutamate can be neurotoxic (15). This may be manifested by an associated increase in intracellular calcium that leads to activation of kinases such as calcium/calmodulin-dependent kinases and proteases such as calpain (16, 17).

NMDA RECEPTOR COMPLEX

The NMDA receptor is a heteromeric integral membrane protein. NMDA receptors are found in high density in the cerebral cortex, hippocampus, striatum, septum and amygdala. Seven genes, *GRIN1, GRIN2A-GRIN2D* and *GRIN3A-GRIN3B*, encode the NMDA receptor subunits. The NR1 subunit undergoes extensive splicing to yield eight variants: NR1-1a, 1b to NR1-4a, 4b. Functional NMDA receptors are formed from the co-assembly of what is termed the obligatory NR1 glycine-binding subunit with NR2 (glutamate binding) and/or NR3 subunits. Association of the NR1 subunit with various NR2 subunits yields four major subtypes, NR1/NR2A, NR1/NR2B, NR1/NR2C and NR1/NR2D (18). Multiple receptor isoforms with distinct brain distributions and functional properties arise by selective splicing of the NR1 transcripts and differential expression of the NR2 subunits.

The NMDA receptor is a unique ionotropic receptor in various ways. Firstly, its opening depends on the presence of glutamate and depolarization of the postsynaptic membrane. Furthermore, it requires a co-agonist, either glycine or D-serine, to bind to a distinct site on the receptor. In the absence of this agonist, NMDA receptor opening is attenuated (4, 7). Increased permeability to calcium can lead to intracellular mechanisms that activate kinases and proteases, which can have significant implications for cell survival. The NMDA receptor is thus distinct in that it is both ligand-gated and voltage-dependent. This NMDA receptor duality makes it possible to pharmacologically modulate activity in a variety of ways. Glutamate and NMDA binding to the receptor site is blocked by competitive antagonists. For example, noncompetitive antagonists also inhibit NMDA activity by binding to a site within the ion channel, termed the phencyclidine (PCP) site (14).

EVIDENCE FOR GLUTAMATERGIC DYSREGULATION IN DEPRESSION

Recent research has indicated that dysregulation of glutamatergic NMDA neurotransmission may be one of the key mechanisms causing depressive symptoms. Evidence pointing to such abnormalities is multifactorial, including alterations in plasma glutamate levels, variations in glutamate receptors, antidepressant effects of NMDA antagonists and effects of antidepressants on NMDA receptors. This section briefly reviews each of these potential mechanisms and the evidence base to support them.

Changes in glutamate levels

Glutamatergic abnormalities have been reported in the plasma of depressed patients, but it is not clear whether the changes in plasma amino acids reflect specific changes in brain concentrations (19, 20). Furthermore, studies have suggested that patients with depression, both during an acute episode and in remission, have elevated levels of glutamate in some brain regions (21, 22). More recently, magnetic resonance spectroscopic studies, which allow reliable measurement of glutamate/glutamine concentrations in various brain regions, have reported a decrease in glutamine levels in frontal regions which is reversed by antidepressants, electroconvulsive shock treatment or sleep deprivation (23-25). There is also substantial evidence suggesting that glutamate dysfunction due to inflammation may contribute to the pathophysiology of depression. McNally et al. reported that peripheral inflammation can lead to activation of microglia, which interferes with excitatory amino acid metabolism, resulting in inappropriate glutamate receptor activation. Inflammatory mediators can, through activation of the kynurenine pathway, increase glutamate receptor agonism. While details regarding this mechanism are beyond the scope of this review, the reader is referred elsewhere for this discussion (26).

Glutamate receptor alterations

Several studies have reported an alteration in NMDA receptor binding affinities and receptor expression in the brain tissue of individuals with MDD. Nowak et al. noted that deficits of NMDA receptors may be found in the frontal cortex of suicide victims, although it is possible that such a reduction may be the result of chronic treatment with antidepressants (27, 28). More recent research has provided direct evidence for NMDA receptor involvement in MDD by showing a reduction of NMDA binding and NR1-IR density in the superior temporal cortex (29). Similarly, decreased expression of hippocampal NR2B, NR1 and NR2A has been reported in subjects with MDD (30).

Antidepressant effects of NMDA antagonists

Currently, perhaps the strongest and most direct evidence for the involvement of NMDA receptors in depression is the antidepressant effect of NMDA antagonists demonstrated in animal models and human studies.

