Metabotropic glutamate receptors as emerging targets for the treatment of schizophrenia

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List of Abbreviations:

BPRS- Brief Psychiatric Rating Scale

DLPFC- Dorsolateral prefrontal cortex

dACC- dorsal anterior cingulate cortex

DA- Dopamine

GWAS- Genome Wide Association Studies

KO- Knockout

mGlu – metabotropic glutamate

MAM- Methamphetamine

NAMs- Negative allosteric modulators

NAc- Nucleus Accumbens

NAAG- N-acetylaspartylglutamate

NMDA- N-methyl-D-aspartate

NS- Central nervous system

PAMs- Positive allosteric modulators

PANSS- Positive and Negative Syndrome Scale

PCP- Phencyclidine

PFC- Prefrontal Cortex

PPI- Prepulse inhibition

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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 schizophrenia patients. In preclinical studies, the mGlu₅ receptor positive allosteric modulators (PAMs) have efficacy in animal models relevant for all symptom domains in schizophrenia. Interestingly, biased pure mGlu₅ receptor PAMs that do not potentiate coupling of mGlu₅ receptors to NMDA receptors lack neurotoxic effects associated with mGlu₅ PAMs that enhance coupling to N-methyl-D-aspartate (NMDA) receptors or have allosteric agonist activity (ago-PAMs). This provides a better therapeutic profile for treating schizophrenia-like symptoms. Additionally, the mGlu₁ receptor PAMs modulate dopamine release in the striatum, which may contribute to their antipsychotic-like effects. Besides group I mGlu (mGlu₁ and mGlu₅) receptors, agonists of mGlu_{2/3} receptor also induce robust antipsychotic-like and pro-cognitive 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 mGlu₃ receptor activation can enhance cognition in rodents suggesting that mGlu₃ 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 efficacious therapeutics for schizophrenia.

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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 efficacious therapeutics for treating schizophrenia.

Introduction

Schizophrenia is a heterogeneous neuropsychiatric disorder that affects around 1% of the population worldwide (Perala 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 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; Hu et al., 2015; Moghaddam and Javitt, 2012; Stahl, 2018). Pharmacological evidence for the role of glutamate in schizophrenia centers on the clinical findings that administration of the non-competitive N-methyl-D-aspartate (NMDA)

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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, motivational and cognitive impairments in rodents (Barnes et al., 2017; Goff and Coyle, 2001; Lee and Zhou, 2019). Interestingly, animals with genetic knockdown of NR1 subunit of NMDA receptor 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 (Belforte et al., 2010; Mohn et al., 1999). Similarly, animals lacking NR2A or NR2B subunits of NMDA receptors show behavioral and neurophysiological changes that may reflect pathophysiology observed in schizophrenia (Belforte et al., 2010; Brigman et al., 2008; Duncan et al., 2004; Ito et al., 1997; Kannangara et al., 2015; Sprengel et al., 1998; von Engelhardt et al., 2008). Collectively, these studies have led to the hypothesis that pathological 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 genes coding for the components of glutamate receptors and maintenance of glutamatergic neurotransmission with schizophrenia (Pers et al., 2016; Pocklington et al., 2015; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Timms et al., 2013). 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

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pharmacological agents that reverse pathological 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 mGlu₁ and mGlu₅ receptors, group II includes mGlu₂ and mGlu₃ receptors and group III includes mGlu₄, mGlu₆, mGlu₇, and mGlu₈ receptors (Dogra and Conn, 2021; Niswender and Conn, 2010). 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 make them exciting targets for developing improved pharmacotherapies for schizophrenia.

