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Group I and group II metabotropic glutamate receptor allosteric modulators as novel potential antipsychotics

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Abstract

Recently, there has been a shift in the schizophrenia field focusing on restoring glutamate signaling. Extensive preclinical data suggests that mGlu₅ PAMs could have efficacy in all three symptom domains but there is concern of potential adverse effects. New insights into mechanisms underlying this toxicity may provide a path for discovery of safe mGlu₅ PAMs. Genetic mutations in mGlu₁ have been described in schizophrenics creating interest in this receptor as a therapeutic target. Preclinical data demonstrated the antipsychotic potential of mGlu_{2/3} agonists but clinical trials were not successful. However, studies have suggested that mGlu₂ is the subtype mediating antipsychotic effects and selective mGlu₂ PAMs are now in clinical development. Finally, recent genetic studies suggest mGlu₃ modulators may be pro-cognitive.

Schizophrenia is a debilitating neuropsychiatric disorder that presents itself as a triad of symptoms. Positive symptoms include visual/auditory hallucinations and delusions as well as disordered thoughts. Negative symptoms are characterized by social withdrawal and anhedonia. Deficits in attention, working memory, executive function, and impaired sensory processing comprise cognitive symptoms [1]. Currently, the most widely used antipsychotic drugs were primarily developed to target the monoaminergic transmitter systems, with particular focus on antagonism of the D₂ dopamine receptor. Although these compounds provide relief from positive symptoms, they do not provide efficacy in reducing negative and cognitive symptoms and produce many side effects that can lead to discontinuation of use by the patient [2]. Thus, there has been an intense effort within the field to discover alternative therapeutic strategies.

There is considerable evidence indicating dysfunction of the glutamate system may contribute to the etiology of schizophrenia. It is well known that administration of N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP) or ketamine, can induce schizophrenic-like state in healthy individuals that includes all three symptom

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domains. Furthermore, these compounds will exacerbate these symptoms when administered to patients with schizophrenia [3]. These observations, as well as extensive preclinical research, have led to the hypothesis that NMDA receptor hypofunction can play a role in the pathophysiology underlying schizophrenia [4, 5]. Decreasing tone at this receptor, moreover, may ultimately cause a dysregulation of thalamocortical circuitry by altering the balance of excitation and inhibition. Below, we discuss evidence indicating activation of metabotropic glutamate receptors (mGlu) may restore this balance and provide therapeutic benefits to schizophrenics.

Allosteric modulators

Individual mGlu receptor subtypes have long been considered highly attractive drug targets for a variety of disease states. Unfortunately, attempts to develop highly selective agonists and antagonists that act at the orthosteric glutamate binding site of mGlu receptor subtypes have been difficult because the glutamate binding site is highly conserved across mGlu subtypes [6]. Not only has this limited the development of clinical compounds, but also hindered the development of selective tool compounds to delineate the roles of mGlu receptor subtypes in modulating neurotransmission and behavior. In recent years, tremendous advances have been made in pharmacologically targeting individual mGlu receptor subtypes by creating compounds that interact with allosteric sites on the receptors that are less highly conserved. Positive allosteric modulators (PAMs) generally do not activate the receptor directly but function to potentiate responses to activation by glutamate. Additionally, some PAMs can also produce allosteric agonist activity by generating receptor signaling in the absence of glutamate as well as potentiating glutamate response. These compounds are often referred to as ago-PAMs. Conversely, negative allosteric modulators (NAMs) decrease act as non-competitive antagonists of responses to glutamate and can also have or inverse agonist activity, reducing constitutive activity of the receptor in the absence of glutamate. Newly available mGlu receptor PAMS and NAMS have allowed major advances in our understanding of the functional roles of specific mGlu subtypes. In addition, these novel compounds have exciting potential as therapeutic agents and are being rapidly advanced in preclinical and early clinical drug development efforts [7, 8].

