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Minireview

Metabotropic Glutamate Receptors As Emerging Targets for the Treatment of Schizophrenia

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ABSTRACT

Accumulating evidence of glutamatergic abnormalities in the brains of schizophrenia patients has led to efforts to target various components of glutamatergic signaling as potential new approaches for schizophrenia. Exciting research suggests that metabotropic glutamate (mGlu) receptors could provide a fundamentally new approach for better symptomatic relief in patients with schizophrenia. In preclinical studies, the $mGlu_5$ receptor positive allosteric modulators (PAMs) show efficacy in animal models relevant for all symptom domains in schizophrenia. Interestingly, biased pure $mGlu_5$ receptor PAMs that do not potentiate coupling of $mGlu_5$ receptors to N-methyl-D-aspartate (NMDA) receptors lack neurotoxic effects associated with $mGlu_5$ PAMs that enhance coupling to NMDA receptors or have allosteric agonist activity. This provides a better therapeutic profile for treating schizophrenia-like symptoms. Additionally, the $mGlu_1$ receptor PAMs modulate dopamine release in the striatum, which may contribute to their antipsychotic-like effects. Besides group I mGlu ($mGlu_1$ and $mGlu_5$) receptors, agonists of $mGlu_{2/3}$ receptors also induce robust antipsychotic-like and procognitive effects in rodents and may be effective in treating symptoms of schizophrenia in a selective group of patients. Additionally, $mGlu_{2/4}$ receptor heterodimers modulate glutamatergic neurotransmission in the prefrontal cortex at selective synapses activated in schizophrenia and therefore hold potential as novel antipsychotics. Excitingly, the $mGlu_3$ receptor activation can enhance cognition in rodents, suggesting that $mGlu_3$ receptor agonist/PAM could provide a novel approach for the treatment of cognitive deficits in schizophrenia. Collectively, the development of mGlu receptor-specific ligands may provide an alternative approach to meet the clinical need for safer and more efficacious therapeutics for schizophrenia.

SIGNIFICANCE STATEMENT

The currently available antipsychotic medications do not show significant efficacy for treating negative symptoms and cognitive deficits in schizophrenia. Emerging preclinical and clinical literature suggests that pharmacological targeting of metabotropic glutamate receptors could potentially provide an alternative approach for designing safer and more efficacious therapeutics for treating schizophrenia.

Introduction

Schizophrenia is a heterogeneous neuropsychiatric disorder that affects around 1% of the population worldwide (Perälä et al., 2007). The clinical features of the disease are characterized by three symptom domains: positive symptoms that include hallucinations, delusions, and thought disorders; negative symptoms including blunted emotions, anhedonia, and social withdrawal; and cognitive deficits such as impairments in attention, executive function, and working memory. The currently prescribed therapeutic agents (both typical and atypical antipsychotics) show efficacy in reducing the severity of positive symptoms but have minimal impact on negative symptoms and cognitive deficits associated with schizophrenia (Li et al., 2016a). Further, a significant portion of patients do not respond to these medications, and many patients discontinue treatment because of the class-related adverse effects, such as extrapyramidal side effects (parkinsonism, bradykinesia, dystonic reactions, tardive dyskinesia, and tremor), sedation, and metabolic side effects (weight gain, hyperlipidemia, and type II diabetes) (Li et al., 2016a). Thus, there is an unmet clinical need for designing safer

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ABBREVIATIONS: ago-PAM, positive allosteric modulator (PAM) with agonist activity; CA1, Cornu Ammonis 1; CNS, central nervous system; DLPFC, dorsolateral prefrontal cortex; DOI, 2,5-Dimethoxy-4-iodoamphetamine; 5-HT, 5-hydroxy-tryptamine; KO, knockout; mGlu, metabotropic glutamate; mPFC, medial prefrontal cortex; NAAG, N-acetylaspartylglutamate; NAM, negative allosteric modulator; NMDA, N-methyl-D-aspartate; PAM, positive allosteric modulator; PANSS, Positive and Negative Syndrome Scale; PCP, phencyclidine; PFC, prefrontal cortex; pharmacoBOLD, pharmacological blood-oxygen-level dependent; PPI, prepulse inhibition; WT, wild-type.

therapeutic agents acting at new targets underlying the pathophysiology of schizophrenia.

Despite evidence for a central role of dysfunction of dopaminergic signaling in schizophrenia, the inability of current antipsychotics to treat schizophrenia effectively suggests that a hyperdopaminergic state does not account for all major symptoms of this disorder. Accumulating evidence suggests that dysfunction of glutamatergic signaling may contribute to the pathogenesis of schizophrenia (Coyle, 2006; Moghaddam and Javitt, 2012; Hu et al., 2015; Stahl, 2018). Pharmacological evidence for the role of glutamate in schizophrenia centers on the clinical findings that administration of the noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists like phencyclidine (PCP) and ketamine induce/exacerbate schizophrenia-like symptoms in healthy individuals (Hu et al., 2015). Based on these clinical observations, NMDA antagonists are used preclinically to induce various schizophrenia-like behaviors, such as hyperactivity, repetitive behavior, sensorimotor gating deficits, and motivational and cognitive impairments in rodents (Goff and Coyle, 2001; Barnes et al., 2017; Lee and Zhou, 2019). Interestingly, animals with genetic knockdown of the NR1 subunit of NMDA receptors exhibit a full range of behavioral phenotypes that may be relevant for schizophrenia, including hyperlocomotion, stereotypy, heightened anxiety-like behavior, lack of cognitive flexibility, and other forms of memory impairments (Mohn et al., 1999; Belforte et al., 2010). Similarly, animals lacking NR2A or NR2B subunits of NMDA receptors show behavioral and neurophysiological changes that may reflect pathophysiology observed in schizophrenia (Ito et al., 1997; Sprengel et al., 1998; Duncan et al., 2004; Brigman et al., 2008; von Engelhardt et al., 2008; Belforte et al., 2010; Kannangara et al., 2015). Collectively, these studies have led to the hypothesis that pathologic changes in glutamatergic circuits and NMDA receptor signaling may contribute to the pathophysiology associated with schizophrenia.

