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REVIEW ARTICLE

CLINICAL ASPECTS OF MODULATION OF GLUTAMATERGIC MECHANISMS IN THE TREATMENT OF SCHIZOPHRENIA

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SUMMARY

Current treatments for schizophrenia all target the dopamine D_2 receptor but may have limited effectiveness, particularly in treating the negative and persistent positive symptoms, as well as the cognitive impairment associated with the disorder. Evidence supporting the glutamate hypothesis of schizophrenia is amassing. The glutamate hypothesis centers around hypofunctioning NMDA receptor system activity, which is unavailable to adequately modulate the activity of cortical pyramidal neurons or their excitatory afferents, and is responsible in part for the clinical manifestations of schizophrenia. Compounds that increase activity at the NMDA receptor or re-equilibrate pyramidal neuron glutamate activity may have potential as add-on or monotherapy to improve the symptoms of schizophrenia. Recent clinical data will be reviewed that support such an approach. The glutamate hypothesis of schizophrenia may therefore provide a direction for the development of new, innovative and hopefully more effective therapies for schizophrenia.

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UNMET NEEDS IN THE TREATMENT OF SCHIZOPHRENIA

Five decades after the introduction of the first effective antipsychotic drug, chlorpromazine, the clinical outcome for patients suffering from schizophrenia remains somewhat limited. Few patients achieve remission, and fewer still achieve recovery (1). Functional outcomes are poor, as many patients are unable to engage in productive employment or to live independent of external financial and social support (2). Furthermore, despite current treatments, the overall suicide rate for patients with schizophrenia remains high at 5-10% (3). Moreover, current therapies have limitations: core disease symptoms, such as primary negative symptoms and cognitive impairment, may be resistant to treatments (4-13). Treatment-emergent adverse events associated with these treatments (such as extrapyramidal symptoms, hyperprolactinemia, weight gain and changes in metabolic parameters) may limit treatment effectiveness, tolerability and patient adherence (14-17), which in turn may affect long-term treatment outcomes (18-20). In addition, patients with schizophrenia have three to six times the risk of having a comorbid substance abuse disorder (21), which complicates the therapeutic management of many patients with schizophrenia through damaging effects on symptom stability, adherence and social functioning. Lastly, clinical and neurobiological evidence suggests that schizophrenia may, to some degree, be a progressive neurodegenerative disease little impacted by most of the older available treatments (22-25). As a result, a new therapeutic approach to the treatment of schizophrenia is desperately needed.

NONDOPAMINE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

All currently available antipsychotic drugs have the ability to block the dopamine D_2 receptor. This commonality has provided inferential evidence for the dopamine hypothesis of schizophrenia, which theorizes that psychosis is related to excessive dopaminergic activity in the brain (26). Despite the clinical effectiveness of these drugs, there is no unequivocal evidence that schizophrenia is the result of an upstream, primary abnormality of dopamine metabolism or receptor signaling (27).

Although dopamine has received the most attention as the key neurotransmitter in schizophrenia, accumulating evidence implicates a dysregulation of the glutamatergic system as the primary cause of

the pathophysiology of the disease. Glutamate is one of the most widely distributed excitatory neurotransmitters in the central nervous system (CNS) and has been implicated in several psychiatric and neurodegenerative disorders (28). The extensive distribution of glutamatergic synapses throughout the CNS –particularly in those regions most affected in schizophrenia (23, 29)– provides plausible evidence that a disequilibrium between glutamate activity and that of other neurotransmitters may generate the multitude of pathological behaviors that characterize schizophrenia.

