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Metabotropic Glutamate Receptors as Therapeutic Targets for Schizophrenia

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Abstract

Treatment options for schizophrenia that address all symptom categories (positive, negative, and cognitive) are lacking in current therapies for this disorder. Compounds targeting the metabotropic glutamate (mGlu) receptors hold promise as a more comprehensive therapeutic alternative to typical and atypical antipsychotics and may avoid the occurrence of extrapyramidal side effects that accompany these treatments. Activation of the group II mGlu receptors ($mGlu_2$ and $mGlu_3$) and the group I $mGlu_5$ are hypothesized to normalize the disruption of thalamocortical glutamatergic circuitry that results in abnormal glutamaterigic signaling in the prefrontal cortex (PFC). Agonists of $mGlu_2$ and $mGlu_3$ have demonstrated efficacy for the positive symptom group in both animal models and clinical trials with $mGlu_2$ being the subtype most likely responsible for the therapeutic effect. Limitations in the chemical space tolerated by the orthosteric site of the mGlu receptors has led to the pursuit of compounds that potentiate the receptor's response to glutamate by acting at less highly conserved allosteric sites. Several series of selective positive allosteric modulators (PAMs) for $mGlu_2$ and $mGlu_5$ have demonstrated efficacy in animal models used for the evaluation of antipsychotic agents. In addition, evidence from animal studies indicates that $mGlu_5$ PAMs hold promise for the treatment of cognitive deficits that occur in schizophrenia. Hopefully, further optimization of allosteric modulators of mGlu receptors will yield clinical candidates that will allow full evaluation of the potential efficacy of these compounds in the treatment of multiple symptom domains in schizophrenia patients in the near future.

Keywords

metabotropic; glutamate; schizophrenia; NMDA; allosteric

1. Introduction

Schizophrenia is a complex central nervous system (CNS) disorder that affects approximately 1% of the world's population and presents itself as a set of symptoms grouped into three categories: positive, negative, and cognitive (Lewis and Lieberman 2000). The positive symptoms include the perception of nonexistent stimuli such as visual and auditory hallucinations and feelings of paranoia. A reduced or lack of normal affect is characteristic of the negative symptoms and includes depression and social withdrawal. The

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cognitive deficits observed in schizophrenia include disorganized thoughts and a decreased ability to process information. Current therapies, which include typical (e.g. haloperidol and chlorpromazine) and atypical (e.g. olanzapine and clozapine) antipsychotics, have been successful at treating the positive symptoms; however, the negative and cognitive symptoms have been less responsive to these classes of drugs (Buchanan et al. 2005; Kirkpatrick et al. 2006).

An understanding of schizophrenia at both the molecular and circuit levels is necessary to validate new targets and devise new strategies for treating this disorder in a maximally effective manner. Longstanding evidence has led to the hypothesis that alterations in dopaminergic systems, specifically through D_2 dopamine (DA) receptors, is a key element in schizophrenia. Supporting this hypothesis are observations that all currently available medications for schizophrenia act in some way to antagonize D_2 receptors and that post-mortem analysis of brain tissue from patients with schizophrenia reveal elevated D_2 receptor density (Seeman 1987; Seeman 2006). In addition, imaging studies have revealed a greater increase in DA levels upon amphetamine challenge in patients with schizophrenia compared to controls as measured by a decrease in D_2/D_3 receptor binding by [^{11}C]raclopride (Breier et al. 1997) and [^{123}I]iodobenzamide (Laruelle and Abi-Dargham 1999) with the latter study showing this difference specifically in patients with active symptoms of the disease. Although both typical and atypical antipsychotics exhibit antagonism at D_2 receptors, these two classes differentiate themselves in their degree of specificity for D_2 over other neurochemical targets, occupancy time at D_2, and their resulting side effect profile (Seeman 2002). Although each drug offers its own distinct pharmacological profile, in general, the atypical group drugs are less selective for, bind with lower affinity to, and have a faster off rate from the D_2 receptor compared to the typical antipsychotics. Related to their selectivity, atypical antipsychotics have been demonstrated to act in varying degrees at serotonergic, histaminergic, adrenergic, and muscarinic receptors (Bymaster et al. 1996; Roth et al. 1994). This diversity of profiles across both classes of antipsychotics necessitates an individualized approach in the clinic to optimize effectiveness and compliance as well as reduce risk associated with undesirable side effects (Seeman 2002).

As a more thorough understanding of this disorder is developing, additions and modifications to the dopaminergic hypothesis have been put forth. It is also becoming more evident that schizophrenia is more than the result of a change in magnitude of neurotransmitter signaling, but it is also a change in the underlying brain circuitry (Lisman et al. 2008; Marek et al. 2010). Much of this evidence points to disruptions in glutamatergic signaling via the ionotropic N-methyl-D-aspartate receptor (NMDAR) in cortical and midbrain circuits and has led investigators to pursue this avenue for therapeutic development. As will be discussed, there is evidence that these targets have potential to address the unmet needs in the treatment of schizophrenia, specifically in the cognitive deficit symptom cluster.

2. Glutamatergic circuitry in schizophrenia

A delineation of the brain regions and circuitry involved in schizophrenia has been achieved (at least partially) through association of the disrupted behaviors to the pathways known to regulate these behaviors as well as observations of 1) current therapies' mechanisms of action, 2) identification of drugs that mimic the symptoms of schizophrenia, 3) patient brain pathophysiology, and 4) genetic models of schizophrenia. The observation that both typical and atypical antipsychotics act to antagonize D2 receptors initially implicated DA hyperfunction in the subcortical regions of the striatum and nucleus accumbens (the primary locations for D2 receptors on DA terminals) for the positive symptom group that responds to this type of therapy. This theory was later revised to include a deficit of dopamine

transmission in the prefrontal cortex (PFC) at D1 receptors; a revision that resulted in a better correlation with the presence of negative and cognitive symptoms (Goldman-Rakic et al. 2000). However, additional research and observations have revealed features of schizophrenia that point to the involvement of glutamatergic pathways and signaling in ways that are not mutually exclusive to the hypothesized involvement of the dopaminergic system.

