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Emerging Approaches for Treatment of Schizophrenia: Modulation of Glutamatergic Signaling

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Abstract

Treatment options for schizophrenia that address all symptom categories (positive, negative, and cognitive) are lacking. Novel compounds that regulate signaling by the major excitatory neurotransmitter in the brain, glutamate, are emerging as a novel approach for the treatment of this disorder. Currently available medications ameliorate positive symptoms but do not have efficacy in reducing negative symptoms or cognitive disturbances. It is possible that agents that target glutamatergic signaling in the CNS could have efficacy in reducing all major symptom clusters, providing a more comprehensive treatment strategy, and also avoiding some of the adverse effects that are seen with currently available treatments. Three major approaches for targeting glutamate signaling are now advancing in preclinical and clinical development. First are inhibitors for a transporter for glycine termed GlyT1. Glycine is a co-agonist with glutamate for a specific subtype of glutamate receptor, termed the NMDA receptor, which is thought to be critically involved in brain circuits that are disrupted in schizophrenia patients. Inhibiting GlyT1 increases glycine levels and can selectively increase NMDA receptor signaling. Another promising approach is to increase activity of another family of glutamate receptors, termed metabotropic glutamate receptors (mGlus), which play important modulatory roles in brain circuits that are thought to be disrupted in schizophrenia patients. Activation of the group I ($mGlu_5$) and the group II ($mGlu_2$ and $mGlu_3$) mGlus is hypothesized to normalize the disruption of aberrant signaling in these circuits. Novel drug-like molecules that increase activity of these receptors have robust efficacy in animal models that predict efficacy in treatment of schizophrenia. Early clinical studies provide some support for potential utility of these targets in reducing symptoms in schizophrenia patients. Clinical studies that are underway will provide further insights into the potential utility of these compounds in the treatment of multiple symptom domains in schizophrenia patients.

Introduction

Schizophrenia is a debilitating psychiatric illness that affects approximately 1% of the world's population. The main symptoms associated with schizophrenia are grouped into three major symptom clusters that include positive symptoms, negative symptoms, and cognitive disturbances (Lewis and Lieberman, 2000). The positive symptoms include visual and auditory hallucinations, delusions, and thought disorder. The negative symptoms include social withdrawal and anhedonia. Cognitive impairments are characterized by disturbances in sensory information processing, attention, working memory, and executive functions

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(Nuechterlein *et al.*, 2004). Current drug therapies for schizophrenia include typical (e.g., haloperidol and chlorpromazine) and atypical (e.g., olanzapine and clozapine) antipsychotics, all of which act as antagonists at D2 dopamine receptors and other monoamine receptor subtypes. Typical and atypical antipsychotics are at least partially effective in reducing the positive symptoms in most patients. However, some patients are refractory and these drugs are not effective in the treatment of the negative and cognitive symptoms (Lieberman *et al.*, 2005; 2003). In addition, available antipsychotic medications induce metabolic syndrome, parkinsonian-like motor effects, and other adverse effects that are tied to their mechanism of action (Lieberman *et al.*, 2005; 2003; Pramyothin and Khaodhiar, 2010). Thus, there is a tremendous need to develop new approaches for treating schizophrenia that provide greater efficacy in reducing all of the major symptoms associated with this disease and have fewer adverse effects.

Discovery of currently available treatment strategies for schizophrenia primarily focused on modulating signaling by dopamine, serotonin, and other monoamine systems. However, it is becoming increasingly clear that the pathophysiology underlying schizophrenia cannot be explained by simple changes in monoamine signaling but reflect more complex alterations in activity through key brain circuits that are critical for sensory, cognitive, and emotional processing (Lisman *et al.*, 2008; Marek *et al.*, 2010). While these brain circuits are modulated by dopamine and serotonin, the major excitatory and inhibitory neurotransmitters that are critical for signaling through these circuits are glutamate and GABA; these circuits can also be regulated by other neuromodulators, such as acetylcholine (for review, (Langmead *et al.*, 2008).