Early clinical observations recognized that the behavioral effects of the anesthetic phencyclidine (PCP), particularly after illicit use, resembled many of the symptoms of schizophrenia, including agitation, delusional thinking, auditory hallucinations, thought disorder, apathy, social withdrawal and cognitive impairment (30-33). Earlier dopaminergic-stimulant models of schizophrenia were able to mimic the positive symptoms of the disorder (e.g., agitation, hallucinations and delusions), but they lacked the ability to produce the negative symptoms of the disease (e.g., apathy, social withdrawal and cognitive impairment). PCP could produce this wide array of behaviors by altering activity in several areas of the brain through its antagonism of the effects of glutamate at the *N*-methyl-D-aspartate (NMDA) receptor complex (where it behaves as a noncompetitive antagonist) (34). Characterization of specific PCP binding in the brain in regions affected in schizophrenia, identification of the PCP receptor as a component of the NMDA receptor complex, demonstration of an association between potency for psychoactive behavioral effects and PCP receptor affinity across several noncompetitive NMDA antagonists, and the initial discovery of low cerebrospinal fluid glutamate levels in schizophrenia helped spawn the "glutamate" hypothesis of schizophrenia (31, 34-38). The hallmark of this hypothesis may be represented by a failure of mechanisms to regulate or synchronize the activity of glutamatergic pyramidal neurons across cortical neuronal networks. Such a failure may lie in hypofunction of the NMDA receptor complex, leading to a direct disinhibition of pyramidal neurons or an indirect failure of the NMDA receptor to drive inhibitory γ-aminobutyric acid (GABA)-ergic interneurons that synapse back onto the pyramidal neurons –either of which would lead to aberrant activity in cortical pyramidal neuron activity.

Dysregulation of glutamate neurons leads to inefficient signal transmission within the prefrontal cortex, which may be responsible for some of the symptoms of schizophrenia (39-44). Synchronized firing of cortical networks plays a critical role in maintaining higher-order cognitive functions (45-52). Activity at the NMDA receptor on cortical GABA interneurons controls the firing rate of cortical pyramidal neurons, and integrates neuronal activity with behavioral events (53, 54). Reduced NMDA activity may lead to a disinhibition of these cortical neurons, resulting in increased glutamatergic activity through the lack of GABAergic interneuron control, which may result in pathological behaviors.

Alternatively, other non-NMDA receptor-linked deficiencies in GABAergic interneuron activity may also result in excessive pyramidal neuron activity, particularly for those neurons modulated by the activity of glutamate receptors.

EVIDENCE FOR NMDA RECEPTOR HYPOFUNCTION IN SCHIZOPHRENIA

In the clinical laboratory, acute exposure to the noncompetitive NMDA antagonist ketamine in normal human volunteers induces transient symptoms that are phenomenologically similar to those of patients suffering from schizophrenia (55-59). The "schizophrenomimetic" effects of PCP in abusers without endogenous psychosis may be prolonged, and not necessarily initially responsive to conventional antipsychotic drugs (30, 60).

Ketamine infusion to patients with schizophrenia produces psychotic symptoms, even in the presence of ongoing haloperidol treatment, and these symptoms are similar to those of previous illness episodes. Likewise, these PCP-induced episodes may be prolonged in some patients (61). The increased sensitivity to ketamine in schizophrenia patients when compared with controls, as well as the recrudescence of previous familiar symptoms, suggests that NMDA antagonists may be exacerbating a pre-existing NMDA receptor hypofunction associated with the illness (62). Positron emission tomography (PET) in humans indicates that the prefrontal cortex is focally activated during ketamine-induced psychosis in healthy individuals (58, 63) and in patients with schizophrenia (64). Interestingly, the atypical antipsychotic drug clozapine has been found to blunt ketamine activation of psychosis in patients with schizophrenia (65). Animal studies demonstrate metabolic activation of brain regions relevant to the pathophysiology of schizophrenia after acute administration of NMDA antagonists (66, 67), and the neurotoxicity produced by these compounds in brain regions comparable with those affected in humans with schizophrenia can be blocked by administration of some second-generation antipsychotics (68, 69).

Furthermore, NMDA antagonists consistently induce schizophrenia-like prepulse inhibition (PPI) deficits in both rodents (70) and monkeys (71, 72), suggesting that some cognitive deficits in schizophrenia may reflect underlying NMDA receptor dysfunction. There is little consistency, however, in the reported effects of ketamine on PPI in healthy humans. For example, van Berckel et al. (73) found no change in PPI with ketamine, whereas Duncan et al. (74) and Abel et al. (75) recently found that ketamine increases PPI in humans, rather than disturbing it (76) as in other species.