It has been known for decades that phencyclidine (PCP), as well as other NMDAR antagonists such as ketamine and MK-801, are psychotomimetic agents in healthy individuals and exacerbate all three symptom clusters in individuals with schizophrenia (Ghoneim et al. 1985; Krystal et al. 1994). These observations suggest a possible role for decreased NMDAR signaling as an explanation for the diverse symptoms observed in this disorder. NMDARs are located postsynaptically at excitatory synapses and are widely distributed in the brain with notable density in cortical and subcortical regions (Monaghan and Cotman 1985; Monaghan et al. 1988; Ozawa et al. 1998). Activation of NMDARs requires the agonists glutamate and glycine in addition to membrane depolarization, resulting in calcium influx through the receptor channel. This process is critically involved in synaptic plasticity, a mechanism required for learning and memory formation (Sweatt 2008) and is relevant to the positive symptoms and cognitive deficits observed in schizophrenia. Within regions associated with the symptoms of schizophrenia, NMDARs are located on GABAergic neurons in subcortical regions such as the nucleus accumbens and on glutamatergic neurons projecting from the mediodorsal thalamus to pyramidal neurons in the PFC. NMDARs on the GABAergic neurons receive excitatory input from glutamatergic afferents and their activation results in an inhibitory regulation of the thalamocortical pathway. A reduction in NMDAR function on these GABAergic neurons results in disinhibition of thalamocortical glutamatergic signaling to the PFC and therefore an increase in excitatory glutamatergic input to pyramidal neurons in the PFC. In support of this model, the psychotomimetic NMDAR antagonists PCP and ketamine have been shown to cause an increase in detected extracellular glutamate levels in the PFC which has been hypothesized to be linked to the effects of these agents on certain aspects of cognitive function and locomotor activity (Moghaddam et al. 1997; Moghaddam and Adams 1998). This signaling pathway as well as pertinent players within it is illustrated in Fig 1.

The role of impaired glutamatergic circuitry and its implication for treatment options has gained momentum in the past several years (Conn et al. 2009b; Marek et al. 2010). While this does not necessarily imply a primary deficit in NMDAR function in the etiology of schizophrenia, there are several possible mechanisms by which NMDAR function could be down regulated in a manner that could contribute to schizophrenia pathology. For example, it is possible that the expression or functioning of the receptor itself may be compromised. NMDAR signal transduction could also be affected by changes in the level or activity of any of a number of proteins as well as any factor influencing glutamate availability at the postsynaptic site or the occurrence of coincident membrane depolarization. Imaging studies directed at glutamatergic targets have found reduced NMDAR binding in medication-free patients with schizophrenia (Pilowsky et al. 2005) as well as evidence of interplay between glutamatergic and dopaminergic neurotransmission (Urban and Abi-Dargham 2010). Evidence of genetic links to NMDAR functioning in schizophrenia has been found and summarized in previous reviews (Harrison and Weinberger 2004) and has served as a basis for the development of several genetic animal models that may be relevant to schizophrenia including subunit NR1 knockdown mice (Mohn et al. 1999; Ramsey 2009)and mice carrying relevant mutations within the NMDAR (Li et al. 2009).

If a change in brain circuitry is induced in a disease state such as schizophrenia, then a means for compensating for the dysfunctional signaling would be a rational strategy for treatment. Targeting the NMDAR or other ionotropic glutamate receptors directly is not

considered to be a viable option due to their widespread role in fast synaptic transmission throughout the CNS and the potential toxicity of overactivation of NMDA receptors (Hirose and Chan 1993). Another approach to regulating transmission through these circuits is to target G protein-coupled metabotropic glutamate receptors which function to modulate synaptic transmission and neuronal excitability. In particular, recent attention has been focused on targeting mGlu receptor subtypes 2, 3, and 5 as novel treatment strategies for treatment of schizophrenia.

3. Metabotropic glutamate receptors

Metabotropic glutamate (mGlu) receptors are family C G-protein coupled receptors that are grouped into three classes based on sequence homology, effector coupling, and pharmacology (Niswender and Conn 2010). Group I mGluRs include $mGlu_1$ and $mGlu_5$ and are located primarily postsynaptically where they couple to G_q/G_{11}. As such, activation of Group I results in phospholipase C (PLC) stimulation, an increase in phosphotinositides (PI) hydrolysis, and increases in intracellular Ca^{+2}. Group II mGlu receptors include $mGlu_2$ and $mGlu_3$ which are localized both pre and postsynaptically and are primarily distributed in forebrain regions (Gu et al. 2008; Petralia et al. 1996). Group II mGlu receptors couple to $G_{i/o}$ and activation of these receptors results in inhibition of adenylyl cyclase and modulation of voltage-dependent ion channels. Group III mGlu receptors include $mGlu_4$, $mGlu_6$, $mGlu_7$, and $mGlu_8$. This third group is localized predominantly presynaptically and is also coupled to $G_{i/o}$ and associated signaling pathways.

Metabotropic glutamate receptors modulate synaptic neurotransmission at least in part through the binding of glutamate at its large extracellular “Venus flytrap” domain which is highly conserved across subtypes and groups. However, its signaling response to glutamate may be modulated (increased or decreased) by compounds that bind to allosteric sites located in the less highly conserved transmembrane regions. This is of major interest in drug design because the allosteric modulator approach may be more amenable to the development of compounds that are selective for a specific target (Conn et al. 2009a). Receptor subtypes from Group I ($mGlu_5$) and Group II ($mGlu_2$ and $mGlu_3$) are involved in the circuitry disruptions implicated in schizophrenia and are associated with NMDARs from a co-localization and functional standpoint. These observations, as well as preclinical evidence supporting these targets as having potential therapeutic benefits in schizophrenia, have led researchers to actively pursue the development of compounds that activate and/or modulate $mGlu_{2/3}$ and $mGlu_5$ for the treatment of this disorder.