Targeting Glutamatergic Signaling for the Treatment of Schizophrenia

Multiple studies over the past 6 decades reveal that selective antagonists at a specific subtype of receptor for the excitatory neurotransmitter glutamate termed the *N*-methyl-*D*-aspartate receptor (NMDA receptor) induce a syndrome in healthy individuals that includes positive, negative, and cognitive symptoms that are remarkably similar to those observed in schizophrenia patients. Furthermore, NMDA receptor antagonists exacerbate all three symptom clusters in individuals with schizophrenia (Conn *et al.*, 2009a; Ghoneim *et al.*, 1985; Krystal *et al.*, 1994). In addition, multiple early studies with agents that increase NMDA receptor signaling, such as the amino acids glycine and serine, suggested that increasing NMDA receptor function may provide a benefit in reducing symptoms in schizophrenia patients. These observations have stimulated intense efforts aimed at developing novel approaches that could be used to increase NMDA receptor signaling. However, excessive activation of the NMDA receptor can induce severe toxicity, including epileptic seizure activity and neuronal death (Hirose and Chan, 1993). Thus, the major focus has been to develop agents that will have more subtle effects on NMDA receptor signaling and increase NMDA receptor responses to glutamate without inducing excessive activation of the NMDA receptor. In addition, major efforts have been focused on developing and understanding the impact of NMDA receptor antagonists on brain circuits that may be disrupted in schizophrenia patients and using this knowledge to identify novel targets to restore signaling balance in those brain circuits that are disrupted by NMDA receptor antagonists.

Glycine Transporter Inhibitors

While glutamate is viewed as the primary neurotransmitter responsible for activation of the NMDA receptor, activation of this receptor also requires binding of glycine, which serves as a co-agonist (Curras and Pallotta, 1996). Based on this observation, it is possible that increasing synaptic glycine levels could enhance NMDA receptor signaling but do so in a

way that maintains a strict dependence of NMDA receptor activation on synaptic release of glutamate. Activators of the glycine site could be viewed as the most direct approaches to increasing NMDA receptor signaling in a manner that maintains activity dependence. Indeed, direct administration of glycine or serine, another amino acid agonist at the glycine site, was the first approach to increasing activation of NMDA receptors that was tested in clinical studies, and multiple studies have reported that glycine and serine can improve symptoms in schizophrenic patients (Coyle and Tsai, 2004; Heresco-Levy *et al.*, 2004; Javitt, 2006; Lane *et al.*, 2005). However, while encouraging, glycine is not optimized as a central nervous system (CNS)-active drug and suffers from a number of limitations, including poor pharmacokinetic profile and low brain exposure that compromise interpretation of clinical findings and make it unsuitable as a therapeutic agent. Indeed, other studies failed to confirm efficacy of glycine and *D*-serine (Buchanan *et al.*, 2007; Weiser *et al.*, 2012). It is unclear whether the conflicting data suggest that this mechanism will not provide robust efficacy in schizophrenia patients or if it is due to limitations in CNS exposure or differences in study design between the different trials.