Group I mGlu receptors

mGlu₅ PAMs

mGlu₅ has emerged as an attractive target in the treatment in schizophrenia largely based on the fact it is a close signaling partner of NMDA receptors. Reports indicate that mGlu₅ interacts with NMDA receptors physically through scaffolding proteins as well functionally by potentiating NMDA receptor-mediated currents [9-13]. Furthermore, mGlu₅ antagonists can potentiate the psychomimetic effects of NMDA antagonists and the behavioral phenotype mGlu₅ knockout mice closely resemble that produced by NMDA antagonists [14-16]. Thus, it is hypothesized that mGlu₅ activators could provide therapeutic benefits to schizophrenic patients through enhancement of NMDA signaling and normalizing glutamatergic tone [8].

There has been rapid progress in the development of potent and selective mGlu₅ PAMs suitable for *in vivo* use [17]. Preclinical studies suggest these compounds may have efficacy for positive, negative, and cognitive symptom domains. For example, multiple reports have demonstrated a variety of chemically diverse mGlu₅ PAMs reverse amphetamine-induced hyperlocomotion and apomorphine-induced disruption of sensory gating, which are models of schizophrenia symptoms in the positive domain [18-21]. Furthermore, an early generation mGlu₅ PAM, CDPPB, was shown to attenuate disruption of sucrose preference by MK-801, indicating potential efficacy against negative symptoms [22]. Finally, several papers report that mGlu₅ PAMs may be pro-cognitive in behavioral tasks such as the Morris water maze [23]. This may be due to the fact that compounds that modulate mGlu₅ can potentially influence forms of synaptic plasticity, such as long-term potentiation (LTP) and long-term depression [23, 24].

Although these early findings are exciting, there has been some caution in advancing mGlu₅ PAMs to clinical development due to reports of adverse effects (AEs) with some compounds. Specifically, convulsions [25-27] and neuronal cell death [25, 27] have been observed in rodents after administration mGlu₅ PAMs. However, progress has been made toward understanding the mechanism of mGlu₅ induced toxicity. Similar to orthosteric agonists of mGlu₅ [28], PAMs with allosteric agonist activity (ago-PAMs) induce convulsions as well as epileptiform activity measured in hippocampal slices and cortical EEG *in vivo*. In contrast, closely related pure PAMs with no intrinsic agonist activity do not induce convulsion or epileptiform activity suggesting they exhibit a safer AE profile [26]. However, some mGlu₅ PAMs that lack allosteric agonist activity can also induce adverse effects and excitotoxicity with chronic dosing (25). Thus, while it is critical to avoid mGlu₅ ago-PAMs, this does not guarantee that individual mGlu₅ PAMs will be devoid of adverse effects. More recently, mGlu₅ receptor PAMs have been identified that have a biased signaling profile such that they induce calcium mobilization in cell lines but do not potentiate NMDA receptor currents in brain slices. Interestingly, these biased mGlu₅ PAMs maintain antipsychotic and pro-cognitive efficacy and may have less propensity to cause seizures or cell death. Interestingly, because they do not potentiate NMDA receptor currents, these PAMs do not affect activity dependent LTP or LTD [27]. These studies clearly call into question the hypothesis that the efficacy of mGlu₅ PAMs is mediated by potentiation of NMDA receptor currents. While the important new insights provided by these studies could shed light on properties of mGlu₅ PAMs that could reduce AE liability, it is unlikely that any single property of mGlu₅ PAMs will be key to developing safe effective compounds. Thus, it will be important to develop compounds that have a balance of properties that provide efficacy without serious risk of adverse effects.

mGlu₁ PAMs

Recently, mutations in the gene encoding the mGlu₁ receptor (*GRM1*) have been identified in samples from schizophrenics which were predicted to result in a loss of receptor function [29]. Although the mGlu₁ receptor has not previously been implicated as a risk factor for schizophrenia, these genetic findings are in accordance with other lines of evidence. For example, mGlu₁ receptor knockout mice show deficits in prepulse inhibition, an animal model of the sensory gating deficits experienced by schizophrenics [14]. Furthermore,

postmortem analysis of brain samples from schizophrenics has demonstrated altered mGlu₁ expression relative to control samples [30]. To determine the effects of these mutations on receptor function, Cho et. al. [31] created cell lines stably expressing nine of the mutant mGlu₁ receptors. As predicted, relative to the cells expressing the wild type receptor, most of the mGlu₁ mutants showed a decrease in receptor function measured by agonist-induced calcium mobilization. These deficits, moreover, could be partially restored by selective mGlu₁ receptor PAMs. However, *in vivo* administration of mGlu₁ PAMs either slightly worsened or showed no effect on amphetamine induced hyperlocomotion.