4. Group II mGlu receptors as therapeutic targets for schizophrenia

4.1 Group II agonists

Activation of group II mGlu receptors has been shown to decrease the evoked release of glutamate and reduce excitatory synaptic transmission in multiple brain regions, including striatum, PFC, and the hippocampus (Battaglia et al. 1997; East et al. 1995; Lovinger and McCool 1995; Yoshino et al. 1996). Psychotomimetic agents have been shown to increase activity of glutamatergic synapses in the PFC (Adams and Moghaddam 1998; Lorrain et al. 2003) and several studies have confirmed that group II agonists reverse this effect (Lorrain et al. 2003; Marek et al. 2000; Moghaddam and Adams 1998). A class of group II agonists (that are essentially constrained amino acid analogues yet retain specificity at these receptors), exemplified by (1*S*,2*S*,5*R*,6*S*)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) (Monn et al. 1997; Schoepp et al. 1997), has provided excellent tools for understanding the roles of group II mGlu receptor subtypes (Table 1). The neurochemical evidence for the ability of group II activation to reverse the effects of psychotomimetic agents has been supplemented by their ability to reverse the behavioral effects in several

animal models that are used to predict efficacy of potential antipsychotic agents (Conn et al. 2008; Schoepp and Marek 2002) although there are exceptions to this effect depending on which compound is being studied, which behavioral paradigm is being tested, and what strain of animal is being used (Cartmell et al. 1999; Imre et al. 2006a; Imre et al. 2006b; Profaci et al. 2011; Takamori et al. 2003). For determining cognitive-enhancing properties, the effects of these agents depend on the type of learning that is being studied as well as whether or not the comparison is to a basal or disrupted level (Amitai and Markou 2010; Aultman and Moghaddam 2001; Greco et al. 2005; Higgins et al. 2004; Krystal et al. 2005; Schlumberger et al. 2009b; Spinelli et al. 2005). These compounds have also been tested in a preclinical model of schizophrenia induced by social isolation rearing, a non-pharmacological neurodevelopmental approach that results in a phenotype demonstrating hyperlocomotion and deficits in several cognitive models. Specifically, LY404039 was shown to reverse the hyperactivity induced by social isolation (Fabricius et al. 2010) and, in a separate study, LY379268 reversed the hyperactivity, deficit in novel object recognition, and disrupted PPI observed in these animals (Jones et al. 2011). However, in the latter study, LY379268 has no effect on conditional emotional response impairments. The reader is directed to Table 3 for a summary of the effects of Group II agonists in common preclinical models used for the assessment of antipsychotic activity and cognitive-enhancing properties.

The selective group II mGlu receptor agonists in this class have been well-characterized and optimized and members of this class have entered into clinical trials for treatment of schizophrenia. The oral prodrug of (-)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY404039), (1R,4S,5S,6S)-2-thiabicyclo[3.1.0]-hexane-4,6-dicarboxylic acid,4-[(2S)-2-amino-4-(methylthio)-1-oxobutyl]amino-, 2,2-dioxide monohydrate (LY2140023), showed significant antipsychotic efficacy for both positive and negative symptoms with no major side effects in a trial involving patients suffering from schizophrenia and also demonstrated a better metabolic profile than the comparator olanzapine (Patil et al. 2007). Unfortunately, in the follow-up study, neither LY2140023 nor the comparator olanzapine separated from the placebo group (due to higher-than expected placebo response) resulting in an inconclusive result for the second clinical study (Kinon et al. 2011). In addition, 4 of the study participants taking the test drug developed convulsions. Follow-up clinical trials with LY2140023 are ongoing (clinicaltrials.gov) and will hopefully result in a more clear resolution regarding the effectiveness of group II agonists for schizophrenia treatment. Additional studies will need to be performed with this or other group II agonist compounds to more fully understand their efficacy and the side-effect profile for this treatment option.

4.2 Group II interactions with other receptor types

Interestingly, the group II mGlu receptor agonists have also been shown to reverse stereotypies induced by PCP and head shakes induced by serotonin 2A (5-HT2A) receptor agonists (Gewirtz and Marek 2000). In addition, there is evidence from a molecular standpoint that the two receptor types are colocalized in the cortex and are jointly implicated in the neuropathology of schizophrenia (Gonzalez-Maeso et al. 2008). Activation of 5-HT2A receptors results in an increase in glutamate release in the PFC, reminiscent of the increase in excitatory drive to the PFC that is seen as a result of disinhibition of thalamocortical neurons induced by NMDAR antagonists. These effects produced by hallucinogenic 5-HT2A agonists can be blocked by 5-HT2A receptor antagonists and also by group II mGluR agonists (Marek et al. 2000) and positive allosteric modulators of $mGlu_2$ (see section 4.4)(Benneyworth et al. 2007). Recently, it was shown that combined, sub-effective doses of the mGlu2/3 agonist (1S,2R,5R,6R)-2-amino-4-oxabicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY379268) and the 5HT2A receptor antagonist, (R)-(+)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-

piperidinemethanol (M100907), are efficacious in an animal model predictive of antipsychotic activity (Uslaner et al. 2009a). Other intriguing associations with group II mGluRs have been discovered that are relevant to current models of schizophrenia including the upregulation of high-affinity D2 dopamine receptors in the striatum of $mGlu_2$ and $mGlu_3$ knockout mice (Seeman et al. 2009). Observations such as these warrant further investigation and should be kept in mind when considering a possible multi-target approach for treatment of psychosis (Wong et al. 2010).