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Genomic variants in *GRM5* and mGlu₅ receptor hypofunction are associated with schizophrenia

GRM5 (the gene encoding for mGlu₅ 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 schizophrenia patients (Matosin et al., 2018). A recent study by Wang *et al.* (2020) has reported reduced mGlu₅ receptor signaling in the postmortem dorsolateral prefrontal cortex (DLPFC) of schizophrenia patients (Wang et al., 2020). The authors also observed increased serine and tyrosine phosphorylation of mGlu₅ receptor in DLPFC which may cause receptor desensitization leading to reduced mGlu₅ receptor signaling observed in the schizophrenia patients (Wang et al., 2020). Interestingly, lower mGlu₅ 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 (Regio Brambilla et al., 2020). These findings support the concept that dysregulation of mGlu₅ receptor signaling/function may underly the pathophysiology of schizophrenia.

These clinical studies are complemented by studies in *Grm5* knockout (KO) mice displaying deficits in sensorimotor gating, spontaneous hyperactivity, and loss of NMDA receptor-mediated components of some forms of synaptic plasticity (Brody et al., 2004a; Brody et al., 2004b; Brody and Geyer, 2004; Burrows et al., 2015; Jia et al., 1998). These KO mice also exhibit abnormalities in sleep and neural oscillatory processing similar to schizophrenia patients (Aguilar et al., 2020). Further, *Grm5* KO mice display impaired performance on discrimination learning and reversal learning in a Trial-Unique Non-Matching to Location task indicating

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learning and memory deficits in these mice (Zelezniak-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 symptoms domains of schizophrenia and reiterate the critical roles of mGlu₅ receptors in schizophrenia pathophysiology. Similarly, administration of mGlu₅ receptor negative allosteric modulators (NAMs), evoke behavioral deficits correlated to schizophrenia (Koros et al., 2007; Swedberg et al., 2014) and potentiate behavioral deficits induced by psychotomimetic agents (Campbell et al., 2004; Henry et al., 2002) providing evidence linking mGlu₅ receptors to schizophrenia.

mGlu₅ potentiators reduce behavioral disruptions that are relevant for schizophrenia in rodent models

The mGlu₅ 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 (Huang et al., 2016; Liu et al., 2008; Schlumberger et al., 2010; Uslaner et al., 2009; Yang et al., 2016). Also, systemic administration of mGlu₅ receptor PAMs, CDPPB and ADX427273, increases hippocampus-dependent spatial learning in the Morris water maze test (Ayala et al., 2009). Similarly, another mGlu₅ receptor PAM, DPFE, enhanced the acquisition of contextual fear conditioning in rats (Gregory et al., 2013). Interestingly, the mGlu₅ receptor agonists/PAMs, CHPG, CDPPB, ADX42723, BMS-955829, DPFE and DFB, were able to reverse the cognitive deficits and motivational impairments induced by NMDA receptor antagonists,

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and hyperactivity induced by amphetamine, apomorphine, and PCP (Gastambide et al., 2012; Gregory et al., 2013; LaCrosse et al., 2015; Liu et al., 2008; Stefani and Moghaddam, 2010; Vales et al., 2010; Yang et al., 2016). These studies support the hypothesis that allosteric potentiation of the mGlu₅ receptors could provide a novel pharmacotherapeutic approach for treating multiple symptom domains in schizophrenia.

Newer mGlu₅ 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, mGlu₅ receptor-selective PAMs, VU0092273 and VU0364289, dose-dependently reversed amphetamine-induced hyperactivity in rodents, a model predictive of antipsychotic activity (Gregory et al., 2013; Noetzel et al., 2012; Rodriguez et al., 2010). Similar antipsychotic-like effects were also observed with a dihydrothiazolopyridone class of mGlu₅ receptor PAM (Bartolome-Nebreda et al., 2013). Since the mGlu₅ 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 mGlu₅ receptors may exert these effects by augmenting NMDA receptor function to mitigate the NMDA receptor hypofunction and symptoms observed in schizophrenia.