Interestingly, genome-wide association studies (GWAS) and linkage studies have shown a significant association of gene encoding for the components of glutamate receptors and maintenance of glutamatergic neurotransmission with schizophrenia (Timms et al., 2013; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Pocklington et al., 2015; Pers et al., 2016). These studies, along with extensive preclinical evidence mentioned above, reinforce the hypothesis that disruption of glutamatergic signaling and NMDA hypofunction may contribute to the pathophysiology of schizophrenia. Based on this, it is conceivable that pharmacological agents that reverse pathologic changes in NMDA receptor function or other aspects of glutamatergic signaling could provide symptomatic relief to patients with schizophrenia. However, direct modulation of NMDA receptors produces neuronal excitotoxicity and seizures, prohibiting direct NMDA receptor targeting as a viable therapeutic option. Therefore, it will be important to develop more optimized compounds targeting other components of the glutamatergic system and testing them in rodent models for treating schizophrenia-like deficits.

A growing body of preclinical and clinical evidence raise the exciting possibility that targeting metabotropic glutamate (mGlu) receptors may allow more subtle regulation of glutamatergic neurotransmission in key brain circuits that are relevant for schizophrenia and may provide novel drug targets for treatment of this disorder. Metabotropic glutamate receptors are G protein-coupled receptors and are classified into three groups based on amino acid sequence homology, G protein binding, pharmacological profile, and signaling. Group I mGlu receptors include $mGlu_1$ and $mGlu_5$ receptors, group II includes $mGlu_2$ and $mGlu_3$ receptors, and group III includes $mGlu_4$, $mGlu_6$, $mGlu_7$, and $mGlu_8$ receptors (Niswender and Conn, 2010; Dogra and Conn, 2021). These receptors signal via coupling with different G-proteins: Group I mGlu receptors typically couple to $G_{q/11}$ proteins and group II and III receptors are coupled to $G_{i/o}$ proteins (Niswender and Conn, 2010). Their ability to modulate the glutamatergic transmission in the brain areas implicated in schizophrenia makes them exciting targets for developing improved pharmacotherapies for schizophrenia.

Genomic Variants in *GRM5* and $mGlu_5$ Receptor Hypofunction Are Associated with Schizophrenia

GRM5 (the gene encoding for $mGlu_5$ receptor) has emerged as a promising target for the treatment of various symptoms of schizophrenia. Polymorphisms in *GRM5* are associated with schizophrenia (Devon et al., 2001) and impaired cognition in patients with schizophrenia (Matosin et al., 2018). A recent study by Wang et al. (2020) has reported reduced $mGlu_5$ receptor signaling in the postmortem dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia. The authors also observed increased serine and tyrosine phosphorylation of $mGlu_5$ receptors in DLPFC, which may cause receptor desensitization leading to reduced $mGlu_5$ receptor signaling observed in the patients with schizophrenia (Wang et al., 2020). Interestingly, lower $mGlu_5$ receptor availability in the left temporal cortex was associated with higher levels of negative symptoms and worse performance in cognitive tasks in male patients with chronic schizophrenia (Régio Brambilla et al., 2020). These findings support the concept that dysregulation of $mGlu_5$ receptor signaling/function may underly the pathophysiology of schizophrenia.

These clinical studies are complemented by studies in *GRM5* knockout (KO) mice displaying sensorimotor gating deficits, spontaneous hyperactivity, and loss of NMDA receptor-mediated components of some forms of synaptic plasticity (Jia et al., 1998; Brody et al., 2004a,b; Brody and Geyer, 2004; Burrows et al., 2015). These KO mice also exhibit abnormalities in sleep and neural oscillatory processing similar to patients with schizophrenia (Aguilar et al., 2020). Further, *GRM5* KO mice display impaired performance on discrimination learning and reversal learning in a trial-unique nonmatching-to-location task indicating learning and memory deficits in these mice (Zeleznikow-Johnston et al., 2018). Also, deletion of *GRM5* from cortical pyramidal neurons causes increased novelty-induced locomotion, and systemic treatment with the psychostimulant methylphenidate can further enhance their locomotion (Jew et al., 2013). These findings indicate that *GRM5* KO mice display deficits modeling all symptom domains of schizophrenia and reiterate the critical roles of $mGlu_5$ receptors in schizophrenia pathophysiology. Similarly, administration of $mGlu_5$ receptor negative allosteric modulators (NAMs) evoke behavioral deficits correlated with schizophrenia (Koros et al., 2007;

Swedberg et al., 2014) and potentiate behavioral deficits induced by psychotomimetic agents (Henry et al., 2002; Campbell et al., 2004), providing evidence linking $mGlu_5$ receptors to schizophrenia.

$mGlu_5$ Potentiators Reduce Behavioral Disruptions That Are Relevant for Schizophrenia in Rodent Models

The $mGlu_5$ receptor positive allosteric modulators (PAMs) can induce cognition-enhancing effects, including improvements in object recognition memory, attenuation of conditioned avoidance response, and reduced impulsivity in the five-choice serial reaction time test in rodents (Liu et al., 2008; Uslaner et al., 2009; Schlumberger et al., 2010; Huang et al., 2016; Yang et al., 2016). Also, systemic administration of the $mGlu_5$ receptor PAMs CDPPB and ADX427273 increases hippocampus-dependent spatial learning in the Morris water maze test (Ayala et al., 2009). Similarly, another $mGlu_5$ receptor PAM, DPFE, enhanced the acquisition of contextual fear conditioning in rats (Gregory et al., 2013). Interestingly, the $mGlu_5$ receptor agonists/PAMs CHPG, CDPPB, ADX47273, BMS-955829, DPFE, and DFB were able to reverse the cognitive deficits and motivational impairments induced by NMDA receptor antagonists as well as hyperactivity induced by amphetamine, apomorphine, and PCP (Liu et al., 2008; Stefani and Moghaddam, 2010; Vales et al., 2010; Gastambide et al., 2012; Gregory et al., 2013; LaCrosse et al., 2015; Yang et al., 2016). These studies support the hypothesis that allosteric potentiation of the $mGlu_5$ receptors could provide a novel pharmacotherapeutic approach for treating multiple symptom domains in schizophrenia.