4.3 $mGlu_2$ is the major contributor of group II agonist effects

As mentioned above, $mGlu_2$ and $mGlu_3$ knockout mice have been developed and studied to better understand the receptor subtype most important for the observed antipsychotic-like effects of the group II mGlu agonists. The antipsychotic actions of group II agonists LY404039 and LY314582 were absent in $mGlu_2$ knockout mice but present in $mGlu_3$ knockout mice, strongly implicating $mGlu_2$ as the predominant player in this effect of the group II agonists (Fell et al. 2008; Spooren et al. 2000). Similar results were observed for the group II agonist LY379268 in that it reversed PCP- and amphetamineevoked hyperactivity in wild type and $mGlu_3$ but not $mGlu_2$ knockout mice (Woolley et al. 2008). These findings highlighted $mGlu_2$ as the target for the development of more specific compounds within this receptor group. However, targeting the orthosteric site for specificity is difficult due to the high degree of conservation across the mGlu receptor subtypes as well as the constraints that this site imposes upon the chemical space tolerated for engagement. In addition, these compounds may be limited in other ways as indicated by tolerance observed for the reversal of PCP- and amphetamine-induced hyperactivity in mice (Galici et al. 2005). As an alternative approach, advances in the development of positive modulators of $mGlu_2$ that exert their actions through interaction with allosteric site(s) within the transmembrane region of the receptor hold promise of overcoming these limitations (Conn et al. 2009a).

4.4 Development of $mGlu_2$ positive allosteric modulators

Multiple positive allosteric modulators (PAMs) that are highly selective for $mGlu_2$ have been developed in recent years. Two of the most well studied chemical classes of $mGlu_2$ PAMs are exemplified by N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine (LY487379) (Galici et al. 2005; Johnson et al. 2003; Schaffhauser et al. 2003) and 3′-(((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3- dihydro-1H-inden-5-yl)oxy)methyl)biphenyl-4-carboxylic acid (BINA) (Bonnefous et al. 2005; Galici et al. 2006; Pinkerton et al. 2005). Both are selective for $mGlu_2$ and their activity is detected as an enhancement in the response induced by an orthosteric agonist or by a shift to the left (increased potency) of a concentration response curve of the orthosteric agonist. These PAMs engage with the receptor within the 7^{th} transmembrane region with 3 amino acids being identified as required for their activity (Rowe et al. 2008; Schaffhauser et al. 2003). The $mGlu_2$ PAMs potentiate the glutamatergic response to group II mGlu agonists (Benneyworth et al. 2007; Galici et al. 2006; Johnson et al. 2003; Poisik et al. 2005; Schaffhauser et al. 2003) including excitatory synaptic responses in the PFC (Benneyworth et al. 2007). Several $mGlu_2$ PAMs from distinct chemical scaffolds have shown efficacy in animal models used for the evaluation of potential antipsychotic agents (Benneyworth et al. 2007; Duplantier et al. 2009; Galici et al. 2005; Galici et al. 2006; Govek et al. 2005; Johnson et al. 2003; Pinkerton et al. 2005) as well as in models demonstrating anxiolytic effects (Johnson et al. 2003) and enhanced cognitive flexibility (Nikiforuk et al. 2010) (see Table 3 for summary). Fell et al. recently reported a novel $mGlu_2$ PAM, N-(4-((2-(trifluoromethyl)-3-hydroxy-4-(isobutyryl)phenoxy)methyl)benzyl)-1-methyl-1H-imidazole-4-carboxamide (THIIC), that produces anxiolytic and antidepressant effects in rodent models of stress and depression, respectively, and found evidence of a low potential for tolerance by this mechanism (Fell et al. 2011). Imaging studies have revealed that the

$mGlu_2$ PAM BINA, at doses that reverse PCP-induced hyperlocomotion, suppresses the imaging response observed in the PFC, caudate-putamen, nucleus accumbens, and mediodorsal thalamus indicating that these are likely key regions involved in BINA's pharmacological effect (Hackler et al. 2010). Because of allosteric modulators' dependence on the presence of a threshold level of agonist to exert their action, it has been postulated that PAMs may provide a safer, better tolerated, therapeutic profile compared to compounds that act to directly stimulate the receptor resulting in a less regulated action and greater potential receptor desensitization (Johnson et al. 2005; Urwyler 2011). While this potential advantage has not been fully established experimentally, these results are promising and support the further optimization of mGlu2 PAMs as a potential therapeutic approach for schizophrenia and possibly other psychiatric disorders (Conn et al. 2009b; Conn et al. 2008; Fraley 2009).

5. $mGlu_5$ as a therapeutic target for schizophrenia

The group I mGlu receptor, $mGlu_5$, has also emerged as a potential target for treatment of schizophrenia. Promising evidence suggests that selective activators of $mGlu_5$ have potential for efficacy in treatment of positive and negative symptoms of schizophrenia and may also have cognitive-enhancing effects (Conn et al. 2009b). In contrast to $mGlu_2$, the preclinical success for mGlu5 has been primarily in the area of allosteric modulators of this receptor as opposed to direct agonists.

5.1 mGlu5 is a close signaling partner with NMDA receptors

As discussed above, the activation of $mGlu_2$ reduces glutamatergic excitatory synaptic transmission in the PFC which may be abnormally increased in disease states such as schizophrenia due to reduced tone at GABAergic projection neurons that help to regulate this signaling pathway. This is likely achieved through a presynaptic mechanism. Theoretically, a similar reduction of excessive activation of projections to the PFC could be achieved further upstream. For instance, potentiation of NMDAR function or other manipulations that increase synaptic excitation of midbrain GABAergic projection neurons could enhance the inhibitory regulation of thalamocortical projections. As stated earlier, inhibition of synaptic excitation of midbrain GABAergic neurons has been postulated to contribute to the psychotomimetic effects of NMDAR antagonists and enhancing transmission at these synapses could provide a beneficial effect. The $mGlu_5$ subtype is a close signaling partner with NMDARs and it has been postulated that activation of this receptor could enhance NMDAR function without inducing the adverse effects that occur with direct activation of NMDARs. $mGlu_5$ interacts physically with NMDARs through binding and scaffolding proteins suggesting that these receptors may be jointly involved in post-synaptic organization and signaling (Ehlers 1999). The activation of group I mGlu receptors through exogenous application of agonist (such as DHPG) potentiates NMDAR responses in forebrain regions. This potentiation has been attributed predominantly to $mGlu_5$-, rather than $mGlu_1$-mediated effects through the use of pharmacological approaches (Attucci et al. 2001; Awad et al. 2000; Doherty et al. 2000; Mannaioni et al. 2001; Pisani et al. 2001; Ugolini et al. 1999) and knockout mice (Pisani et al. 2001). In addition, selective PAMs of $mGlu_5$ enhance the $mGlu_5$-mediated potentiation of NMDAR currents in hippocampal pyramidal cells (O'Brien et al. 2004) and DHPG-induced depolarization of STN neurons (Chen et al. 2007).