Biased mGlu₅ receptor PAMs that do not potentiate coupling of mGlu₅ receptors to NMDA receptors or exert allosteric agonist activity (ago-PAMs), do not induce observable adverse effects

Despite the promising effects of mGlu₅ 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 and excessive

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activation of NMDA receptors (Parmentier-Batteur et al., 2014; Rook et al., 2013). Early studies revealed that mGlu₅ receptor ago-PAMs induce seizures and other adverse effects that are not as prominent with pure mGlu₅ receptor PAMs that lack intrinsic allosteric agonist activity (Parmentier-Batteur et al., 2014; Rook et al., 2013). Furthermore, the known adverse effects associated with overactivation of NMDA receptors raised the possibility that mGlu₅ receptor PAMs which are biased away from NMDA receptor potentiation may lack excitotoxic/seizure-inducing profiles (Rook et al., 2015). Supporting this theory, a biased mGlu₅ receptor PAM, VU0409551, that does not enhance mGlu₅ 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 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 mGlu₅ receptor PAMs lacking mGlu₅ receptor-mediated potentiation of NMDAR currents retain antipsychotic-like and cognition-enhancing effects in rodent models relevant for schizophrenia. Thus, the initial hypothesis that mGlu₅ 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 mGlu₅ receptor PAM may increase cognition by mGlu₅ receptor-mediated potentiation of excitability of CA1 pyramidal neurons (Mannaioni et al., 2001) or endocannabinoids mediated depression of inhibitory neurotransmission onto pyramidal neurons (Xu et al., 2014). Collectively, the above-mentioned studies propose that a detailed

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understanding of the mechanisms of action of mGlu₅ receptor PAMs might help to develop safer compounds with robust efficacy for treating schizophrenia.

mGlu₁ receptor PAMs may have potential antipsychotic effects

In 2011, Frank and coworkers identified non-synonymous single nucleotide polymorphisms (nsSNPs) within a functionally important cysteine-rich domain and the first transmembrane helix of the mGlu₁ receptor in patients with schizophrenia (Frank et al., 2011). Subsequently, a study involving 605 controls and 450 schizophrenia patients confirmed the presence of deleterious mutations in *GRM1* (the gene encoding for mGlu₁ receptor) in schizophrenia patients (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 mGlu₁ 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, selective mGlu₁ receptor PAMs, Ro 07-11401, VU0483605 and VU0483737, were able to potentiate signaling by the mutant receptors, and thereby reduce deficits in mGlu₁ receptor signaling (Cho et al., 2014). Similarly, another set of mGlu₁ receptor PAMs based on an N-(3-chloro-4-(1,3-dioxoisindolin-2-yl)phenyl)-3-methylfuran-2-carboxamide scaffold also potentiated the function of mGlu₁ 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 mGlu₁ receptor PAMs and highlight the effect of the clinical heterogeneity of schizophrenia on disease prognosis.

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The mGlu₁ receptor ligands display antipsychotic-like effects in rodents

Interestingly, recent studies revealed that the mGlu₁ receptor PAM, VU6004909, reduced amphetamine-induced hyperlocomotion and disruptions in prepulse inhibition (PPI) in mice (Yohn et al., 2020). These effects were absent following administration of CB₂ antagonist which indicates that the antipsychotic-like effects of VU6004909 are dependent on CB₂ receptor activation. Further, mechanistic studies reveal that VU6004909 inhibits dopamine (DA) release in the striatum, not in the nucleus accumbens (NAc), and a cross-talk between mGlu₁ and muscarinic M4 receptors has been suggested for this inhibition on DA release (Yohn et al., 2020). Because the mutations in *GRM1* reduce mGlu₁ receptor signaling and *Grm1* KO mice display deficits in PPI (Brody et al., 2003), there is a possibility that altered receptor expression may contribute to hyperdopaminergic state observed in schizophrenia. Therefore, mGlu₁ receptor PAMs may act by correcting striatal dopamine hyperactivity leading to the anti-psychotic-like activity in models mimicking schizophrenia symptomatology. Recently, it has been reported that mGlu₁ 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 mGlu₁ 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 mGlu₁ receptor antagonism as a pharmacotherapeutic approach to schizophrenia. For example, mGlu₁ receptor NAMs, FTIDC and CFMTI, blocked methamphetamine (MAM)-induced hyperactivity and reduced MAM-induced disruption in PPI in rodents (Satow et al., 2008; Satow et al., 2009). Also, CFMTI and JNJ16259685 (mGlu₁ receptor antagonist) improved MK801-