Newer $mGlu_5$ receptor-selective PAMs also show efficacy in rodent models that have traditionally been used to predict therapeutic efficacy of various drugs for schizophrenia. For example, the $mGlu_5$ receptor-selective PAMs VU0092273 and VU0364289 dose-dependently reversed amphetamine-induced hyperactivity in rodents, a model predictive of antipsychotic activity (Rodriguez et al., 2010; Noetzel et al., 2012; Gregory et al., 2013). Similar antipsychotic-like effects were also observed with a dihydrothiazolopyridone class of $mGlu_5$ receptor PAM (Bartolomé-Nebreda et al., 2013). Since the $mGlu_5$ receptors are closely associated with NMDA receptors (Alagarsamy et al., 1999; Benquet et al., 2002; Collett and Collingridge, 2004; O'Riordan et al., 2018), an early hypothesis was that targeting $mGlu_5$ receptors may exert these effects by augmenting NMDA receptor function to mitigate the NMDA receptor hypofunction and symptoms observed in schizophrenia.

Biased $mGlu_5$ Receptor PAMs That Do Not Potentiate Coupling of $mGlu_5$ Receptors to NMDA Receptors or Exert Allosteric Agonist Activity Do Not Induce Observable Adverse Effects

Despite the promising effects of $mGlu_5$ receptor PAMs in the preclinical studies, the development of these compounds for the treatment of schizophrenia has been hampered by neurotoxicology issues, possibly related to intrinsic allosteric agonist activity (ago-PAMs) and excessive activation of NMDA receptors (Rook et al., 2013; Parmentier-Batteur et al., 2014). Early studies revealed that $mGlu_5$ receptor ago-PAMs induce seizures and other adverse effects that are not as prominent with pure $mGlu_5$ receptor PAMs that lack intrinsic allosteric agonist activity (Rook et al., 2013; Parmentier-Batteur et al., 2014). Furthermore, the known adverse effects associated with overactivation of NMDA receptors raised the possibility that $mGlu_5$ receptor PAMs that are biased away from NMDA receptor potentiation may lack excitotoxic/seizure-inducing profiles (Rook et al., 2015). Supporting this theory, the biased $mGlu_5$ receptor PAM VU0409551, which does not enhance $mGlu_5$ receptor-mediated potentiation of NMDA receptor currents, induces robust antipsychotic-like (MK801-induced hyperlocomotion) and cognition-enhancing effects (novel object recognition and contextual fear conditioning) in wild-type (WT) mice (Rook et al., 2015). It also rescued deficits in contextual fear conditioning and synaptic plasticity in serine racemase KO mice, a genetic model that exhibits several behavioral abnormalities observed in schizophrenia (Balu et al., 2016). The studies with VU0409551 suggest that biased $mGlu_5$ receptor PAMs lacking $mGlu_5$ receptor-mediated potentiation of NMDA receptor currents retain antipsychotic-like and cognition-enhancing effects in rodent models relevant for schizophrenia. Thus, the initial hypothesis that $mGlu_5$ receptor PAMs induce their beneficial effects by potentiating NMDA receptor currents must be reevaluated. The mechanistic studies revealed that VU0409551 could enhance cognition independent of NMDA receptor activation (Balu et al., 2016). Further, biased $mGlu_5$ receptor PAM may increase cognition by $mGlu_5$ receptor-mediated potentiation of excitability of hippocampal Cornu Ammonis 1 (CA1) pyramidal neurons (Mannaioni et al., 2001) or endocannabinoid-mediated depression of inhibitory neurotransmission onto pyramidal neurons (Xu et al., 2014). Collectively, the above-mentioned studies propose that a detailed understanding of the mechanisms of action of $mGlu_5$ receptor PAMs might help to develop safer compounds with robust efficacy for treating schizophrenia.

$mGlu_1$ Receptor PAMs May Have Potential Antipsychotic Effects

Frank and coworkers (2011) identified nonsynonymous single nucleotide polymorphisms (nsSNPs) within a functionally important cysteine-rich domain and the first transmembrane helix of the $mGlu_1$ receptor in patients with schizophrenia. Subsequently, a study involving 605 controls and 450 patients with schizophrenia confirmed the presence of deleterious mutations in *GRM1* (the gene encoding for $mGlu_1$ receptor) in patients with schizophrenia (Ayoub et al., 2012). Also, these mutations were inheritable and were also detected in relatives with other neuropsychiatric disorders, including depression and anxiety. *In vitro* analysis using $mGlu_1$ receptors bearing various schizophrenia-associated *GRM1* mutations indicated altered cell surface receptor expression and reduced downstream signaling (Ayoub et al., 2012; Cho et al., 2014). Excitingly, the selective $mGlu_1$ receptor PAMs Ro 07-11401, VU0483605, and VU0483737 were able to potentiate signaling by the mutant receptors and thereby reduce deficits in $mGlu_1$ receptor signaling (Cho et al., 2014). Similarly, another set of $mGlu_1$ receptor PAMs based on an N-(3-chloro-4-(1,3-dioxoisoindolin-2-yl)phenyl)-3-methylfuran-2-carboxamide scaffold

also potentiated the function of $mGlu_1$ receptors mutated for schizophrenia-associated deleterious *GRM1* mutations (Garcia-Barrantes et al., 2015). These findings indicate that schizophrenia patients with specific mutations may be responsive to interventions with $mGlu_1$ receptor PAMs and highlight the effect of the clinical heterogeneity of schizophrenia on disease prognosis.