Additional evidence pointing towards a role for NMDA receptor hypofunction in schizophrenia is provided by the preclinical observation that genetically altered mice which are substantially deficient in NMDA receptors display spontaneous hyperactivity, stereotypy and social withdrawal –analogous to the positive and negative symptoms of schizophrenia (77). Further clinical evidence of NMDA receptor hypofunction in schizophrenia is suggested by the demonstration of reduced NMDA receptor binding, receptor expression and biomarkers in patients with schizophrenia (78-85). In addition, levels of *N*-acetylaspartylglutamate (NAAG), a putative endogenous antagonist of glutamate at the NMDA receptor, may be elevated in schizophrenia (86).

Taken together, these data support not only a role for glutamate dysfunction in the neuropharmacology of schizophrenia, but also for it being the upstream, primary cause of the disease.

EVIDENCE FOR DOWNSTREAM DEFICIENCY OF GABAERGIC INHIBITORY MECHANISMS IN SCHIZOPHRENIA

As previously discussed, the synchronized firing of cortical pyramidal neurons is mediated in part by GABAergic interneurons (54, 55). Therefore, dysregulation of cortical pyramidal neurons may also be a direct consequence of a deficiency in activity of inhibitory GABA interneurons. Post mortem studies have found markers of decreased synthesis and release of GABA from parvalbumin-positive chandelier neurons in the prefrontal cortex of patients with schizophrenia (49). A deficit in synchronization of pyramidal cell activity may contribute to impaired cognitive performance in schizophrenia (50). This does not negate the hypothesis of glutamate as being the primary dysfunction, since the activity of GABAergic interneurons is modulated by NMDA receptors, which, if hypofunctioning, will decrease the ability of these interneurons to regulate cortical pyramidal cell activity.

Interestingly, activation of cannabinoid receptors on basket cells, cholecystokinin-containing GABAergic interneurons not associated with parvalbumin that target pyramidal neurons, may also suppress GABA release and thus disinhibit (or deregulate) glutamatergic activity in these neurons (87-89). Cannabis abuse may therefore exacerbate an intrinsic deficit in GABA synthesis, providing a mechanism by which cannabis use increases the risk for and the severity of schizophrenia (49, 90). The above findings are also consistent with the possibility that the psychotomimetic effects of PCP are mediated by its ability to suppress GABA release from GABAergic interneurons.

THERAPEUTIC INTERVENTIONS LINKED TO INCREASING NMDA RECEPTOR FUNCTION

Implicit in the hypothesis of NMDA receptor hypofunction as a basis for schizophrenia is the strategy that increasing NMDA receptor function –directly or indirectly– may ameliorate some of the symptoms of schizophrenia. Accumulating evidence may support the utility of this strategy.

Evidence from current antipsychotic treatments

Although the prototype atypical antipsychotic drug clozapine shares the common attribute of D_2 receptor antagonism with all currently available antipsychotic drugs, some studies suggest that clozapine distinguishes itself in part through greater clinical efficacy compared to conventional antipsychotic drugs (91) and certain other atypical antipsychotics (92). Unlike conventional antipsychotic drugs, clozapine may preferentially enhance activity at the NMDA receptor, thus restoring function to a more normal level. This is inferred by the ability of clozapine, but not haloperidol, to blunt the psychoactive effects of ketamine infusion in schizophrenia (61, 93). In preclinical behavioral models, clozapine, but not haloperidol, was able to improve PCP-induced performance impairment in the water maze test (94) and deficits in sensory motor gating (95-97). Additional evidence for a preferential effect is demonstrated by the ability of clozapine (and again, not haloperidol) to block PCP-induced hyperpolarization of pyramidal neurons (98), as well as MK-801-induced increased firing of prefrontal cortex neurons (54). Clozapine and other atypical antipsychotic drugs such as olanzapine, risperidone and quetiapine were able to augment electrically or NMDA-evoked responses in pyramidal cells of the medial prefrontal cortex (99), whereas the conventional antipsychotics (such as haloperidol, chlorpromazine and loxapine) were not. The effect of the atypical antipsychotics may in part be related to their preferential ability to increase dopamine, as well as glutamate, release in the prefrontal cortex (100-107). These findings suggest that the improved clinical efficacy of clozapine over typical antipsychotic drugs, for example, particularly in the realm of negative symptom improvement, may be due to some amelioration of NMDA receptor hypofunction in schizophrenia, possibly mediated by increased availability of glutamate at the NMDA receptor or by a clozapine-induced upregulation of NMDA receptors (108).