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induced impairments in social memory (Hikichi et al., 2013; Satow et al., 2009) suggesting that mGlu₁ receptor NAMs could be effective for the treatment of some impairments associated with schizophrenia. At present, the mechanistic basis for overlapping actions of mGlu₁ receptor PAMs and mGlu₁ 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 hallucinogen DOI in rodents, including c-Fos expression in the cortex. (Gonzalez-Maeso et al., 2008; Zhai et al., 2003), increased excitatory synaptic responses in the mPFC, (Marek et al., 2000) and head twitch response (Gewirtz and Marek, 2000; Gonzalez-Maeso et al., 2008). In addition, mGlu_{2/3} receptor agonists, MGS0008 and LY404039, inhibited conditioned avoidance responses in WT mice (Rorick-Kehn et al., 2007; Takamori et al., 2003). Recently, our group reported that 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 mGlu₂ and mGlu₃-receptor specific NAMs, we showed that mGlu₃ receptor is mediating cognition-

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enhancing effects of LY379268. Interestingly, mGlu_{2/3} receptor agonist, LY379268 was able to revert PCP-induced deficits in associative learning (Dogra et al., 2021). All 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 to placebo control in early phase II clinical trial (Kinon and Gomez, 2013; Patil et al., 2007). 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 where neither LY2140023 nor olanzapine demonstrated significant efficacy compared to 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 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.

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However, a post hoc analysis of all clinical trials showed that LY2140023 displayed therapeutic efficacy in subgroups of patients who were early in disease (≤ 3 years), or previously treated with dopamine D2 receptor drugs, and were never treated with 5-HT_{2A} receptor blockers (Kinon et al., 2015). These promising results indicate the need for testing mGlu_{2/3} receptor agonists in schizophrenia patients recruited based on disease duration, history of previous medication, and genetic background. Further, it will be important to tease apart the relative contributions of mGlu₂ and mGlu₃ receptors in mediating beneficial effects of mGlu_{2/3} receptor agonists. Recently, LY2140023 was tested in phase Ib proof of concept studies where high dose of LY2140023 (320 mg/d 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 pharmacBOLD in the dorsal anterior cingulate cortex (dACC) suggesting that the tested dose might still be low for optimal target engagement. Besides LY2140023, a novel mGlu_{2/3} receptor agonist prodrug, TS-134 (MGS0274 besylate) entered the clinical trials and found to be safe and well-tolerated in double-blinded and placebo-controlled dose response phase -1 clinical trial conducted in healthy subjects (Watanabe et al., 2020). Further clinical studies reported reductions in both ketamine-induced BPRS positive symptoms and pharmacBOLD in the dACC, left caudate and NAc after treatment with low-dose of TS-134 (20 mg/d 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

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agonists. Also, it will be exciting to evaluate the therapeutic effects of TS-134 in the schizophrenia patients.

mGlu₂ receptor PAMs may have potential antipsychotic activity

In terms of subtype selectivity, based on the studies performed with *Grm2* (the gene encoding for mGlu₂ receptor)- and *Grm3* (the gene encoding for mGlu₃ receptor)-KO mice, it has been suggested that mGlu₂ receptor, not mGlu₃ 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 mGlu₂ receptor PAMs, CBiPES, BINA, TASP0443294, TASP0433864, JNJ40411813/ADX71149 and JNJ-42153605 (Benneyworth et al., 2007; Galici et al., 2005; Galici et al., 2006; Govek et al., 2005; Hikichi et al., 2015; Hiyoshi et al., 2014; Johnson et al., 2003; Johnson et al., 2005; Lavreysen et al., 2015). Another mGlu₂ 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 towards 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 mGlu₂ 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