The $mGlu_1$ Receptor Ligands Display Antipsychotic-Like Effects in Rodents

Interestingly, recent studies revealed that the $mGlu_1$ receptor PAM VU6004909 reduced amphetamine-induced hyperlocomotion and disruptions in prepulse inhibition (PPI) in mice (Yohn et al., 2020). These effects were absent after administration of cannabinoid type 2 (CB_2) receptor antagonist, which indicates that the antipsychotic-like effects of VU6004909 are dependent on CB_2 receptor activation. Further, mechanistic studies reveal that VU6004909 inhibits dopamine release in the striatum, not in the nucleus accumbens, and a crosstalk between $mGlu_1$ and muscarinic M4 receptors has been suggested for this inhibition on dopamine release (Yohn et al., 2020). Because the mutations in *GRM1* reduce $mGlu_1$ receptor signaling and *GRM1* KO mice display deficits in PPI (Brody et al., 2003), it is possible that altered receptor expression may contribute to the hyperdopaminergic state observed in schizophrenia. Therefore, $mGlu_1$ receptor PAMs may act by correcting striatal dopamine hyperactivity leading to the antipsychotic-like activity in models mimicking schizophrenia symptomatology. Recently, it has been reported that the $mGlu_1$ receptor PAM VU6004909 can reverse the cortical hyperactivity and cognitive deficits induced by MK801 treatment (Maksymetz et al., 2021). Future studies are needed to investigate the efficacy of $mGlu_1$ receptor PAMs on other behavioral correlates of cognitive and negative symptoms of schizophrenia.

It is important to note that early preclinical behavioral studies also argued in favor of employing $mGlu_1$ receptor antagonism as a pharmacotherapeutic approach to schizophrenia. For example, the $mGlu_1$ receptor NAMs FTIDC and CFMTI blocked methamphetamine-induced hyperactivity and reduced methamphetamine-induced disruption in PPI in rodents (Satow et al., 2008, 2009). Also, CFMTI and JNJ162-59685 ($mGlu_1$ receptor antagonists) improved MK801-induced impairments in social memory (Satow et al., 2009; Hikichi et al., 2013), suggesting that $mGlu_1$ receptor NAMs could be effective for the treatment of some impairments associated with schizophrenia. At present, the mechanistic basis for overlapping actions of $mGlu_1$ receptor PAMs and $mGlu_1$ receptor NAMs is not understood.

Group II ($mGlu_{2/3}$) Receptor Agonists Show Efficacy for Treating Behavioral Correlates of Schizophrenia

Agonists of $mGlu_{2/3}$ receptors can reverse the behavioral effects of NMDA receptor antagonists, including induction of hyperlocomotion, stereotypy, and heightened anxiety in rodents (Moghaddam and Adams, 1998; Rorick-Kehn et al., 2007; Watanabe et al., 2020). Further, the $mGlu_{2/3}$ receptor agonist LY354740 reduced PCP-induced working memory deficits in mice (Moghaddam and Adams, 1998) and improved working memory impairments induced by ketamine infusion in healthy human subjects (Krystal et al., 2005). These and other studies have stimulated efforts to develop $mGlu_{2/3}$ receptor agonists as novel potential antipsychotic agents. Also, $mGlu_{2/3}$ receptor agonists attenuate various effects induced by the hallucinogen 2,5-Dimethoxy-4-iodoamphetamine (DOI) in rodents, including expression of immediate early gene, c-FOS, in the cortex (Zhai et al., 2003; González-Maeso et al., 2008), increased excitatory synaptic responses in the medial prefrontal cortex (mPFC) (Marek et al., 2000), and head twitch response (Gewirtz and Marek, 2000; González-Maeso et al., 2008). In addition, the $mGlu_{2/3}$ receptor agonists MGS0008 and LY404039 inhibited conditioned avoidance responses in WT mice (Takamori et al., 2003; Rorick-Kehn et al., 2007). Recently, our group reported that the $mGlu_{2/3}$ receptor agonist LY379268 enhances associative learning as evidenced by increased freezing in trace fear conditioning in WT mice (Dogra et al., 2021). Further, using $mGlu_2$ and $mGlu_3$ receptor-specific NAMs, we showed that the $mGlu_3$ receptor is mediating cognition-enhancing effects of LY379268. Interestingly, the $mGlu_{2/3}$ receptor agonist LY379268 was able to revert PCP-induced deficits in associative learning (Dogra et al., 2021). All of these studies indicate the potential utility of $mGlu_{2/3}$ receptor agonists for the treatment of various schizophrenia-associated symptoms.

Clinical Trials Using $mGlu_{2/3}$ Receptor Agonists Yielded Inconclusive Results

Based on the extensive preclinical literature, Eli Lilly & Co. launched LY2140023 (pomaglumetad methionil, prodrug of the active $mGlu_{2/3}$ receptor agonist LY404039) into clinical trials, where it showed efficacy for improving total Positive and Negative Syndrome Scale (PANSS) scores as well as positive and negative symptoms of schizophrenia compared with placebo control in early phase II clinical trials (Patil et al., 2007; Kinon and Gómez, 2013). Excitingly, LY2140023 treatment did not induce any extrapyramidal side effects, increase in mean serum prolactin, or weight gain (Patil et al., 2007).

These encouraging proof-of-concept trials were followed by a second phase II dose-response trial in which neither LY21-40023 nor olanzapine demonstrated significant efficacy compared with placebo (Kinon et al., 2011). This led to inconclusive clinical trials which were likely due to high placebo response in patients with schizophrenia. Another phase II study assessed the efficacy of LY2140023 for 24 weeks and found improvements in PANSS total score similar to the standard of care (olanzapine, risperidone, or aripiprazole) group over the initial 6 to 8 weeks of treatment, but at the endpoint lesser improvement was observed in the LY2140023 group (Adams et al., 2013). Besides, trials including LY2140023 as a monotherapy or adjunctive treatment failed to show efficacy for improving symptoms (Adams et al., 2013; Stauffer et al., 2013), which led to the cessation of the LY2140023 drug development program for schizophrenia. However, a post hoc analysis of all clinical trials showed that LY2140023 displayed therapeutic efficacy in subgroups of patients who were early in disease ($\leq$3 years) or who were previously treated with dopamine D2 receptor drugs and were never treated with 5-hydroxy-tryptamine $(5\text{-HT})_{2A}$ receptor blockers (Kinon et al., 2015). These promising results indicate the need for testing $mGlu_{2/3}$ receptor agonists in

patients with schizophrenia recruited based on disease duration, history of previous medication, and genetic background. Further, it will be important to tease apart the relative contributions of $mGlu_2$ and $mGlu_3$ receptors in mediating beneficial effects of $mGlu_{2/3}$ receptor agonists.