Interestingly, several reports have demonstrated antipsychotic-like efficacy of mGlu₁ receptor NAMs in preclinical models [31-33]. Taken together, this raises the intriguing possibility that mGlu₁ receptor PAMs may only be beneficial to patients bearing *GRM1* mutations.

Group II mGlu receptors

mGlu_{2/3} orthosteric agonists

Historically, there has been intense interest in targeting group II mGlu (mGlu₂ and mGlu₃) for the treatment of psychosis in schizophrenia. In a seminal preclinical study, the Moghaddam lab demonstrated that pre-treatment with the highly selective orthosteric mGlu_{2/3} agonist LY354740 blocked the hyperlocomotive and stereotypy inducing effects of the NMDA receptor antagonist PCP in rats [34]. Subsequent studies confirmed these results and also demonstrated that compounds targeting group II mGlu also block excessive release of dopamine, glutamate, and norepinephrine *in vivo* triggered by NMDA antagonists [35-37]. It is hypothesized that efficacy of these compounds is achieved by decreasing excessive glutamate release and subsequently normalizing aberrant firing patterns within the prefrontal cortex that results from NMDA receptor blockade [38]. Thus, group II mGlu receptor activation is thought to primarily modulate malfunctioning thalamocortical circuitry instead of directly increasing NMDA receptor function. Although mGlu_{2/3} agonists have been shown to potentiate NMDA receptor currents in several neuronal populations, including pyramidal neurons in prefrontal cortex [39-41], the contribution of this mechanism to the antipsychotic efficacy requires further exploration.

Both tolerability and efficacy of a selective orthosteric group II agonist developed by Eli Lilly has been evaluated in clinical studies [extensively reviewed in 42]. LY2140023 demonstrated efficacy in the treatment of positive and negative symptoms and was generally well-tolerated in a 4-week phase II trial [43]. However, an additional study produced inconclusive results, largely due to an abnormally large placebo effect. This second study reported an increase risk of seizures associated with LY2140023 treatment, but an additional 24-week study determined that tolerability of this compound is comparable to other widely used antipsychotics such as olanzapine, aripiprazole and risperidone [44]. Unfortunately, based on negative results of an additional clinical study, Eli Lilly recently announced that they will not pursue further development of this compound for the treatment of schizophrenia [45].

mGlu₂ PAMs

Although the negative clinical results from Eli Lilly are disappointing, there is still interest in pursuing group II mGlu receptor subtypes as antipsychotics. In particular, the antipsychotic effects of mGlu_{2/3} agonists is thought to be primarily mediated by activation of the mGlu₂ receptor subtype. Specifically, the efficacy of selective group II mGlu receptor orthosteric agonists in reducing PCP- and amphetamine-induced hyperlocomotion is lost in mGlu₂, but not mGlu₃ receptor, knockout mice [46, 47]. Because the orthosteric binding site is highly conserved between mGlu₂ and mGlu₃, researchers have focused on the discovery of compounds that act through allosteric mechanisms to achieve subtype selectivity. Several chemically distinct mGlu₂ receptor PAMs have been reported to display antipsychotic efficacy in preclinical animal studies [see 48 for review]. For example, both LY487379 and BINA can attenuate the PCP- and AMPH-induced hyperlocomotion and PPI disruptions in a manner similar to orthosteric agonists with activity at mGlu₂ and mGlu₃ [49, 50]. Furthermore, electrophysiological studies have shown that BINA can modulate excitatory transmission in prefrontal cortex in a manner similar to mGlu_{2/3} agonists [51]. Finally, data indicating that mGlu₂ PAMs may not produce tolerance through desensitization could provide additional therapeutic benefits to patients [52, 53]. Therefore, the current hypothesis is that achieving subtype selectivity and leveraging the advantages of allosteric modulation will improve the antipsychotic efficacy of these compounds.