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most likely to benefit from treatment with JNJ40411813. The second compound, AZD8529 did not show any extrapyramidal motor side effects, however, failed to show any significant improvement in positive and negative symptom subscale, and PANSS total score as compared to 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 mGlu₂ 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 of translating preclinical research findings to clinics. Furthermore, considering the underlying heterogeneity of schizophrenia patients, it may be best to test mGlu_{2/3} receptor agonists/ mGlu₂ 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 (Bishop et al., 2011; Bishop et al., 2015; Chang et al., 2015; Egan et al., 2004; Fujii et al., 2003; Saini et al., 2017). Interestingly, polymorphisms in *GRM3* may predict improvement in negative symptoms in schizophrenia patients treated with antipsychotic medications (Bishop et al., 2005; Bishop et al., 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 these genetic association studies suggest an important pharmacogenetic relationship between *GRM3* polymorphisms and changes in cognitive and negative symptom response to antipsychotic

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treatment. Further, this information can be used to identify schizophrenia patients 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 (De Filippis et al., 2015; Lainiola et al., 2014) further stipulating an essential role of the mGlu₃ receptor in some forms of cognition.

mGlu₃ 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 mGlu₃ receptor regulates cognition and cognitive impairments associated with schizophrenia. Owing to the lack of receptor-specific compounds, early preclinical studies utilized N-acetylaspartylglutamate (NAAG) peptidase (an enzyme that inactivates the peptide transmitter) inhibitors. NAAG is a peptide neurotransmitter that activates mGlu₃ receptor (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 mGlu₃ receptor 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 PCF and the NAc (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

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mGlu₃ receptors) in cognition. In summary, the above-mentioned literature raises the potential therapeutic utility of targeting mGlu₃ receptors for treating schizophrenia and the need for further studies aimed at understanding the mechanisms by which mGlu₃ receptors may enhance cognition in schizophrenia.

Using recently developed mGlu₃ specific ligands, mechanistic studies revealed that the mGlu₃ receptor modulates synaptic plasticity within PFC and hippocampus (Dogra et al., 2021; Joffe et al., 2019; Walker et al., 2015). Interestingly, mGlu₃ receptors functionally interact with mGlu₅ receptors in the CNS (Di Menna et al., 2018; Dogra et al., 2021) and enhance mGlu₅ receptor-mediated somatic Ca²⁺ mobilization in the cortical pyramidal neurons. Also, activation of mGlu₅ receptor is required for mGlu₃ receptor-mediated long-term depression in the PFC (Di Menna et al., 2018) and extinction of fear memories (Walker et al., 2015). Furthermore, a non-human primate study showed that an increase in the endogenous mGlu₃ receptor agonist, NAAG, enhances DLPFC Delay cell firing during a working memory task (Jin et al., 2018). These studies illuminate the mechanisms by which mGlu₃ receptors can modulate PFC function and cognition and suggest that mGlu₃ receptor PAMs have the potential to reduce the PFC-dependent cognitive impairments associated with CNS disorders like schizophrenia.

This mGlu₃ receptor-induced potentiation of mGlu₅ receptor function in PFC is also observed in the hippocampus (Dogra et al., 2021). Our group discovered that activation of mGlu₃ receptors in the CA1 pyramidal neurons induces metaplastic changes to induce long-term potentiation at SC-CA1 synapse through a mGlu₅ receptor-dependent, endocannabinoid-mediated disinhibition (Dogra et al., 2021). Further, the mGlu₃ receptor has been shown to shape the influence of mGlu₅ receptors on excitotoxic insults (Di Menna et al., 2018). Given the fact that activation of

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mGlu₃ receptor may provide neuroprotection (Caraci et al., 2011), pharmacological agents activating mGlu₃ receptors may reduce the risk for neurotoxicity while improving schizophrenia-related cognitive deficits.