Evidence from glutamate agonists

The NMDA receptor contains an allosteric modulatory site sensitive to the endogenous amino acids glycine and D-serine (109, 110). Co-agonism of the NMDA receptor with glycine increases the receptor response to glutamate, and may offer another opportunity to improve the symptoms of schizophrenia associated with NMDA receptor hypofunction. Preclinical studies have demonstrated the ability of high-dose glycine and D-serine to block PCP- or MK-801-induced behavioral effects in rodents (111-113).

Initial small-sample clinical trials had shown glycine to be effective in improving negative symptoms in patients with schizophrenia when added to ongoing antipsychotic therapy, and no clinically significant adverse events were reported (114-116). Add-on treatment with the glycine partial agonist D-cycloserine also demonstrated efficacy against negative symptoms and some cognitive improvement when given in a restricted optimal dose range, but only when added to conventional antipsychotic treatment (117-122). A meta-analysis was conducted of 16 short-term trials involving 324 randomized patients who received glycine, D-serine or D-cycloserine to enhance antipsychotic treatment (123). The analysis concluded that the NMDA receptor co-agonists glycine and D-serine were moderately effective in reducing negative symptoms of schizophrenia; D-cycloserine was less effective in treating negative symptoms. Positive symptoms failed to respond to these glutamatergic medications. Available derived data on cognitive functioning did not indicate a significant effect of glycine or D-serine. The most common adverse events were nausea, insomnia, constipation and diarrhea, although the incidence of these events was low.

Since the majority of glycine and D-cycloserine clinical trials were small, primarily inpatient samples, a large (N = 157) multicenter, 16-week, double-blind, randomized clinical trial of adjunctive glycine, D-cycloserine or placebo for the treatment of negative symptoms and cognitive impairment in schizophrenia was conducted (124). The trial results suggested that neither glycine nor D-cycloserine was effective for the treatment of negative symptoms or cognitive impairment when given as monotherapy. The most common adverse events were nausea and dry mouth. Also, a significant effect for glycine was observed for inpatients, but not outpatients (125).

Due to the inherent limitations of delivering high-dose co-agonists to the NMDA receptor target, an alternative strategy would be to utilize inhibition of the glycine transporter GlyT-1 to effectively increase CNS glycine levels in close proximity to the NMDA receptor. Initial studies with sarcosine (*N*-methylglycine), a naturally occurring glycine transporter inhibitor, suggest improvement in positive and

negative symptoms when added to risperidone and other antipsychotics in chronic stable and acutely ill patients with schizophrenia (126, 127). The effect of add-on sarcosine in acutely ill patients led to a subsequent clinical trial of sarcosine monotherapy in this population (128). Twenty patients entered and were randomized in a double-blind manner to receive either 1 or 2 g/day (anticipated effective dose) for 6 weeks. No significant effect of sarcosine dose was found for any primary efficacy outcomes, including the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS) or the Quality of Life Scale. Five of 11 patients in the 2 g/day dose group responded to treatment (defined as 20% or more improvement in PANSS total score) compared with 0 of 9 in the 1 g/day dose group (P = 0.038). All responders were antipsychotic-naïve patients. The most common adverse events in these trials were constipation, insomnia and light weight gain (~1-2 kg). The conclusions were limited based on the small sample size, but the results suggest a role for glutamate dysfunction in the pathology of schizophrenia. Further clinical trials with sarcosine are needed to better understand the optimal clinically effective dose, appropriate patient population and the full adverse event profile. If effectiveness can be confirmed, such findings would strengthen the NMDA hypofunction hypothesis of schizophrenia and validate GlyT-1 as a target for the treatment of schizophrenia.