5.2 mGlu5 is involved in mechanisms of learning and memory

Long-term potentiation (LTP) and long-term depression (LTD) are two forms of synaptic plasticity that are thought to play important roles in multiple forms of cognitive function. There is evidence that a balance exists between LTP and LTD and that a disruption of this

balance may be characteristic of cognition-impairing pathologies such as observed in models of Fragile X (Bear et al. 2004; Godfraind et al. 1996; Huber et al. 2002; Lauterborn et al. 2007; Li et al. 2002; Nosyreva and Huber 2006; Paradee et al. 1999). Therefore, the differential effects on LTP and LTD resulting from the up- or down-regulation (either through a change in expression level, functional activity, or pharmacological manipulation) should be considered when characterizing a potential target for CNS disorders.

Genetic or pharmacological disruption of signaling through $mGlu_5$ can lead to impaired LTP in hippocampus and other brain regions. For instance, $mGlu_5$ knockout mice exhibit reduced NMDARmediated LTP in the hippocampus that can be recovered by stimulating PKC (Jia et al. 1998). These mice also show a reduction in the ability to perform NMDAR-dependent memory tasks (Lu et al. 1997). Thetaburst stimulation-induced LTP in hippocampal slices is blocked by the $mGlu_5$ noncompetitive antagonist 2-Methyl-6-(phenylethynyl)pyridine (MPEP), a compound that interacts with an allosteric site on the receptor (Francesconi et al. 2004; Shalin et al. 2006). This effect is also produced in vivo where a correlation was drawn between spatial learning and both synaptic plasticity and $mGlu_5$ expression levels in two strains of rat (Manahan-Vaughan and Braunewell 2005). In addition to the impairment of LTP by disruption of $mGlu_5$ signaling, the stimulation of $mGlu_5$ either through agonist application or synaptic glutamate has been observed to facilitate, or “prime”, induced LTP in area CA1 of hippocampus (Cohen et al. 1998; Raymond et al. 2000). Interestingly, DHPG, a group I agonist, induces an NMDA-independent LTD on its own which is blocked by $mGlu_5$ antagonists (Faas et al. 2002; Gasparini et al. 1999; Huang and Hsu 2006; Huang et al. 2004; Huber et al. 2001) and is absent in $mGlu_5$ knockout mice (Huber et al. 2001). These observations provide evidence that suggests that $mGlu_5$ plays a role in learning and memory and may therefore be a target for the development of compounds to treat cognitive disturbances that occur in disorders such as schizophrenia. However, the pursuit of traditional agonists for this purpose has not been encouraged due to their tendency to induce LTD as well as seizure activity in hippocampal slices and in animals (Wong et al. 2005). Thus, an approach that serves to modulate the response to glutamate at $mGlu_5$, rather than evoke it, may be more effective for achieving restoration of cognitive deficits without inducing seizure activity.

5.3 Development of $mGlu_5$ PAMs for use in animal models of schizophrenia

Efforts to discover and optimize highly selective $mGlu_5$ PAMs have progressed over recent years to a point where there now exists a rich set of tools with which to study and validate this mechanism. The first reported $mGlu_5$ PAM was [(3-Fluorophenyl)methylene]hydrazone-3-fluorobenzaldehyde (DFB) (O’Brien et al. 2003) which was successful in demonstrating the feasibility of producing a compound with specificity for $mGlu_5$ that increased the receptor’s response to orthosteric agonists without causing a response on its own. This compound was shown to interact with the MPEP site on $mGlu_5$. However, its utility was limited to in vitro proof-of-concept due to its relatively low potency (2- 5 μM) in in vitro assays and its limited solubility. A point to note is that, within the family of compounds exemplified by DFB, there exist compounds with not only PAM activity but also compounds that act as negative allosteric modulators (NAMs) as well as neutral, or “silent” allosteric modulators. The latter class of compounds has no effect on their own but blocks the ability of PAMs and NAMs to exert their effects. This range of effects of allosteric modulators of $mGlu_5$ within closely related compounds is observed in other series of allosteric modulators and may be exploited to more fully understand the structure-function relationship of the effect of these modulators at the allosteric site.

An improvement in potency compared to DFB was achieved with the discovery of N-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl}-2-hydroxybenzamide (CPPHA), a compound which enabled further studies including the demonstration of an

enhancement of NMDAR currents in hippocampal slices (O'Brien et al. 2004), a critical finding with respect to the desired effect of the compounds in relation to the hypothesized disease model. Interestingly, this compound was found to act at a site distinct from the MPEP site but within the same transmembrane domain (Chen et al. 2008). Unfortunately, with the exception of a couple of studies using icv introduction of compound (Balschun et al. 2006; Chan et al. 2008), in vivo studies could not be performed with these early compounds due to limited solubility, pharmacokinetic properties, and limited central penetration.