Given the unfavorable properties of glycine, a preferable approach to direct administration of glycine would be to develop highly selective inhibitors of the glycine transporter, GlyT1. GlyT1 is expressed on glia and glutamatergic neurons of the forebrain, and is responsible for regulating glycine concentrations in glutamatergic synapses. Thus, blockade of GlyT1 could elevate synaptic glycine concentrations thereby facilitating NMDA receptor responses (for reviews, see Javitt, 2012; Moghaddam and Javitt, 2012). Early GlyT1 inhibitors were based on the chemical scaffold of the endogenous GlyT1 inhibitor, sarcosine. These agents have efficacy in rodent models that predict efficacy in reducing symptoms in schizophrenia patients (Kinney *et al.*, 2003a) but also induce severe adverse effects, such as compulsive walking, respiratory distress, and eventually death (Perry *et al.*, 2008; Yang and Svensson, 2008). Thus, most recent efforts have focused on selective GlyT1 inhibitors that are structurally unrelated to sarcosine. Multiple newer generation GlyT1 inhibitors have been developed that have robust efficacy in animal models that predict efficacy in the positive, negative, and cognitive symptoms observed in schizophrenia patients and are devoid of serious adverse effects at doses that have robust efficacy (Black *et al.*, 2009; Boulay *et al.*, 2010; Lindsley *et al.*, 2006). Some of these newer GlyT1 inhibitors have now advanced into clinical development and are showing some promise in treatment of schizophrenia. While initiation of multiple clinical trials have been announced, data from the majority of these studies have not yet been reported and reports that are available only include abstracts and press releases, making it difficult to fully assess current clinical findings. However, a phase II study with a novel GlyT1 inhibitor developed by Roche, RG1678 (Pinard *et al.*, 2010), administered as an add-on treatment in schizophrenic patients treated with atypical antipsychotic agents demonstrated significant improvement in negative symptoms (Hopkins, 2011; Umbricht *et al.*, 2010). Interestingly, efficacy was observed at 10 and 30 mg dosage groups but not with a higher dose of 60 mg. While the safety profile for RG1678 was favorable with all three doses, this biphasic dose response relationship may present challenges in establishing appropriate doses in individual patients. Nevertheless, these clinical results are encouraging and led to initiation of a phase III clinical development program for this compound.

More recently, D'Souza *et al.* (2012) reported that another GlyT1 inhibitor, Org 25935, developed by Organon (now Merck) reversed some schizophrenia-like psychotic symptoms, perceptual alterations, and subjective effects of the NMDA receptor antagonist ketamine in healthy male subjects, providing further support for the hypothesis that GlyT1 inhibitors may provide a novel approach to the treatment of schizophrenia. However, Szegedi *et al.* (2011) and Dogterom *et al.* (2011) presented unpublished findings from Merck suggesting that ORG 25935 does not provide further improvement in negative symptoms in patients

treated with atypical antipsychotic agents. Thus, while some early data are encouraging, it will be important to fully evaluate emerging clinical data from studies assessing the potential efficacy of GlyT1 inhibitors in schizophrenia patients.

Metabotropic Glutamate Receptor $mGlu_5$

In addition to signaling through the NMDA receptor and other glutamate-gated cation channels, glutamate can also modulate or fine-tune activity in brain circuits by actions on a family of G-protein coupled glutamate receptors termed metabotropic glutamate (mGlu) receptors (Niswender and Conn, 2010). Eight different subtypes of mGlu receptors, termed $mGlu_1$ - $mGlu_8$ exist in the mammalian brain where they play multiple roles in regulating CNS function. Interestingly, one mGlu subtype, $mGlu_5$, has emerged as a closely associated signaling partner with NMDA receptors and may play an integral role in regulating NMDA receptor function in a variety of forebrain regions. NMDA receptors physically interact with $mGlu_5$ via binding to scaffolding proteins (Ehlers, 1999) and functionally interact via a reciprocal positive feedback system in which $mGlu_5$ potentiates NMDA receptor currents (Attucci *et al.*, 2001; Awad *et al.*, 2000; Doherty *et al.*, 2000; Mannaioni *et al.*, 2001; Marino and Conn, 2002; Ugolini *et al.*, 1999). NMDA receptors also regulate responses to activation of $mGlu_5$ through activation of the protein phosphatase calcineurin or a protein kinase (Alagarsamy *et al.*, 1999; Alagarsamy *et al.*, 2005). Thus, selective activators of $mGlu_5$ may provide a viable approach to increasing NMDA receptor function for the treatment of symptoms associated with schizophrenia. Consistent with this hypothesis, $mGlu_5$ knock-out mice display a behavioral phenotype resembling some behavioral effects of NMDA receptor antagonists (Brody *et al.*, 2004; Kinney *et al.*, 2003b). Furthermore, selective $mGlu_5$ antagonists potentiate the psychotomimetic effects of NMDA receptor antagonists in animal models (Brody *et al.*, 2004; Campbell *et al.*, 2004; Kinney *et al.*, 2003b). Taken together, these findings led to the hypothesis that $mGlu_5$ may represent a viable target for the development of novel agents for treatment of schizophrenia (Conn *et al.*, 2009a). Promising evidence in animal models provides support for this hypothesis, such that selective activators of $mGlu_5$ have been shown to have potential for efficacy in treatment of positive and negative symptoms of schizophrenia and may also have cognitive-enhancing effects (Conn *et al.*, 2009a).