Evidence from AMPA receptors

Activity at the NMDA receptor may also be increased through activation of α-amino-3-hydroxyl-5-methyl-4-isoxazole propionate (AMPA) receptors, and this strategy has been initially pursued as possibly beneficial in the treatment of schizophrenia. NMDA and AMPA receptors interact in a complementary fashion to control excitatory neurotransmission (129). NMDA receptors are coincidence detectors, in that they detect co-occurring activity at both the presynaptic (glutamate release) and postsynaptic cells (membrane depolarization). Glutamate binds to the NMDA receptor, but the ion channel does not open because of voltage-dependent magnesium (Mg^{2+}) blockade. Once the membrane is depolarized by co-localized AMPA receptors, the channel is open, thereby allowing calcium influx through the NMDA receptor (130). Therefore, the presence of AMPA receptors can greatly affect NMDA receptor activity. Decreased AMPA receptor density in the hippocampus of patients with schizophrenia has provided strong evidence for dysregulation of glutamatergic activity in this disease (131). Thus, a reduction in activity at the AMPA receptor would be associated with NMDA receptor hypofunction.

Ampakines are positive allosteric modulators (PAMs) of the AMPA receptor, and they offer a mechanism for enhancing receptor activity while avoiding risks associated with direct AMPA receptor activation (e.g., seizures, excitotoxicity and receptor desensitization [128]). Preclinical studies with ampakines have demonstrated an improvement in some cognitive paradigms (132, 133). In the first clinical trial of an ampakine in schizophrenia, piracetam or placebo was added to haloperidol treatment in a randomized, double-blind fashion to 34 acutely ill, neuroleptic-free patients for 8 weeks (134). Both the PANSS total and the PANSS positive scores demonstrated greater improvement in the piracetam add-on group; negative symptoms did not differ significantly between treatments. A pilot study compared the ampakine CX-516 with placebo as a double-blind add-on to clozapine in 19 stable patients with schizophrenia (135). After 4 weeks of add-on treatment, the CX-516 group demonstrated a large therapeutic effect compared with placebo for improvement in attention and memory; some improvement in negative symptoms was also noted. In a subsequent larger 4-week clinical trial of add-on CX-516 in 105 patients with schizophrenia already on clozapine, olanzapine or risperidone, no improvement in cognition or psychopathology was seen with CX-516 treatment relative to placebo (136). The failure to replicate earlier findings was interpreted, in part, as reflecting our limited understanding of the exact role of AMPA receptors in influencing the complexity of potential outcomes in schizophrenia.

Evidence from other non-NMDA compounds

The anticonvulsant lamotrigine blocks sodium channels on pyramidal neurons, and may reduce glutamate release by inhibiting cell depolarization (137). Lamotrigine has demonstrated reversal of NMDA antagonist-induced disruption of PPI in mice (138, 139) and of ketamine stimulation of psychotic symptoms in healthy human volunteers (140). A summary of results in human trials of lamotrigine (141) suggested that it might be used as an adjunctive therapy to antipsychotics for some patients, particularly to treat positive symptoms. Two large clinical trials were undertaken to determine the efficacy of lamotrigine add-on therapy in treatment-resistant patients with schizophrenia currently treated with atypical antipsychotic drugs (142). A total of 429 patients were randomized to receive add-on therapy with either lamotrigine or placebo in 2 double-blind studies of 12 weeks' duration. The results of these two trials did not find lamotrigine to be effective in improving psychotic symptoms compared with placebo. Failure to find a lamotrigine treatment effect may have been due to a larger-than-anticipated placebo response in a patient population that was not necessarily treatment-resistant, as had initially been sought for enrollment. Lamotrigine did improve measures of cognition compared with placebo in one of the two trials.