The ability to test the in vivo efficacy of $mGlu_5$ PAMs came with the development of 3-Cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (CDPPB) which not only provided better potency than the previous two series, but, was more soluble and centrally penetrant (Chen et al. 2007; Kinney et al. 2005; Lindsley et al. 2004). CDPPB was found to be selective for $mGlu_5$ across mGluR subtypes as well as in a panel of 175 proteins that commonly interact with drugs. An analog of CDPPB, 4-Nitro-*N*-(1,3-diphenyl-1*H*pyrazol-5-yl)benzamide (VU29), was shown to selectively potentiate $mGlu_5$-mediated responses in midbrain neurons (Chen et al. 2007) and in hippocampus (Ayala et al. 2009). This series of compounds was found to interact with the MPEP site on $mGlu_5$ (Chen et al. 2007) and, interestingly, also demonstrate agonist-like activity at higher concentrations (Kinney et al. 2005). An exciting finding was that CDPPB demonstrated efficacy in reducing both amphetamine-induced hyperlocomotion and amphetamine-induced disruption of pre-pulse inhibition (PPI) in rats, two different animal models predictive of antipsychotic efficacy (Kinney et al. 2005). In addition, studies suggest that $mGlu_5$ may have effects in animal models that are relevant to the negative symptoms in schizophrenia. Specifically, CDPPB attenuated the MK-801-induced deficit in sucrose preference in rats (Vardigan et al. 2010). However, although CDPPB can be used to demonstrate in vivo efficacy, it was still not optimal for formulations that are typically used for animal dosing.

Several improved $mGlu_5$ PAMs have since been developed that have enabled the use of these compounds in animal models for the study of their effectiveness. The first of such compounds, S-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone (ADX47273), is active in several different models predictive of antipsychotic efficacy as well as in cognition enhancement (Epping-Jordan et al. 2005; Liu et al. 2008) and lacks the sedative effect sometimes seen with traditional antipyschotics (Schlumberger et al. 2009a). ADX47273 has also been compared vis-à-vis the group II agonist LY354740 and the former, but not the latter, shows efficacy in reducing deficits in PPI (Schlumberger et al. 2009a).

Other structurally diverse $mGlu_5$ PAMs have become available in recent months indicating the wide chemical space tolerated within the available allosteric site(s) within $mGlu_5$. Optimization of an HTS hit on $mGlu_5$ resulted in N-cyclobutyl-6-((3-fluorophenyl)ethynyl)nicotinamide (VU0360172), an orally active $mGlu_5$ PAM, and several other biphenyl acetylenes that produce a dose-dependent effect in reducing amphetamine-induced hyperlocomotion in rats (Rodriguez et al. 2010; Williams et al. 2011). It should be noted that a NAM from the same series showed efficacy in an anxiolytic rodent model. The same HTS campaign revealed a NAM that is structurally distinct from the MPEP scaffold and subsequent attempts at optimization of this *N*-Aryl Piperazine resulted in the identification of a PAM, 2-{4-[2-(benzyloxy)acetyl]piperazin-1-yl}benzonitrile (VU0364289), that also exhibits antipsychotic activity in preclinical models (Zhou et al. 2010). A series of 4-aryl piperazine and piperidine amides analogs has also been disclosed as $mGlu_5$ PAM compounds (Xiong et al. 2010) with 1-(4-(2-chloro-4-fluorophenyl) 29 piperazin-1-yl)-2-(pyridin-4-ylmethoxy)ethanone (CPPZ) shown to have activity in two models predictive of antipsychotic activity (Spear et al. 2011). Interestingly, the newly

disclosed $mGlu_5$ PAM 4-butoxy-N-(2,4-difluorophenyl)benzamide (VU0357121) has been shown to interact at a structurally distinct site from MPEP and CPPHA but still functionally interacts with the MPEP site(Hammond et al. 2010), further illustrating the complexity of interactions that occur within the allosteric binding domain(s).

5.4 Effectiveness of $mGlu_5$ PAMs for cognition enhancement

As discussed earlier, there is evidence that $mGlu_5$ is involved in mechanisms of learning and memory. It is therefore important to establish what effect is exerted by $mGlu_5$ PAMs at the circuit level and confirm that they do not disproportionately affect LTP or LTD, which would have a potential to impair rather than improve cognitive function. To directly address the effect of $mGlu_5$ activation on the balance between LTD and LTP, a series of studies was performed to determine the effects of the CDPPD analog, VU29, on afferent stimulation-induced (as opposed to exogenously applied agonists) hippocampal LTP and LTD at the Schaffer collateral (SC)-CA1 synapse (Ayala et al. 2009). These studies found that the tested PAMs of $mGlu_5$ enhanced both LTP and LTD but did not alter the normal presynaptic activity required to induce each of these forms of synaptic plasticity. The same study also revealed enhanced performance in the Morris water maze task by mice treated with the two structurally distinct $mGlu_5$ PAMs, CDPPB and ADX47273. This study reinforced other findings of the enhancement of cognitive function in animal models by $mGlu_5$ PAMs (Chan et al. 2008; Darrah et al. 2008; Liu et al. 2008; Uslaner et al. 2009b; Vales et al. 2010) (see Table 3 for summary).

The preclinical evidence observed with $mGlu_5$ PAMs thus far presents exciting potential for these compounds to be developed as an alternative treatment for disorders such as schizophrenia where there is currently an unmet need in the cognitive dysfunction symptom cluster. Additionally, these compounds may improve the extrapyramidal side effect profile observed with current therapies. A recent study showing possible desensitization to repeated administration of CDPPB warrants more investigation to determine whether this mechanism will provide a robust profile for the reversal of the different symptom clusters in schizophrenia (Parmentier-Batteur et al. 2010). The next few years will be key in determining if $mGlu_5$ PAMs will move forward for clinical evaluation.