Recently, LY2140023 was tested in phase Ib proof-of-concept studies in which high doses of LY2140023 (320 mg/day for 10 days) significantly reduced ketamine-induced Brief Psychiatric Rating Scale (BPRS) total symptoms (Kantrowitz et al., 2020). However, it did not significantly inhibit ketamine-induced changes in the pharmacological blood-oxygen-level dependent (pharmacoBOLD) signals in the dorsal anterior cingulate cortex, suggesting that the tested dose might still be too low for optimal target engagement. Besides LY2140023, a novel $mGlu_{2/3}$ receptor agonist prodrug TS-134 (MGS0274 besylate) entered the clinical trials and was found to be safe and well tolerated in a double-blinded and placebo-controlled dose-response phase I clinical trial conducted in healthy subjects (Watanabe et al., 2020). Further clinical studies reported reductions in both ketamine-induced BPRS positive symptoms and pharmacoBOLD in the dorsal anterior cingulate cortex, left caudate, and nucleus accumbens after treatment with a low dose of TS-134 (20 mg/day for 6 days) (Kantrowitz et al., 2020). These results provide evidence of symptom reduction and target engagement by a $mGlu_{2/3}$ receptor agonist and further suggest that dose optimization and characterization of changes in the glutamatergic neurotransmission are required to fully harness the therapeutic potential of $mGlu_{2/3}$ receptor agonists. Also, it will be exciting to evaluate the therapeutic effects of TS-134 in patients with schizophrenia.

$mGlu_2$ Receptor PAMs May Have Potential Antipsychotic Activity

In terms of subtype selectivity based on the studies performed with *GRM2* (the gene encoding for $mGlu_2$ receptor) and *GRM3* (the gene encoding for $mGlu_3$ receptor) KO mice, it has been suggested that the $mGlu_2$ receptor, not the $mGlu_3$ receptor, mediates the antipsychotic effects of $mGlu_{2/3}$ receptor agonists in rodents (Spooren et al., 2000; Woolley et al., 2008). In the past decade, several preclinical studies have shown antipsychotic-like and anxiolytic-like effects of the $mGlu_2$ receptor PAMs CBiPES, BINA, TASP0443294, TASP0433864, JNJ40411813/ADX71149, and JNJ-42153605 (Johnson et al., 2003, 2005; Galici et al., 2005, 2006; Govek et al., 2005; Benneyworth et al., 2007; Hiyoshi et al., 2014; Hikichi et al., 2015; Lavreysen et al., 2015). Another $mGlu_2$ receptor PAM, SAR218645, has been shown to improve cognitive symptoms induced by an NMDA receptor antagonist, reverse working memory impairments in NR1 KO mice, and reverse amphetamine-induced disruptions in sensory processing and attention (Griebel et al., 2016). These studies point toward the SAR218645 class of PAMs as a promising candidate for the treatment of cognitive impairments in schizophrenia, especially in patients with anomalous attention and sensory gating abilities.

Based on the preclinical studies, two $mGlu_2$ receptor PAMs, JNJ40411813 (Salih et al., 2015) and AZD8529 (Litman et al., 2016), have entered clinical trials. Both PAMs displayed safety and tolerability in healthy subjects. JNJ40411813 ameliorated deficits in attention and episodic memory in the selective population and reduced ketamine-induced negative symptoms (Salih et al., 2015). These promising trials suggest that patients with residual negative symptoms are most likely to benefit from treatment with JNJ40411813. The second compound, AZD8529, did not show any extrapyramidal motor side effects, but it failed to show any significant improvement in positive and negative symptom subscale and PANSS total score as compared with placebo (Litman et al., 2016). To note, AZD8529 was tested at only one dose selected from tolerability data obtained from the prior healthy volunteer and preclinical studies. Thus, it is possible that low systemic exposure at this dose failed to engage $mGlu_2$ receptors or induce detectable effects. Therefore, further studies including multiple dosages of AZD8529 are warranted. Taken together, these studies reveal the potential shortcomings of preclinical research and the difficulty in translating preclinical research findings to clinics. Furthermore, considering the underlying heterogeneity of patients with schizophrenia, it may be best to test $mGlu_{2/3}$ receptor agonists/$mGlu_2$ receptor PAMs in patient populations recruited based on genotype and clinical symptoms.

Genetic Variants in *GRM3* Are Associated with Schizophrenia

Emerging evidence suggests an association between genetic variations in *GRM3* and risk for schizophrenia and cognitive deficits in schizophrenia (Fujii et al., 2003; Egan et al., 2004; Bishop et al., 2011, 2015; Chang et al., 2015; Saini et al., 2017). Interestingly, polymorphisms in *GRM3* may predict improvement in negative symptoms in patients with schizophrenia treated with antipsychotic medications (Bishop et al., 2005, 2015; Fijal et al., 2009). Also, one *GRM3* polymorphism, rs1468412, was associated with worsening of spatial working memory performance after antipsychotic treatment (Bishop et al., 2015). All of these genetic association studies suggest an important pharmacogenetic relationship between *GRM3* polymorphisms and changes in cognitive and negative symptom response to antipsychotic treatment. Furthermore, this information can be used to identify patients with schizophrenia who are susceptible to adverse cognitive effects induced by antipsychotic medications. These gene polymorphisms studies are supported by findings indicating impaired working memory in *GRM3* KO mice (Lainiola et al., 2014; De Filippis et al., 2015), further stipulating an essential role of the $mGlu_3$ receptor in some forms of cognition.