Based on this hypothesis, mGlu₂ PAMs are entering clinical trials for evaluation as antipsychotics. Currently the most advanced program is through a cooperative agreement between Addex Therapeutics and Jansen Pharmaceuticals for development of the compound ADX71149, which acts as a PAM at mGlu₂. In a recent press release, Addex reported interim results from a Phase IIa study with ADX71149 where this compound was evaluated as a mono- and adjunct therapy in the EU. Although the full results have yet to be detailed in the peer review literature, Addex has reported that ADX71149 demonstrated a good safety and tolerability profile with an optimal dose of 50mg administered two times per day. Moreover, results from this study indicate that when the compound was used as an adjunct therapy to a patient currently prescribed an antipsychotic, it may alleviate residual negative symptoms.

mGlu₃

Similar to mGlu₁, evidence from human genetic studies has shown genetic mutations in the gene encoding the mGlu₃ receptor subtype (*GRM3*) as a risk factor for the development of schizophrenia. Several early family based studies identified single nucleotide polymorphisms (SNPs) associated with schizophrenia. These mutations have been associated with poor performance on cognitive tasks as well as alterations to prefrontal activity during working memory tasks as measured by functional magnetic resonance imaging [reviewed in 54]. Recently, *GRM3* was identified as a potential genetic locus for schizophrenia in a genome wide association study of over 36,000 cases [55]. Furthermore, studies in healthy patients have also demonstrated a relationship between SNPs in *GRM3* and cognitive performance [56, 57]. Although the functional impact of these mutations has not been determined, recent studies have demonstrated cognitive impairment in mGlu₃ receptor knockout mice [58, 59]. Thus, one hypothesis may be that mGlu₃ function is impaired in

patients with these SNPs and a selective PAM may be beneficial, particularly for the cognitive symptoms.

Conclusion

There is a significant unmet medical need for the treatment of schizophrenia. Currently available antipsychotics do not adequately treat all symptom domains and often result in many undesirable side effects. Based on the NMDA receptor hypofunction model, enhancement of group I and group II mGlu signaling have emerged as attractive strategies to rebalance dysfunctional thalamocortical circuits, albeit by distinct mechanisms. There has been tremendous success in developing compounds selective for mGlu₂ and mGlu₅ through targeting allosteric sites. Excitingly, both mGlu₂ and mGlu₅ PAMs have shown efficacy in multiple preclinical models predictive of antipsychotic efficacy. However there are challenges associated with both strategies that need to be considered. In the case of mGlu₂, selectivity over mGlu₃ may be necessary to achieve general clinical benefits while mGlu₅ PAMs should be devoid of any agonist activity should not potentiate NMDA receptor currents for safety purposes. Based on human genetic association studies, mGlu₁ and mGlu₃ have recently emerged as putative targets for the treatment of schizophrenia with mGlu₃ possibly an important target for the cognitive symptoms. Compounds targeting either mGlu₁ or mGlu₃ may be most beneficial to patients identified as carriers of SNPs in the genes encoding these receptors. Although the preclinical evidence is increasingly convincing, the results of the future clinical trials for both targets will be eagerly anticipated. Positive results from any of these programs would represent a major breakthrough for patients.

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Highlights

- mGlu₅ PAMs treat positive, negative, and cognitive symptoms in animal models
- Genetic mutations in mGlu₁ have been identified in some schizophrenic patients
- Early clinical data showed efficacy of mGlu_{2/3} agonists, but later trials did not
- mGlu₂ PAMs are now in clinical development
- Mutations in mGlu₃ have been identified in schizophrenics and may affect cognition