6. Newly available tools and future directions

The possibility of addressing unmet needs in the treatment of schizophrenia and other psychiatric disorders is exciting and provides a clear motive for furthering our understanding of the metabotropic glutamate receptors in this context. Several genetic models have recently been developed that may serve as informative tools in the study of targeting mGluRs (van den Buuse 2010). The neuron-specific protein Norbin (also known as Neurochondrin) interacts with $mGlu_5$ and serves to increase the cell surface localization of the receptor and positively regulate $mGlu_5$ signaling (Wang et al. 2009). Norbin knockout mice show deficits in sensori-motor gating (as measured with PPI) as well as increased locomotor activity similar to those of $mGlu_5$ knockout mice and psychotomimetic-induced models of psychosis (Wang et al. 2009). In addition, genetic models directly targeting the NMDA receptor have resulted in mice showing similar phenotypes. Mice in which the NR1 subunit of the NMDA receptor has been reduced to 5% of wild type levels show both increased motor activity and social deficits and respond to treatment with haloperidol and clozapine (Mohn et al. 1999; Ramsey 2009). Furthermore, knock-in mice bearing NMDARs in which a specific phosphorylation site known to be reduced in patients with schizophrenia (serine 897) (Li et al. 2009) is substituted with an alanine (thereby preventing phosphorylation) exhibit deficits in social interaction and sensorimotor gating. Interestingly, the group I agonist, DHPG, has been shown to induce phosphorylation at both S896 and

S897 in vivo. In future studies, it will be important to determine the effects of $mGlu_5$ PAMs in these genetic models that selectively alter specific aspects of glutamate signaling.

In conclusion, the development of novel treatments for schizophrenia based on normalizing dysfunctional glutamatergic circuitry through activation of $mGlu_2$ and $mGlu_5$ has shown promise both in preclinical models and initial clinical trials. Approaching these targets using allosteric modulators, as opposed to orthosteric agonists, opens up the chemical space for active compounds and may result in an improved therapeutic profile compared to direct agonism of these receptors. Further refinement and investigation will be required to determine the full potential of these agents especially in the realm of the unmet need of treating the cognitive deficits and negative symptoms that occur in schizophrenia. Specifically, results from follow-up trials of $mGlu_2$ agonist LY2140023 that will more definitively reveal its efficacy are highly anticipated and the progression of $mGlu_2$ and $mGlu_5$ PAMs into clinical safety and efficacy evaluations will provide a guide for the next steps for these classes of compounds.

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Abbreviations

CNS	central nervous system
DA	dopamine
mGlu	metabotropic glutamate receptor
PAM	positive allosteric modulator
NAM	negative allosteric modulator
MPEP	2-Methyl-6-(phenylethynyl)pyridine
NMDA	N-methyl-D-aspartate
PCP	phencyclidine
MK-801	(5*S*,10*R*)-(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*, *d*]cyclohepten-5,10-imine maleate
PFC	prefrontal cortex
DHPG	dihydroxyphenylglycine
CDPPB	3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl) benzamide
CPPHA	N-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl}-2-hydroxybenzamide
GPCR	Gprotein- coupled receptor
VU0360172	N-cyclobutyl-6-((3-fluorophenyl)ethynyl)nicotinamide
LY354740	(1*S*,2*S*,5*R*,6*S*)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
LY404039	(-)-(1R,4S,5S,6S)-4-amino-2- sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid
LY2140023	(1R,4S,5S,6S)-2-thiabicyclo[3.1.0]-hexane-4,6-dicarboxylic acid,4-[(2S)-2-amino-4-(methylthio)-1-oxobutyl]amino-, 2,2-dioxide monohydrate

LY379268	(1S,2R,5R,6R)-2-amino-4-oxabicyclo[3.1.0]hexane-2,6-dicarboxylic acid
LY487379	N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine
BINA	3′-(((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy)methyl)biphenyl-4- carboxylic acid
THIIC	N-(4-((2-(trifluoromethyl)-3-hydroxy-4-(isobutyryl)phenoxy)methyl)benzyl)-1- methyl-1H-imidazole-4-carboxamide
DFB	[(3-Fluorophenyl)methylene]hydrazone-3- fluorobenzaldehyde
CDPPB	3-Cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide
VU29	4-Nitro-*N*-(1,3- diphenyl-1*H*-pyrazol-5-yl)benzamide
ADX47273	S-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
VU0357121	4-butoxy-N-(2,4- difluorophenyl)benzamide
LTP	Long-term potentiation
LTD	long-term depression
M100907	(R)-(+)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol
icv	intracerebroventricular
VU0364289	2-{4-[2-(benzyloxy)acetyl]piperazin-1-yl}benzonitrile
NOR	novel object recognition

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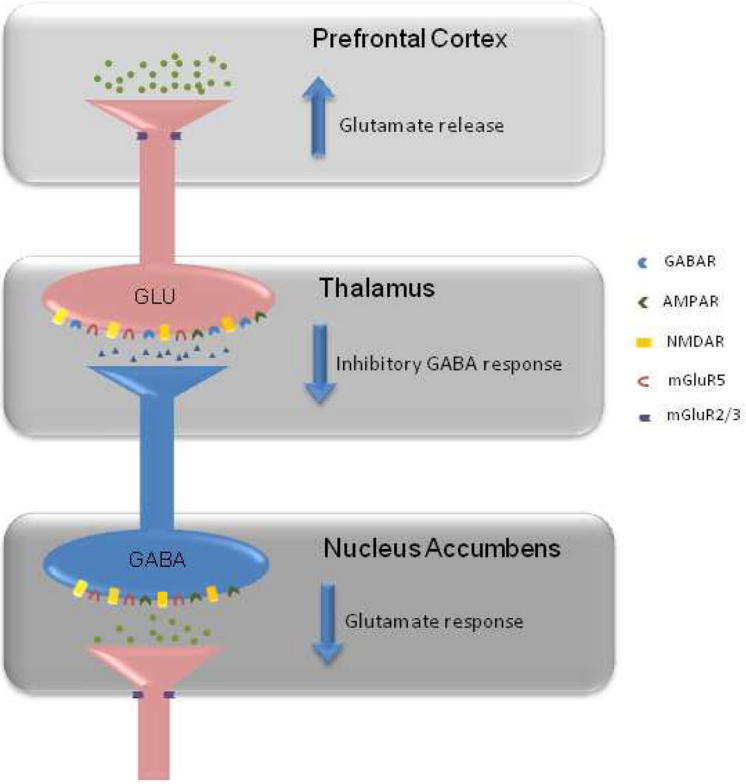


Figure 1.