mGlu₄ 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 (Palucha-Poniewiera et al., 2008). Similar antipsychotic-like effects were also observed with mGlu₄ receptor selective agonists, LSP1-2111 (Wieronska et al., 2012) and LSP4-2022 (Wozniak et al., 2016). In addition, LSP4-2022 improved negative symptoms and cognition in MK801-treated mice (Wozniak et al., 2016). Interestingly, mGlu₄ receptors co-operate with other neurotransmitter receptors to induce antipsychotic-like effects in rodents (Wozniak et al., 2016; Wozniak et al., 2017). For example, the antipsychotic-like activity of mGlu₄ receptor agonist, LSP4-2022, was reversed by GABAB receptor antagonist, CGP55845. Further, coadministration of sub-effective doses of LSP4-2022 and GABAB receptor PAM acted synergistically to produce antipsychotic-like effects (Wozniak et al., 2016). Similarly, 5-HT_{1A} receptor antagonist, WAY100635, reversed antipsychotic-like actions of mGlu₄ receptor agonist, LSP4-2022. While administration of a sub-effective dose of 5-HT_{1A} receptor agonist with an ineffective dose of LSP4-2022 enhanced the effects of ineffective dosage of LSP4-2022 (Wozniak 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 PAM induced a robust antipsychotic-like effects (Cieslik et al., 2018b). Similar antipsychotic-like

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properties has also been reported with other mGlu₄ receptor PAMs, Lu AF21934 (Slawinska et al., 2013) and ADX88178 (Kalinichev et al., 2014). These studies further support the potential utility of selective mGlu₄ receptor activators for treating positive symptoms of schizophrenia.

Potential utility of mGlu₂-mGlu₄ receptor heterodimers as novel-antipsychotics

Emerging studies suggest that mGlu₄ and mGlu₂ 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 where 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 BLA 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 role 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 LSD (Inserra et al., 2021; Marek et al., 2001; Preller et al., 2019; Scruggs et al., 2000), 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, mGlu₄ receptor PAM with activity at mGlu_{2/4} receptor heterodimers, has been shown to inhibit MK801- and

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amphetamine-induced hyperactivity and reverse of DOI-induced head twitch in rodents (Slawinska et al., 2013; Wieronska et al., 2015). Considering the fact that mGlu₄ 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 mGlu₂- and mGlu₄ 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 mGlu₇ receptor impairs cognition

Genetic variations in *Grm7* (the gene encoding for mGlu₇ receptor) are associated with schizophrenia (Chaumette et al., 2020; Li et al., 2016b; Niu et al., 2015). Specifically, a polymorphism, rs1396409, was associated with performance intellectual quotient in a discovery cohort of 144 first-episode of psychosis patients 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 highlight the impact of mGlu₇ receptor signaling in cognitive impairments in early psychotic episodes. These studies are supported by pharmacological studies where systemic administration of mGlu₇ 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 8-arm radial maze test and decreased social interaction in rats. These results are complemented by the

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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 (Fisher et al., 2020; Goddyn et al., 2008). Further, these mice showed impaired spatial working memory in the water-maze test and eight-arm radial maze test (Callaerts-Vegh et al., 2006; Holscher et al., 2004). These deficits in cognition were accompanied by disruption of social behavior where deletion of the mGlu₇ 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 mGlu₇ receptor in mediating cognition and social behaviors and the underlying circuitry is worth investigating.

mGlu₇ 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) head twitches as compared to the control mice (Wieronska et al., 2012). These effects were consistent with pharmacological studies showing beneficial effects of mGlu₇ receptor NAMs, ADX71743 and MMPIP, in rodent models of schizophrenia-relevant behavioral responses (Cieslik et al., 2018a; Kalinichev et al., 2013). Both compounds have been shown to decrease MK-801-induced hyperlocomotion and DOI-induced head twitches in mice, and rescue MK801-induced reduction in recognition index in novel object recognition test (Cieslik et al., 2018a). Further, ADX71743 significantly reversed MK801-induced impairments in social behavior and acoustic startle response, while MMPIP had no effects on any of 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

