Do Glutamatergic Agents Represent a New Class of Antidepressant Drugs? Part 2

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As reviewed in part 1, mounting evidence suggests that changes in glutamate neurotransmission are associated with both the pathophysiology and treatment of major depressive disorder (MDD). The complexity of the glutamatergic neurotransmitter system provides many potential pharmacologic targets that could be exploited in the development of novel antidepressant and mood-stabilizing medications. The preceding section provided a brief overview of drugs targeting glutamate release and uptake as well as the metabotropic glutamate receptors. This section will focus on recent work on the ionotropic *N*-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors.

NMDA Receptor

NMDA receptors are ion channels that exist primarily as a complex composed of NR1, NR2, and NR3 subunits. There are multiple splice variants of each of the subunits, resulting in many different versions of the receptor with slightly varied properties. In addition to glutamate, glycine serves as a coagonist for the NMDA receptor, and binding of both molecules is necessary to open the receptor's ion channel. Of further potential pharmacologic interest, magnesium and zinc concentrations also modulate NMDA receptor function. NMDA receptors are present throughout the CNS, serve complex roles in the regulation of brain function, and are known to promote both neuronal survival and cell death.[1,2]

Studies reporting antidepressant-like activities associated with the NMDA receptor–active drug cycloserine date back to the late 1950s[3] (prior even to knowledge that glutamate was a neurotransmitter), and the glutamatergic system has been considered by some as a potential target for antidepressant drug development for several years.[4] However, the recent interest in the receptor as a target in relationship to MDD was markedly spurred by a somewhat serendipitous finding from Berman et al[5] showing that ketamine, a noncompetitive NMDA antagonist, dramatically improved depressive symptoms in a group of 7 subjects with MDD. The study, originally designed to examine the acute effects of a subanesthetic dose of ketamine on cognitive function, unexpectedly yielded data showing the patients' depression severity decreased markedly within hours after receiving a single 40-minute infusion of the drug. This finding of a rapid and sustained (at least for several days) improvement in depression symptoms following a single dose of ketamine was later replicated by Zarate et al[6] in a study involving 17 MDD subjects. In this study, 71% of the subjects showed > 50% reduction in depression severity as measured by the Montgomery-Asberg Depression Rating Scale, and 29% of the subjects met criteria for remission within 24 hours of dosing. Several recently published open-label studies and case reports further bolster the initial observations of ketamine's acute antidepressant-like properties (see reference 7, for example). In addition to the clinical studies, rodent studies, some dating back nearly 35 years, demonstrate that NMDA antagonists possess antidepressant-like properties.[8–10]

The potential ability to pharmacologically target specific subunits of the NMDA receptor provides some promise that the antidepressant properties of ketamine may be captured while avoiding its major effects on perception and cognition. Along these lines, a recently published study by Preskorn et al[11] using an NMDA NR2B-selective drug (CP-101606) suggests this approach may be fruitful.[11] However, studies with memantine, another low-to-moderate affinity noncompetitive NMDA receptor antagonist (but with noted pharmacologic differences from ketamine[12]), appear less conclusive. Zarate et al[13] failed to show any antidepressant advantage of memantine at doses up to 20 mg/d compared to placebo in a double-blind randomized controlled trial of 32 subjects over a period of 8 weeks. A second study of 80 alcohol-dependent outpatients with MDD did suggest that memantine had effects equivalent to escitalopram; however, no placebo control was included in the design.[14]

There has also been increased interest surrounding the potential utility of drugs that modulate the effects of glycine on NMDA receptor activation in the treatment of various psychiatric disorders. d-Cycloserine, a glycine partial agonist, has been shown in several rodent studies and small clinical trials to facilitate fear extinction.[15] However, despite the early reports of cycloserine's antidepressant-like activities previously mentioned,[3] the only recent study examining the antidepressant effects of d-cycloserine in a small sample of depressed subjects did not show a significant effect.[16] There are many potential factors limiting the conclusions from this study, including the fact that d-cycloserine was not augmented with a behavioral therapy as in the studies using d-cycloserine to treat anxiety disorders.[17] In addition to d-cycloserine, there is also a growing interest in using glycine transport inhibitors to treat neuropsychiatric disorders[18,19]; however, there are no reports of studies using glycine transport inhibitors in humans with MDD to date.

AMPA and Kainate Receptors

Similar to the NMDA receptor, the AMPA and kainate (KA) receptors are composed of a complex of subunits, affording the opportunity for pharmacologic specificity by targeting individual subunits. Modification of synaptic AMPA receptors is now recognized to be a critically important mechanism for regulating various forms of synaptic plasticity,[20] and trafficking of AMPA receptors is believed to underlie several experience-driven phenomena ranging from neuronal circuit formation to the modification of behavior.[21] A series of studies suggesting the receptors are altered in animal models of mood disorders and in some depressed individuals[22–24] have helped the AMPA and KA receptors gain attention in the area of mood disorder research. Additional studies showing that AMPA receptor function is modified by many classes of existing mood stabilizers and antidepressant agents suggest the receptor may be involved in a common mechanism of action for the drugs.[25] A recent rodent study illustrating the ability of an AMPA antagonist to block the antidepressant properties of 2 NMDA antagonist drugs suggests that in fact the increased activation of the AMPA receptors may be driving the antidepressant-like response to the NMDA antagonists.[26] There is a growing interest in targeting AMPA receptors for both cognitive enhancement and the treatment of neuropsychiatric disorders. A new class of compounds referred to as AMPA potentiators or ampakines, which indirectly modulate the receptors through effects on receptor desensitization and deactivation, is currently being evaluated for a variety of indications ranging from cognition to Parkinson's disease. Preclinical studies suggest the class of agents possesses antidepressant properties.[22] Although a single clinical trial has been initiated for the treatment of MDD (www.clinicaltrials.gov, NCT00113022), no results have been reported to date.

Summary

Both preclinical and early-phase clinical studies suggest that drugs targeting the ionotropic glutamate receptors possess potent antidepressant properties. The seeming effectiveness in previously treatment-resistant patients, the novelty of the mechanism of action, and the rapid antidepressant response associated with the NMDA antagonist drugs have stimulated great interest both at academic centers and within the pharmaceutical industry. However, it is important to acknowledge the limitations of clinical studies reported to date in this area. None of the studies have truly been conducted in a double-blind fashion because the acute effects of the ketamine and even CP-101606 on cognition and perception were discernable by both the subjects and the treaters when compared to a saline placebo. In addition, the studies provide no information on the longer-term effectiveness and safety of the NMDA receptor antagonists in treating depression. This is especially important considering that under certain conditions NMDA receptor antagonists themselves can be neurodestructive.[27] According to clinicaltrials.gov listings, there are 8 ongoing clinical trials examining the antidepressant and mood-stabilizing efficacy of NMDA antagonists, in addition to several others that were recently completed. Undoubtedly, the results of these studies will provide more information on this class of drugs in the near future.

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