Preclinical studies

Various animal models of depression have been validated for testing the effects of antidepressants in the laboratory. Typically, these

models are based on behavioral despair after exposure to acute stress, learned helplessness and/or chronic stress models. The forced swim test (FST) and tail suspension test (TST) confirm that animals subjected to short-term, inescapable stress will develop an immobile posture. In the learned helplessness model, animals exposed to a noxious stimulus with no opportunity to escape thereafter display decreased escape from a noxious stimulus despite having an opportunity. In the chronic stress model, rodents submitted to a regimen of chronic, mild, unpredictable stress exhibit behavioral deficits consistent with a loss of responsiveness to reward, such as decreased sucrose consumption, decreased ability to associate rewards with a distinctive environment and decreased sensitivity to rewarding electrical brain stimulation. Chronically stressed animals also exhibit REM sleep abnormalities resembling those observed in depressed patients and recognized as biological markers of depression.

Several studies have shown the effectiveness of NMDA antagonists, including MK-801 (dizocilpine), a noncompetitive NMDA antagonist, and AP-7, a competitive NMDA antagonist, in decreasing immobility time in the FST (31). These antidepressant-like effects were comparable to those of tricyclic antidepressants. These findings not only indicate that the NMDA receptor complex may be involved in the behavioral deficits induced by inescapable stress, but also that substances capable of reducing neurotransmission at the NMDA receptor complex may represent a new class of antidepressants.

Ketamine is a noncompetitive antagonist at the PCP site of the NMDA receptor. At doses of 10 and 15 mg/kg ketamine and 20 and 30 mg/kg imipramine, rats displayed reduced immobility time in the FST model compared to the saline group, with no effect on locomotor activity in the open-field model (32). Another preclinical study evaluated the noncompetitive, open-channel NMDA antagonist memantine and found a dose-dependent decrease in immobility time in the FST in rats (33).

Rogóz et al. studied the synergistic effect of noncompetitive NMDA receptor antagonists and antidepressant drugs in rats in the FST. These researchers investigated the possibility of synergistic interactions between three antidepressants (imipramine, venlafaxine and fluoxetine) with three uncompetitive NMDA receptor antagonists (amantadine, memantine and neramexane). Most combinations resulted in synergistic antidepressant-like effects in the FST. The most interesting observation was that fluoxetine, which was inactive when given alone, showed a positive effect when combined with amantadine (10 and 20 mg/kg), memantine (2.5 and 5 mg/kg) or neramexane (2.5 and 5 mg/kg). The results of this study suggested that such a combination of traditional antidepressant drugs and NMDA receptor antagonists may produce enhanced antidepressant effects, which may be especially pertinent to treatment-resistant depression (34).

Clinical studies

Ketamine has been shown to have antidepressant effects in humans (5). In a double-blind, placebo-controlled, crossover study, Zarate et al. found that a single intravenous (i.v.) dose of ketamine (0.5 mg/kg over 40 min) resulted in rapid and significant antidepressant effects in patients with treatment-resistant MDD within 2 h; this effect remained significant for 7 days. Seventy-one percent of the subjects met response criteria and 29% achieved remission 24 h following the infusion of ketamine. Thirty-five percent of the subjects maintained a response to ketamine for at least 1 week; two of these maintained a response for at least 2 weeks. In contrast, no subject on placebo responded on day 1 or 7. Mild perceptual disturbances occurred in most patients, but in all cases lasted less than 1 h. No serious adverse events were reported in this study (6).

A randomized, controlled trial and an open-label study of memantine for the treatment of depression yielded conflicting results. In the double-blind, placebo-controlled study, Zarate et al. investigated the antidepressant effects of memantine in 32 subjects with major depression. The patients received either memantine 5-20 mg/day or placebo for 8 weeks and improvement was measured with the Montgomery-Åsberg Depression Rating Scale (MADRS). The study concluded that memantine did not have antidepressant effects in patients with major depression (35). In the open-label study, 8 patients with MDD were administered memantine for 12 weeks and memantine was titrated to 20 mg/day for 4 weeks. Nonresponders were titrated to 30 mg/day at week 8 and to 40 mg/day at week 10. Response was measured by the MADRS score, with additional outcome measures of the Hamilton Depression Rating Scale (HAM-D), the Clinical Global Impression-Severity of Illness (CGI-S) and the Clinical Global Impression-Improvement (CGI-I) scales, the Patient Global Evaluation and the DSM-IV major depressive episode checklist. It was determined that patients' depressive symptoms improved within 1 week and reached and maintained maximal improvement from week 8 to 12. Six of these eight patients no longer met DSM-IV criteria for MDD at the end of the study. Discrepancies in outcome in these studies may, however, be related to patient selection criteria and doses used (36).