Evidence from activity at the $mGlu_5$ receptor

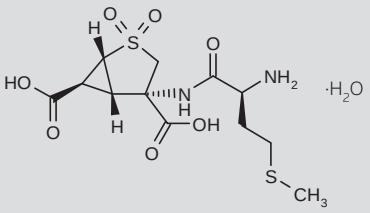
Although not yet tested in the clinic, an additional possible strategy to increase activity at the NMDA receptor may involve metabotropic glutamate $mGlu_5$ receptor PAMs. $mGlu_5$ receptor PAMs offer the potential to increase the efficiency of glutamate transmission at the NMDA receptor, without the risk of inappropriate stimulation of the system (143). Such molecules have demonstrated potentiation of second messenger signaling after activation of the NMDA receptor, reversal of the behavioral and electrophysiological effects of NMDA antagonists (144), and reduction of the conditioned avoidance response and apomorphine-induced climbing in the mouse –both tests of potential antipsychotic efficacy (145).

THERAPEUTIC INTERVENTIONS TO COMPENSATE FOR NMDA RECEPTOR HYPOFUNCTION

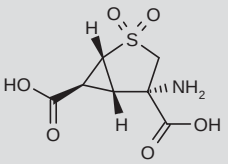
Agonists of $mGlu_{2/3}$ receptors may provide therapeutic potential for treating the symptoms of schizophrenia. Metabotropic glutamate receptors primarily modulate the activity of glutamate, GABA and other neurotransmitters (146). Therefore, activation of $mGlu_{2/3}$ receptors may also present a viable strategy to normalize dysregu-

lated pyramidal cell activity, regardless of whether this pathophysiological state is due to an NMDA or non-NMDA receptor-mediated action. **LY2140023** monohydrate is the methionine amide prodrug of the $mGlu_{2/3}$ receptor agonist **LY404039**. Unlike LY404039, LY2140023 monohydrate is efficiently absorbed in humans. Once absorbed, LY2140023 monohydrate is efficiently hydrolyzed to produce the active $mGlu_{2/3}$ receptor agonist LY404039.

In a recent proof-of-concept, double-blind, placebo-controlled phase II study (H8Y-BD-HBBD [147]), a total of 196 patients suffering from an acute exacerbation of chronic schizophrenia were enrolled and randomly assigned to receive LY2140023 monohydrate (40 mg b.i.d.), placebo or olanzapine (15 mg/day) in a 3:2:1 ratio after a 3- to 9-day antipsychotic taper-off period and a 1-day lead in for placebo. All patients were hospitalized, withdrawn from any pretrial antipsychotic medications and treated in a double-blind manner for 4 weeks. The dose of LY2140023 monohydrate was determined from early clinical and toxicological studies to be safe and also to provide CNS exposure in humans equivalent to CNS exposure that blocked PCP-induced hyperactivity in rats.



LY2140023 monohydrate



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Compared with placebo, treatment with LY2140023 monohydrate or olanzapine resulted in statistically significant improvements in PANSS total scores, as well as in other outcome measures, such as Clinical Global Impression-Severity (CGI-S) scores and PANSS positive and negative subscores. Both the LY2140023 monohydrate and olanzapine treatment groups showed a rapid onset of efficacy, with statistically significant effects manifesting at week 1. Significant improvements in all efficacy measures were sustained for subsequent weeks after week 1 through the end of the study. After 4 weeks of treatment, both the LY2140023 monohydrate (32.0%) and the olanzapine treatment group (41.2%) showed significantly greater response rates (25% or greater decrease in PANSS total score) compared with the placebo treatment group (3.2%).

LY2140023 monohydrate was found to be generally well tolerated in this study. There were no clinically significant alterations in vital signs, laboratory analyses or electrocardiograms. Notably, there were no significant elevations in serum prolactin levels or significant treatment-emergent extrapyramidal motor signs with any of the three treatments, suggesting that LY2140023 monohydrate did not have a clinically discernible effect on D_2 receptors. LY2140023 monohydrate was not associated with any significant weight change compared with placebo.

Post hoc analysis of item-by-item change of each of the 30 items on the PANSS suggested that LY2140023 monohydrate improved positive, negative and general psychopathological symptoms and signs to a similar degree. Although no formal cognitive testing was obtained in the trial, post hoc analysis demonstrated a significant improvement on the PANSS cognition subscore for LY2140023 monohydrate compared with placebo (148).