A simplified schematic illustration of glutamatergic-GABAergic microcircuitry between subcortical and cortical regions. A disruption of this circuit is thought to contribute to the pathophysiology of schizophrenia. For example, a decreased glutamatergic response of inhibitory GABAergic neurons in the nucleus accumbens will result in a decreased inhibition of glutamatergic signaling to the PFC. This decreased inhibition subsequently results in hyper-glutamatergic signaling in this terminal region. The metabotropic glutamate receptors, $mGlu_2$, $mGlu_3$, and $mGlu_5$, are localized in regions where their modulation of glutamatergic signaling may serve to normalize such disruptions.

Table 1

Structures of Group II agonists and PAMs discussed. Note the narrow chemical space exhibited by the agonist compounds

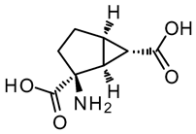
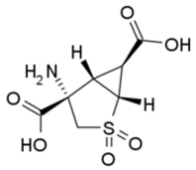
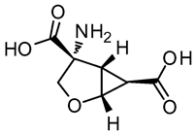
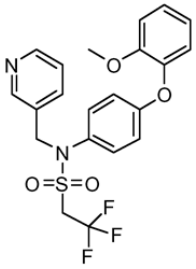
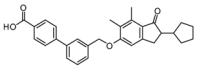
NAME	DESCRIPTION	STRUCTURE
LY354740	Agonist	
LY404039	Agonist	
LY379268	Agonist	
LY487379	PAM	
BINA	PAM	

Table 2

$mGlu_5$ PAMs discussed in text

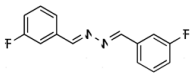
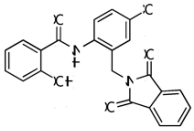
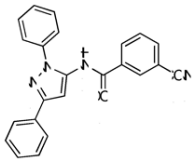
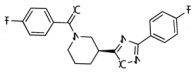
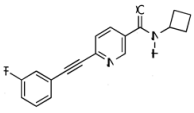
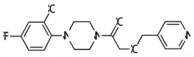
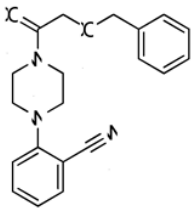
NAME	STRUCTURE
DFB	
CPPHA	
CDPPB	
ADX47273	
VU0360172	
CPPZ	
VU0364289	

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Table 3

Effects of Group II agonists, $mGlu_2$ PAMs, and $mGlu_5$ PAMs in common preclinical behavioral models relevant to symptom clusters in schizophrenia

Preclinical Behavioral Model Response (rodent unless noted)	Group II Agonists	$mGlu_2$ PAMs	$mGlu_5$ PAMs	NOTES
Antipsychotic Models				
Attenuation of hyperlocomotion/ stereotypies induced by NMDAR antagonists (PCP, Ketamine, or MK-801)	+/−[5, 7, 8, 11, 13, 20–22, 28, 29, 36, 38, 45, 48, 52]	+[13–15, 17, 33]	+/−[6, 12, 27, 39, 42]	21 did not observe effect with LY354740 but 22 did observe effect with LY379268 27 observed effect with ADX47273, 39 did not
Attenuation of hyperlocomotion induced by amphetamine, methamphetamine, or apomorphine	+/−[5, 10, 11, 13, 32, 36, 37, 48, 52]	+/−[10, 13, 14]	+[24, 27, 31, 35, 37, 41, 51, 53]	5 observed effects only at higher doses in the amphetamine model compared to the PCP model and efficacy was conditional on type of activity measured 37 did not observe effect with LY354740 48 observed effect with LY379268 at a dose that also decreased spontaneous locomotor activity 14 did not observed effect with BINA
Reversal of disruption of PPI induced by NMDAR antagonists (PCP, Ketamine, or MK-801)	−/+[21, 22, 34, 38, 40, 47]	+[14]	−[6]	34 was the only study showing effect (LY354740) and was dependent on strain of mouse used 6 performed with icv administration of DFB
Reversal of disruption of PPI induced by amphetamine or apomorphine	−[13, 37]	+[13]	+[24, 26, 37, 39]	
Reduction of conditioned avoidance response	+/−[36, 46]	ND	+[27, 39, 42]	46 observed effect with MGS compounds and LY418426 but not LY354740
Cognitive Models				
Reduction of MK-801 impairment in active allothetic place avoidance	ND	−[50]	+[50]	
Increase in novel object recognition or social novelty discrimination	+[18, 23]	+[18]	+[6, 27, 49]	18 investigated social novelty discrimination induced by neonatal PCP 23 investigated disruption by isolation rearing 49 investigated unimpaired and disruption of NOR by MK-801 and observed U-shaped dose effect
Improvement in five-choice serial reaction time test	−/+[1, 16, 43]	ND	+[27]	1 and 16 looked at PCP-induced disruptions; 1 observed mixed effects; 16 observed reduction in anticipatory and perseverative responding but no improvement in accuracy in DBA/2N mice 43 performed in non-human primates and observed a decrease in sustained attention by LY354740 27 saw improvement in impulsivity
Improvement in set-shifting task	ND	+[30]	+[9, 44]	30 also reported an improvement in DRL72 schedule of food reinforcement for LY487379
Improvement in spatial learning and memory	−[19]	ND	+[3, 4]	
Improvement in working memory	−/+[2, 19, 25, 28, 38, 43]	ND	ND	25 was performed in human subjects and 43 was performed in non-human primates All studies showed either no improvement or an impairment except for 25 and 28

+: compounds tested in the model and gave the indicated response

−: compounds tested in the model and did not give the indicated response

ND: compound not tested for given model

Notes column describes differences observed in each pharmacological group for the same model

Table References:

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