Unfortunately, it has been extremely difficult to develop selective agonists of $mGlu_5$ that have suitable properties for use as therapeutic agents. The glutamate binding site is highly conserved across the eight mGlu subtypes (Conn and Pin, 1997; Niswender and Conn, 2010), making it difficult to develop selective glutamate-site ligands. However, there has been tremendous progress in developing highly selective $mGlu_5$ activators that do not act at the conserved glutamate binding site but instead act as positive allosteric modulators (PAMs) of $mGlu_5$ (for review, see Stauffer, 2011). These prototypical $mGlu_5$ PAMs do not activate the receptor directly but potentiate responses to glutamate through binding at an allosteric site. Progress in optimizing $mGlu_5$ PAMs for use in animal studies has been rapid and these compounds have robust activity in a number of animal models that provide support for the hypothesis that selective $mGlu_5$ PAMs have potential as a novel therapeutics for the treatment of schizophrenia. For instance, several structurally distinct $mGlu_5$ PAMs have efficacy in multiple rodent models that are traditionally used to predict efficacy in reducing positive symptoms in schizophrenia patients (Epping-Jordan *et al.*, 2005; Kinney *et al.*, 2005; Liu *et al.*, 2008; Rodriguez *et al.*, 2010; Schlumberger *et al.*, 2009a; Xiong *et al.*, 2010; Vinson and Conn, 2012). These include models such as amphetamine-induced hyper-locomotion and apomorphine-induced disruption of sensory motor gating that reflect increases in dopaminergic signaling and are responsive to existing typical and atypical antipsychotic agents. However, unlike currently marketed antipsychotics, $mGlu_5$ PAMs do not inhibit dopamine and other monoamine receptors (Kinney *et al.*, 2005). This suggests

that these agents modulate circuits that are important for the pathophysiology underlying schizophrenia and that these same circuits are also modulated by dopaminergic systems. Especially encouraging is the finding that $mGlu_5$ PAMs belonging to multiple chemical scaffolds have efficacy in these models and these compounds span a range of chemical series that are known to only have activity at $mGlu_5$. In addition to demonstrating efficacy in animal models that predict effects on positive symptoms, early studies suggest that $mGlu_5$ PAMs may have effects in animal models that are relevant to the negative symptoms in schizophrenia. Specifically, one of the first systemically active $mGlu_5$ PAMs, CDPPB, attenuates the ability of an NMDA receptor antagonist, MK-801, to induce deficits in sucrose preference in rats (Vardigan *et al.*, 2010). Finally, abundant evidence from animal studies now supports the hypothesis that $mGlu_5$ PAMs may have efficacy in improving multiple domains of cognitive function. Selective $mGlu_5$ PAMs enhance forms of synaptic plasticity that are thought to provide a cellular mechanism for specific forms of cognitive function (Ayala *et al.*, 2009; Noetzel *et al.*, 2012) and $mGlu_5$ PAMs enhance multiple forms of cognitive function in animal models that are thought to reflect specific domains of cognition that are disrupted in schizophrenia patients (Ayala *et al.*, 2009; Chan *et al.*, 2008; Clifton *et al.*, 2012; Darrah *et al.*, 2008; Gastambide *et al.*, 2012; Horio *et al.*, 2012; Liu *et al.*, 2008; Uslaner *et al.*, 2009).