Riluzole, a glutamate-modulating agent, has also been studied in major depression. While most studies indicate that riluzole may not be a direct NMDA antagonist per se, it is appropriate here given its antiglutamatergic action via inhibition of neuronal voltage-dependent sodium channels and efficacy in depression (37). Zarate et al. carried out an open-label trial of riluzole in patients with treatment-resistant major depression. In this study, 19 adult subjects with a diagnosis of recurrent major depression and an MADRS score ≥ 20 were treated with riluzole (100-200 mg/day) for 6 weeks. With a mean dose of 169 mg/day, significant improvement was reported during weeks 3 through 6 for all patients. Response and remission rates were found to be comparable to other antidepressants in studies of treatment-resistant depression. The most common adverse events reported in this study were headache (58%), gastrointestinal distress (43%), decreased salivation (47%), constipation (32%) and tension or inner unrest (26%); no serious side effects were reported (38). Similar adverse effects were also reported in a trial of riluzole in patients with amyotrophic lateral sclerosis (ALS) (39). Riluzole is believed to exert its effects on the glutamatergic system through inhibition of voltage-dependent sodium channels, resulting in a reduction in glutamate release, and also indirectly via kainate receptors (37). Riluzole may also exert neurotrophic effects by stimulating the synthesis of brain-derived neurotrophic factor (BDNF) (40). Similar positive results with riluzole in depression have also been reported in smaller case studies, although larger double-blind studies are still pending (41).

Effects of antidepressants on the NMDA receptor

Further evidence for NMDA receptor involvement comes from research that has studied the effects of antidepressants on cultured rat cortical neurons. Some of these studies have revealed an antidepressant-induced acute inhibition of NMDA-related calcium increase (42). An interesting study in this area found that chronic (14 days) but not acute (1 day) administration of 17 different antidepressants to mice produced adaptive changes in radioligand binding to NMDA receptors. Detailed studies with three depression therapies (imipramine, citalopram and electroconvulsive shock) have shown that these changes develop slowly, persist for some time after cessation of treatment and (for imipramine and citalopram) are dose-dependent. Furthermore, after chronic treatment with imipramine, these changes in radioligand binding to NMDA receptors appear restricted to the cerebral cortex. Based on the consistency of these effects across antidepressant treatments, it is possible that adaptive changes in NMDA receptors may be the final common pathway for antidepressant action (43).

CONCLUSIONS AND FUTURE DIRECTIONS

The psychopharmacological treatment of depression can often be limited by a lack of efficacy or the presence of adverse effects. Novel agents that are well tolerated, safe and effective are needed for future progress in reducing the burden of depressive disease. In this regard, growing research has focused on the role of glutamate in the pathophysiology and treatment of depression. Glutamate is the most abundant excitatory amino acid neurotransmitter and is widely distributed in major circuits throughout the CNS. The characterization of modulatory sites on NMDA receptors and the identification of allosteric modulators of metabotropic receptors have suggested many potential targets for drug development. Ketamine and riluzole are two such glutamatergic-modulating agents which have shown promising preliminary results in preclinical and clinical studies of depression. Ketamine warrants continued trials because it has been shown to produce rapid and relatively sustained antidepressant effects. Likewise, in bipolar depression, there is a growing understanding that lamotrigine, and possibly lithium, may also work through direct or indirect modulation of glutamatergic neurotransmission. In the near future, exciting research will continue to clarify the role of glutamate in depression, with larger, double-blind, randomized trials with ketamine and riluzole of particular importance. Furthermore, AMPA receptor potentiators may have significant promise in addressing the cognitive dimension of depression. Another area of substantial interest involves the role of inflammation in the pathogenesis of depression. This likely occurs through an interference with glutamatergic systems, at least in a subgroup of depressed patients. It remains to be determined whether all patients with depression or only a selected subgroup will benefit from these glutamate-based approaches. Identifying predictors of pharmacological response will continue to be an active area of research, with the aim of promoting individualization of optimal treatment approaches for depression. Further elucidation of the cellular and subcellular actions of these agents, especially with regards to long-term potentiation, will help us to further understand the pathophysiology of depression.

DISCLOSURE

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