$mGlu_3$ Receptor Is a Promising Target for Enhancing Cognition in Schizophrenia

The exciting gene association studies encouraged the researchers to investigate the mechanisms by which the $mGlu_3$ receptor regulates cognition and cognitive impairments associated with schizophrenia. Owing to the lack of receptor-specific compounds, early preclinical studies used N-acetylaspartylglutamate (NAAG) peptidase (an enzyme that inactivates the peptide transmitter) inhibitors. NAAG is a peptide neurotransmitter that activates $mGlu_3$ receptors (Wroblewska et al., 1997) and is known to enhance cognition

(Neale and Olszewski, 2019). Therefore, drugs that block the inactivation of synaptically released NAAG (NAAG peptidase inhibitors) activate $mGlu_3$ receptors and can enhance cognition (Neale and Olszewski, 2019). Also, NAAG peptidase inhibitors blocked MK801-induced impairments in object recognition and motor activation induced by PCP and amphetamine (Olszewski et al., 2012b). These inhibitors were able to rescue PCP-induced motor activation and stereotypic behavior in WT mice (Olszewski et al., 2004) but not in *GRM3* KO mice (Olszewski et al., 2012a). Interestingly, they reduced PCP-induced glutamate and dopamine release in the prefrontal cortex (PFC) and the nucleus accumbens (Zuo et al., 2012) that may account for their antipsychotic-like effects. To note, mice lacking the enzymes that synthesize NAAG in the central nervous system (CNS) have impaired object recognition memory (Becker et al., 2021), suggesting an important role of NAAG (and $mGlu_3$ receptors) in cognition. In summary, the above-mentioned literature raises the potential therapeutic utility of targeting $mGlu_3$ receptors for treating schizophrenia and the need for further studies aimed at understanding the mechanisms by which $mGlu_3$ receptors may enhance cognition in schizophrenia.

Using recently developed $mGlu_3$ specific ligands, mechanistic studies revealed that the $mGlu_3$ receptor modulates synaptic plasticity within the PFC and hippocampus (Walker et al., 2015; Joffe et al., 2019; Dogra et al., 2021). Interestingly, $mGlu_3$ receptors functionally interact with $mGlu_5$ receptors in the CNS (Di Menna et al., 2018; Dogra et al., 2021) and enhance $mGlu_5$ receptor-mediated somatic Ca^{2+} mobilization in the cortical pyramidal neurons. Also, activation of $mGlu_5$ receptor is required for $mGlu_3$ receptor-mediated long-term depression in the PFC (Di Menna et al., 2018) and extinction of fear memories (Walker et al., 2015). Further, a nonhuman primate study showed that an increase in the endogenous $mGlu_3$ receptor agonist NAAG enhances DLPFC delay cell firing during a working memory task (Jin et al., 2018). These studies illuminate the mechanisms by which $mGlu_3$ receptors can modulate PFC function and cognition and suggest that $mGlu_3$ receptor PAMs have the potential to reduce the PFC-dependent cognitive impairments associated with CNS disorders like schizophrenia.

This $mGlu_3$ receptor-induced potentiation of $mGlu_5$ receptor function in the PFC is also observed in the hippocampus (Dogra et al., 2021). Our group discovered that activation of $mGlu_3$ receptors in the CA1 pyramidal neurons induces metaplastic changes to induce long-term potentiation at the SC-CA1 synapse through an $mGlu_5$ receptor-dependent, endocannabinoid-mediated disinhibition (Dogra et al., 2021). Further, the $mGlu_3$ receptor has been shown to shape the influence of $mGlu_5$ receptors on excitotoxic insults (Di Menna et al., 2018). Given the fact that activation of $mGlu_3$ receptor may provide neuroprotection (Caraci et al., 2011), pharmacological agents activating $mGlu_3$ receptors may reduce the risk for neurotoxicity while improving schizophrenia-related cognitive deficits.

$mGlu_4$ Receptor Ligands Have the Potential To Treat Positive Symptoms of Schizophrenia

The availability of brain-penetrable receptor-selective ligands has facilitated the study of group III mGlu receptors in schizophrenia. Peripheral administration of pan-group III mGlu receptor agonist ACPT-I exerted antipsychotic-like effects (reducing MK801- and amphetamine-induced hyperactivity and DOI-induced head twitches) in rats (Pałucha-Poniewiera et al., 2008). Similar antipsychotic-like effects were also observed with $mGlu_4$ receptor-selective agonists LSP1-2111 (Wierońska et al., 2012) and LSP4-2022 (Woźniak et al., 2016). In addition, LSP4-2022 improved negative symptoms and cognition in MK801-treated mice (Woźniak et al., 2016). Interestingly, $mGlu_4$ receptors cooperate with other neurotransmitter receptors to induce antipsychotic-like effects in rodents (Woźniak et al., 2016, 2017). For example, the antipsychotic-like activity of the $mGlu_4$ receptor agonist LSP4-2022 was reversed by the $GABA_B$ receptor antagonist CGP55845. Further, coadministration of subeffective doses of LSP4-2022 and $GABA_B$ receptor PAMs acted synergistically to produce antipsychotic-like effects (Woźniak et al., 2016). Similarly, the $5\text{-}HT_{1A}$ receptor antagonist WAY100635 reversed antipsychotic-like actions of the $mGlu_4$ receptor agonist LSP4-2022, whereas administration of a subeffective dose of the $5\text{-}HT_{1A}$ receptor agonist with an ineffective dose of LSP4-2022 enhanced the effects of ineffective dosage of LSP4-2022 (Woźniak et al., 2017). The receptor interaction has also been extended to the M4 muscarinic receptor, where coadministration of subactive doses of LSP4-2022 and M4 receptor PAMs induced a robust antipsychotic-like effects (Cieślik et al., 2018b). Similar antipsychotic-like properties have also been reported with the $mGlu_4$ receptor PAMs Lu AF21934 (Sławińska et al., 2013) and ADX88178 (Kalinichev et al., 2014). These studies further support the potential utility of selective $mGlu_4$ receptor activators for treating positive symptoms of schizophrenia.