A second 4-week, randomized, double-blind, placebo- and active comparator-controlled phase II trial (H8Y-MC-HBBI [149]) was designed to examine efficacy over a larger dose range of LY2140023 monohydrate (5, 20, 40 or 80 mg b.i.d.; N = 669). Efficacy was measured as 4-week baseline-to-endpoint mean change in PANSS total score. The results were inconclusive, as neither any LY2140023 monohydrate dose nor olanzapine (15 mg/day) had significantly greater efficacy compared with placebo. A large and greater than historically anticipated placebo response was observed. In contrast to the anomalous placebo response, the response in the olanzapine treatment group and the 40-mg b.i.d. LY2140023 monohydrate treatment group was consistent with historical olanzapine studies and with the HBBD study results. As in the first study, LY2140023 monohydrate was generally well tolerated with regard to weight, vital signs, ECGs, laboratory analyses, prolactin and extrapyramidal symptoms, although five convulsions were reported in four patients, who all recovered fully without any sequelae.

Findings from the HBBD proof-of-concept study were consistent with a nondopaminergic-based antipsychotic effect associated with LY2140023 monohydrate and support the continued clinical assessment of LY2140023 monohydrate and $mGlu_{2/3}$ receptor agonists as a novel treatment for schizophrenia.

POSSIBLE MECHANISM FOR THE EFFICACY OF $mGLU_{2/3}$ RECEPTOR AGONISTS IN SCHIZOPHRENIA

LY404039 does not have any direct effects on dopamine or serotonin receptors (148). It is not known whether agonism at either the $mGlu_2$ or $mGlu_3$ receptor, or both, is required for a possible antipsychotic effect in schizophrenia; preclinical studies indicate that reversal of the behavioral effects of NMDA receptor antagonism requires activation of the $mGlu_2$ receptor (150), although a mechanism of antipsychotic drug activity selective for the $mGlu_3$ receptor has also been reported (151). The development of selective $mGlu_2$ receptor PAMs may make possible the pharmacological evaluation of $mGlu_2$ receptors in the absence of any potential confounding activation of $mGlu_3$ receptors. Promising compounds will hopefully be available soon for clinical testing in schizophrenia and provide an additional strategy to potentially normalize aberrant pyramidal cell activity.

CONCLUSIONS

The significance of the glutamate hypothesis of schizophrenia, similar to that of the dopamine hypothesis, lies in part in the theoretical

framework that it provides for the rational development of new pharmacotherapies. As reviewed above, numerous targets have been identified for their potential to restore equilibrium to presumed dysregulated glutamatergic brain circuits that may be pathologically involved in schizophrenia. Much excitement accompanies the early proof-of-concept trials that test our present understanding of glutamatergic mechanisms and provide us with promising initial results, but this is often followed by frustration, as anticipated results may fail to replicate in subsequent larger clinical trials. Interpretation of early trial results should be approached cautiously, as small sample size as well as lack of validated targets may contribute to poor generalizability of findings.

As we search for nondopaminergic-based treatments for schizophrenia, we must also be prepared to appreciate that nondopaminergic-based clinical outcomes may be the result of such efforts. New models of treatment effectiveness may need to be defined by targeted versus global symptom change, or by proximal biomarkers predictive of later disease course alteration. Change in illness symptoms and signs that correlate with improvement in key aspects of social behavior and function or in markers associated with neuroprotection from disease progression may indicate the validity of glutamatergic drug targets. Furthermore, glutamatergic nondopaminergic-based treatments may have utility as add-on therapies for persistent symptom domains such as negative symptoms or cognitive impairment in those patients whose positive symptoms are adequately controlled with traditional dopaminergic-based antipsychotic medications.

We may need to also consider the appropriate patient population in which to evaluate these new glutamate-based therapies. The glutamate hypothesis of schizophrenia may describe a pathophysiologically dynamic state that some patients are more at risk to enter and exit rather than a persistent trait. New treatment efficacy may only be apparent in acute rather than partially remitted, early-onset rather than chronic, stressed versus nonstressed (152), or some yet-to-be defined patient subgroup.

Despite the many challenges, having multiple, well-studied hypotheses for schizophrenia presents exciting opportunities to potentially improve patient outcomes.

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