While the studies outlined above are encouraging, to date no $mGlu_5$ PAMs have been advanced into clinical studies. As with most novel targets for CNS disorders, there are clear challenges that must be overcome before $mGlu_5$ PAMs could be used for the treatment of schizophrenia. For instance, Parmentier-Batteur *et al.* (2012) recently reported that repeated administration of the $mGlu_5$ PAM CDPPB may lead to desensitization and a diminished response. It is not clear whether this represents a pharmacodynamic tolerance that will be seen with all $mGlu_5$ PAMs or if this will impact efficacy with chronic dosing. However, the possibility that efficacy could be lost with chronic administration of $mGlu_5$ PAMs warrants further investigation. More importantly, recent studies suggest that some $mGlu_5$ PAMs may also have severe target-dependent adverse effects, including induction of behavioral convulsions and excitotoxicity (Parmentier-Batteur *et al.*, 2011; Rook *et al.*, 2012). If these adverse effects are common to all $mGlu_5$ PAMs, this could prevent these agents from advancing to clinical development. However, some $mGlu_5$ PAMs have been shown to have efficacy without inducing obvious adverse effects. Furthermore, a recent study suggests that some $mGlu_5$ PAMs can directly activate $mGlu_5$ as allosteric agonists (Noetzel *et al.*, 2012; Rook *et al.*, 2012). Interestingly, closely related $mGlu_5$ PAMs that differ in terms of allosteric agonist activity also differ in their propensity to induce these adverse effects. Thus, $mGlu_5$ PAMs that have been optimized to have robust agonist activity induce severe adverse effects including behavioral convulsions, whereas closely related $mGlu_5$ PAMs with no observable agonist activity exhibit *in vivo* efficacy in animal models predictive of antipsychotic activity but do not induce seizure activity or other observable adverse effects. It is likely that multiple factors can contribute to the safety profiles of $mGlu_5$ PAMs. However, these data suggest that relatively subtle differences in the properties of different $mGlu_5$ PAMs can dramatically influence the overall *in vivo* profile of these compound. Understanding the potential liabilities of $mGlu_5$ PAMs and the factors that influence different *in vivo* profiles of these compounds will be critical for advancing $mGlu_5$ PAMs into clinical testing in patients suffering from schizophrenia.

Group II Metabotropic Glutamate Receptors

In addition to $mGlu_5$, major efforts have been focused on selective activation of two other mGlu subtypes, $mGlu_2$ and $mGlu_3$, as a novel approach for treatment of schizophrenia. The $mGlu_2$ and $mGlu_3$ receptor subtypes are closely related in terms of primary sequence, signaling, and pharmacological profile, and together these subtypes are referred to as the

group II mGlu receptors. Studies dating back to the 1990s reveal that highly selective group II mGlu agonists have robust activity in a range of animal models predictive of antipsychotic activity (Lorrain *et al.*, 2003; Marek *et al.*, 2000; Moghaddam and Adams, 1998; Schoepp and Marek, 2002). These group II mGlu agonists have similar agonist activity at $mGlu_2$ and $mGlu_3$, but are highly selective for the group II mGlus relative to all other mGlu subtypes. Unlike $mGlu_5$ PAMs and GlyT1 inhibitors, $mGlu_{2/3}$ agonists do not directly potentiate NMDA receptor currents in most neuronal populations. Instead, these agents are thought to act at a circuit level to restore signaling balance of transmission through forebrain circuits that are disrupted by NMDA receptor antagonists and are thought to be disrupted in schizophrenia patients (Battaglia *et al.*, 1997; Lovinger and McCool, 1995; Moghaddam *et al.*, 1997; Moghaddam and Adams, 1998). For example, NMDA receptor antagonists and other psychotomimetic agents increase activity at synapses of glutamatergic projections from the thalamus to the prefrontal cortex (PFC). This increase in spontaneous activity is thought to reflect a loss of normal inhibitory control of transmission to the PFC and has been postulated to play a critical role in the pathophysiology of schizophrenia. Activation of group II mGlu receptors can dramatically reduce excessive excitatory transmission at these synapses in the PFC and thus may provide a mechanism by which these agents could provide antipsychotic effects.