Potential Utility of $mGlu_2$-$mGlu_4$ Receptor Heterodimers As Novel Antipsychotics

Emerging studies suggest that $mGlu_4$ and $mGlu_2$ receptors can form heterodimers in native brain tissues (Yin et al., 2014). Excitingly, a recent study demonstrated that activation of $mGlu_{2/4}$ receptor heterodimers inhibits DOI-induced increase in glutamatergic neurotransmission in the PFC ex vivo (Xiang et al., 2021). Further mechanistic studies revealed a synapse-specific role of these heterodimers in which these heterodimers presented activity at synapses to medial PFC (mPFC) originating from the thalamus (thalamo-mPFC) but not at the synapses to the mPFC originating from basolateral amygdala and ventral hippocampus (Xiang et al., 2021). This indicates that $mGlu_{2/4}$ receptor heterodimers could selectively modulate specific functions associated with thalamo-mPFC synapses (Xiang et al., 2021). Interestingly, thalamic nuclei and the projections from the thalamus are widely known to play roles in the actions of NMDA receptor antagonists (Santana et al., 2011; Zhang et al., 2012). Moreover, the thalamocortical system is an important site of action of hallucinogenic drugs like DOI and lysergic acid diethylamide (LSD) (Scruggs et al., 2000; Marek et al., 2001; Preller et al., 2019; Inserra et al., 2021), and agents that modulate or depress transmission over this synapse may show antipsychotic-like effects. Therefore, the $mGlu_{2/4}$ receptor heterodimer at the same synapse could be a

novel therapeutic target for the treatment of positive symptoms associated with schizophrenia.

In line with the cellular effects of $mGlu_{2/4}$ receptor activation, Lu AF21934, an $mGlu_4$ receptor PAM with activity at $mGlu_{2/4}$ receptor heterodimers, has been shown to inhibit MK801- and amphetamine-induced hyperactivity and reverse of DOI-induced head twitch in rodents (Sławińska et al., 2013; Wierońska et al., 2015). Considering the fact that the $mGlu_4$ receptor homodimer-specific PAMs PHCCC and VU0418506 fail to potentiate L-AP4-mediated inhibition of thalamo-PFC transmission in slices (Xiang et al., 2021), it is conceivable that the previously reported antipsychotic-like effects of LuAF21934 are likely to be mediated by actions on $mGlu_{2/4}$ receptor heterodimers. Nevertheless, it will be important to test the behavioral effects of homomer-selective $mGlu_2$ and $mGlu_4$ receptors PAMs relative to $mGlu_{2/4}$ receptor modulators in rodent models of NMDA hypofunction to develop a better understanding of their role in treating positive symptoms of schizophrenia.

Deletion or Blockade of $mGlu_7$ Receptor Impairs Cognition

Genetic variations in *GRM7* (the gene encoding for $mGlu_7$ receptor) are associated with schizophrenia (Niu et al., 2015; Li et al., 2016b; Chaumette et al., 2020). Specifically, the polymorphism rs1396409 was associated with performance intellectual quotient in a discovery cohort of 144 patients with first-episode psychosis and was further replicated in 121 ultra-high-risk patients (Chaumette et al., 2020). This polymorphism is also associated with the cognitive deficits during the onset of psychosis and highlights the impact of $mGlu_7$ receptor signaling in cognitive impairments in early psychotic episodes. These studies are supported by pharmacological studies in which systemic administration of the $mGlu_7$ receptor NAM MMPIP impaired cognitive performances in WT mice as depicted by reduction in the recognition index and location index in the object recognition and object location test, respectively (Hikichi et al., 2010). Also, MMPIP treatment increased the total time to complete the task in the eight-arm radial maze test and decreased social interaction in rats. These results are complemented by the behavioral profiling studies indicating deficits in various forms of cognition tasks in *GRM7* KO mice. For example, *GRM7* KO mice displayed deficits in fear response immediately after and 1 day after exposure to foot shock (Masugi et al., 1999) and in both contextual and cued fear learning (Goddyn et al., 2008; Fisher et al., 2020). Further, these mice showed impaired spatial working memory in the water maze test and eight-arm radial maze test (Hölscher et al., 2004; Callaerts-Vegh et al., 2006). These deficits in cognition were accompanied by disruption of social behavior in which deletion of the $mGlu_7$ receptor impacted social preference but not sociability or social recognition (Fisher et al., 2020). As cognitive deficits and social withdrawal are core symptoms of schizophrenia, the role of the $mGlu_7$ receptor in mediating cognition and social behaviors and the underlying circuitry are worth investigating.

$mGlu_7$ Receptor NAMs Can Rescue Schizophrenia-Like Symptoms in Rodents

Interestingly, *GRM7* KO mice exhibited a blunted effect of amphetamine on locomotor activity (Fisher et al., 2020) and DOI-induced head twitches as compared with the control mice (Wierońska et al., 2012). These effects were consistent with pharmacological studies showing beneficial effects of the $mGlu_7$ receptor NAMs ADX71743 and MMPIP in rodent models of schizophrenia-relevant behavioral responses (Kalinichev et al., 2013; Cieślik et al., 2018a). Both compounds have been shown to decrease MK801-induced hyperlocomotion and DOI-induced head twitches in mice and rescue MK801-induced reduction in recognition index in novel object recognition tests (Cieślik et al., 2018a). Further, ADX71743 significantly reversed MK801-induced impairments in social behavior and acoustic startle response, whereas MMPIP had no effect on these behaviors. Besides these effects, ADX71743 caused a slight reduction in amphetamine-induced hyperlocomotion in mice (Kalinichev et al., 2013), and the activity of MMPIP in this behavior has not been tested so far. To note, MMPIP and ADX71743 did not exert their own effects on spontaneous locomotor activity in rodents (Hikichi et al., 2010; Cieślik et al., 2018a). Taken together, these studies suggest that $mGlu_7$ receptor NAMs may provide a novel therapeutic approach for treating all symptom domains of schizophrenia. On the other hand, the $mGlu_7$ receptor atypical agonist AMN082 (Mitsukawa et al., 2005) exacerbated MK801-induced hyperactivity and DOI-induced head twitches in mice (Wierońska et al., 2012). Also, the propsychotic-like effects of AMN082 were absent in *GRM7* KO mice, consistent with the hypothesis that the $mGlu_7$ receptor mediates psychosis-like effects of AMN082 in rodents. These studies suggest that activation/potentiation of the $mGlu_7$ receptor at selective synapses may induce antipsychotic-like effects. Nevertheless, more research is certainly needed to fully evaluate the potential utility of the $mGlu_7$ receptor ligands in models mimicking schizophrenia symptoms.