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not been tested so far. To note, MMPIP and ADX71743 did not exert their own effects on spontaneous locomotor activity in rodents (Cieslik et al., 2018a; Hikichi et al., 2010). Taken together, these studies suggest that mGlu₇ receptor NAMs may provide a novel therapeutic approach for treating all symptom domains of schizophrenia. On the other hand, mGlu₇ receptor atypical agonist, AMN082 (Mitsukawa et al., 2005) exacerbated MK-801-induced hyperactivity and DOI-induced head twitches in mice (Wieronska et al., 2012). Also, the pro-psychotic-like effects of AMN082 were absent in *Grm7* KO mice, consistent with the hypothesis that the mGlu₇ receptor mediates psychosis-like effects of AMN082 in rodents. Interestingly, AMN082 reduces thalamocortical synaptic transmission (Tassin et al., 2016), high functional connectivity of which is observed in schizophrenia. Therefore, it is plausible that activation/potential of the mGlu₇ receptor at selective synapses may induce antipsychotic-like effects. Nevertheless, more research is certainly needed to fully evaluate the potential utility of the mGlu₇ 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 mGlu₈ 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 following electric shock which suggests that the mechanisms mediating responses to aversive stimuli might be altered in these mice (Gerlai et

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al., 2002). To note, the *Grm8* KO and the control mice used in this study were on the ICR backbone 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 test 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 mGlu₈ 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 mGlu₈ receptor is not directly involved in behaviors that are relevant for the schizophrenia. Pharmacological studies using mGlu₈ receptor orthosteric agonist (S)-3,4-DCPG showed decrease amphetamine, but not PCP-induced hyperactivity when tested at 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 mGlu₈ receptor is not a viable target for novel antipsychotics. Further, considering the role of mGlu₈ receptor in regulating memory tasks and anxiety, mGlu₈ receptor ligands could be beneficial in treating the anxiety phenotype and some cognitive deficits associated with schizophrenia.

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Concluding remarks

Emerging preclinical and clinical evidence suggests the involvement of glutamatergic neurotransmission in the pathophysiology of schizophrenia. Based on that, several NMDA receptor antagonists are currently used to mimic schizophrenia-related behavioral deficits in preclinical studies. Considering the side effects associated with drugs targeting NMDA receptors, attention has shifted to find 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, mGlu₁ 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 mGlu₅ receptor PAMs show efficacy for reducing behavioral deficits related to all three symptoms domains (positive, negative and cognitive deficits) in schizophrenia. Interestingly, biased mGlu₅ 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 of testing biased mGlu₅ 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 mGlu₂ 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 towards the need of testing mGlu_{2/3} receptor agonists in the patients recruited based on disease severity and genetic background.

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Excitingly, a functional interaction between mGlu₅ and mGlu₃ receptors in the PFC and hippocampus has been reported and might be responsible for the cognition-enhancing effects of mGlu₃ receptor potentiators. In the future, it will be crucial to investigate the role of mGlu₃-mGlu₅ receptor interaction in a broad range of cognitive assays regulated by mGlu₅ receptors. Given the neuroprotective effects of mGlu₃ receptor activation, this information will be helpful in guiding design of safer drugs for treating cognitive deficits associated with schizophrenia. Also, the mGlu₂-mGlu₄ 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.

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Authors' contributions

Contributed to the writing of the manuscript: Dogra, S. and Conn, P.J.

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Declaration of interests

P.J.C. receives research support from Acadia Pharmaceuticals and Boehringer Ingelheim. P.J.C. is an inventor on multiple patents for allosteric modulators of metabotropic glutamate receptors. S.D. has no competing interests to declare.

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