Early clinical studies provided exciting support for the hypothesis that group II mGlu agonists could provide efficacy in the treatment of schizophrenia. In a phase II trial, LY2140023, a selective group II mGlu agonist developed by Eli Lilly, improved ratings for positive and negative symptoms in patients suffering from schizophrenia (Patil *et al.*, 2007). Furthermore, there were no major liabilities associated with current medications, including sedation, amnesic symptoms, withdrawal upon discontinuation of the drug, prolactin elevation, extrapyramidal symptoms, or weight gain. Unfortunately, subsequent studies have not provided a clear confirmation of the efficacy of $mGlu_{2/3}$ agonists in the treatment of schizophrenia. For instance, in a larger multicenter trial, Kinon *et al.* (2011) reported that LY2140023 did not differentiate from placebo on standard scales of positive and negative symptoms. However, the placebo response in this study was higher than expected and the positive comparator, olanzapine, also failed to significantly separate from placebo. Thus, the results from this trial were inconclusive and did not provide a clear interpretation in terms of the potential efficacy of the group II mGlu receptor agonist. Unfortunately, further clinical studies of the effects of group II mGlu agonists have not been published in the peer reviewed literature. However, Eli Lilly recently announced that they had terminated development of LY2140023 based on a third clinical study in which they failed to observe efficacy in reducing symptoms of schizophrenia. In this latest study, the placebo response was reported to be within normal range and the positive comparator showed clear efficacy in separating from placebo (Carroll, 2012).

While the results of the Eli Lilly trial are disappointing, a possibility remains that future agents that target group II mGlu receptors will provide more reliable results. It is likely that subsequent clinical studies will shift from $mGlu_{2/3}$ agonists to focus on novel PAMs that are highly selective for $mGlu_2$ and have no activity at $mGlu_3$. As discussed above for $mGlu_5$ PAMs, these compounds do not activate $mGlu_2$ directly but bind to a site distinct from the glutamate binding site to increase responses of $mGlu_2$ to glutamate. Multiple $mGlu_2$ PAMs have been identified and these compounds have similar effects to those of $mGlu_{2/3}$ agonists on excitatory transmission in the PFC (Benneyworth *et al.*, 2007) and in animal models that predict antipsychotic efficacy (Duplantier *et al.*, 2009; Galici *et al.*, 2005; 2006; Govek *et al.*, 2005; Johnson *et al.*, 2003; Pinkerton *et al.*, 2005). While it is not known whether $mGlu_2$ PAMs will offer advantages over $mGlu_{2/3}$ agonists, it is conceivable that selectively targeting $mGlu_2$ will provide more reliable efficacy. Also, it is possible that chronic administration of traditional agonists leads to receptor desensitization and this could reduce

the clinical response to the agonists. Thus, selective $mGlu_2$ PAMs may provide an alternative approach that could have advantages to $mGlu_{2/3}$ agonists. At present, clinical data using $mGlu_2$ PAMs have not been reported. However, Addex Pharmaceuticals and Johnson and Johnson have advanced a novel $mGlu_2$ PAM termed ADX71149 into phase II efficacy studies in schizophrenia patients.

Summary

Current treatment strategies for schizophrenia primarily address the positive symptoms of the disorder. This leaves a large unmet need in the treatment of the negative and cognitive symptoms. Evidence suggests that targeting aberrant glutamatergic signaling may provide a new approach that could be used to treat all three symptom clusters in schizophrenia; a considerable improvement over the current therapeutics. The coming years will be instrumental in determining the feasibility of modulating glutamate signaling as therapeutic treatments for schizophrenia using compounds that act as GlyT1 inhibitors, $mGlu_5$ PAMs and/or $mGlu_{2/3}$ agonists or PAMs. Other targets may also be viable approaches to address glutamatergic tone for the treatment of schizophrenia; AMPA receptor expression is decreased while *D*-amino acid oxidase (DAAO) activity is elevated in schizophrenia, raising the possibility of these proteins as possible targets (for review, see de Bartolomeis *et al.*, 2012). Interestingly, AMPAkines are allosteric modulators of AMPA receptors, increasing channel opening, which may compensate for the lower expression levels (de Bartolomeis *et al.*, 2012). Inhibitors are sought for DAAO, thereby decreasing the degradation of *D*-serine, mediated by this enzyme (Madeira *et al.*, 2008). There are multiple avenues for glutamate based therapies for the treatment of schizophrenia. It will be important to continue to explore these possibilities to ultimately improve patient outcomes.

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