Deletion of *GRM8* Does Not Induce Consistent Endophenotypes of Schizophrenia

A study by Gerlai and coworkers (2002) reported that *GRM8* (the gene encoding for $mGlu_8$ receptor) KO mice showed a reduced fear response to the electric shocks presented during the training. Further, in the context test, *GRM8* KO mice showed a delayed fear response with reduced freezing relative to WT mice at the beginning of the contextual test. However, the freezing increased with time, and by the end of the test session they exhibited total freezing that was greater than that observed in the control mice (Gerlai et al., 2002). *GRM8* KO mice also showed a reduction in amplitude to jump after electric shock, which suggests that the mechanisms mediating responses to aversive stimuli might be altered in these mice (Gerlai et al., 2002). To note, the *GRM8* KO and the control mice used in this study were on the Institute of Cancer Research (ICR) background and experienced an impaired vision that can affect the performance of mice in behavioral tasks. Furthermore, other research groups found either a robust decrease (Fendt et al., 2010) or no impairments in the freezing response in contextual fear conditioning (Goddyn et al., 2015). Similarly, no

consistent genotype-specific effects in novel object recognition tests were reported by different groups (Duvoisin et al., 2005; Fendt et al., 2010). Also, the studies involving *GRM8* KO did not report consistent deficits in cognition (Gerlai et al., 2002; Goddyn et al., 2015), leading to inconclusive results about the role of the $mGlu_8$ receptor in regulating cognitive function. Moreover, no deficits in PPI, spontaneous locomotor activity, and spatial learning in the Morris water maze test have been documented in these KOs (Duvoisin et al., 2005; Fendt et al., 2010; Goddyn et al., 2015), which may suggest that the $mGlu_8$ receptor is not directly involved in behaviors that are relevant for schizophrenia. Pharmacological studies using $mGlu_8$ receptor orthosteric agonist (S)-3,4-DCPG showed decrease amphetamine but not PCP-induced hyperactivity when tested at a higher dosage (80 mg/kg; i.p.) in mice (Ossowska et al., 2004). Also, it evoked extrapyramidal effects at a dose closer to the efficacious dose (100 mg/kg; i.p.). From these studies, along with KO mice reports, it is conceivable that the $mGlu_8$ receptor is not a viable target for novel antipsychotics. Further, considering the role of $mGlu_8$ receptors in regulating memory tasks and anxiety, $mGlu_8$ receptor ligands could be beneficial in treating the anxiety phenotype and some cognitive deficits associated with schizophrenia.

Concluding Remarks

Emerging preclinical and clinical evidences suggest the involvement of glutamatergic neurotransmission in the pathophysiology of schizophrenia. Based on that, several NMDA receptor antagonists are currently being used to mimic schizophrenia-related behavioral deficits in preclinical studies. Considering the side effects associated with drugs targeting NMDA receptors, attention has shifted to finding novel drug targets with a safer therapeutic profile. Among these, the mGlu receptors have emerged as promising targets for the treatment of schizophrenia. The development of transgenic animals and receptor-selective pharmacological tools have advanced our understanding of the role of mGlu receptors in schizophrenia. For example, $mGlu_1$ receptor PAMs can reverse receptor dysregulation induced by selective deleterious mutations expressed in a heterologous system and induce robust antipsychotic-like activity in rodents. Also, the $mGlu_5$ receptor PAMs show efficacy for reducing behavioral deficits related to all three symptoms domains (positive, negative, and cognitive deficits) in schizophrenia. Interestingly, biased $mGlu_5$ receptor PAMs that do not potentiate NMDA receptor signaling are equally efficacious as ago-PAMs but lack excitotoxicity and seizure-inducing effects. These exciting findings suggest a need for testing biased $mGlu_5$ PAMs in various preclinical models to investigate the safety and efficacy profiles before efforts to optimize compounds suitable for clinical development. Further, based on robust antipsychotic-like effects, $mGlu_{2/3}$ receptor agonists and $mGlu_2$ receptor PAMs entered the clinical trials. These compounds failed to show efficacy for the treatment of schizophrenia but were efficacious in a selected group of patients. These trials point toward a need for testing $mGlu_{2/3}$ receptor agonists in the patients recruited based on disease severity and genetic background.

Excitingly, a functional interaction between $mGlu_5$ and $mGlu_3$ receptors in the PFC and hippocampus has been reported and might be responsible for the cognition-enhancing effects of $mGlu_3$ receptor potentiators. In the future, it will be crucial to investigate the role of $mGlu_3$-$mGlu_5$ receptor interaction in a broad range of cognitive assays regulated by $mGlu_5$ receptors. Given the neuroprotective effects of $mGlu_3$ receptor activation, this information will be helpful in guiding design of safer drugs for treating cognitive deficits associated with schizophrenia. Also, the $mGlu_2$-$mGlu_4$ receptor heterodimers with a distinct pharmacological profile may provide novel approaches to optimize desired therapeutic efficacy and safety profile. Knowledge about the role of other group III mGlu receptors is still in its infancy, and more receptor-selective compounds are needed to understand their pharmacology and physiology.

In conclusion, a broad number of preclinical and clinical studies illuminate the potential of targeting mGlu receptors to develop safe and efficacious drugs for the treatment of schizophrenia.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Dogra, Conn.

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