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Activation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia

P. Jeffrey Conn¹, Craig W. Lindsley^{1,2}, and Carrie K. Jones¹

¹ Department of Pharmacology, Vanderbilt Program in Drug Discovery, Vanderbilt Medical Center, Nashville, TN, USA

² Department of Chemistry, Vanderbilt University, Nashville, TN, USA

Abstract

In recent years, the metabotropic glutamate (mGlu) receptors have emerged as potential new drug targets for treatment of a range of CNS disorders. Some of the most compelling advances have been made in targeting specific mGlu receptor subtypes as a fundamentally new approach to the treatment of schizophrenia. Recent animal and clinical studies provide strong evidence that agonists of group II mGlu receptors (mGluR2 and mGluR3) are effective in the treatment of the positive symptoms of schizophrenia, and animal studies suggest that mGluR5 agonists could provide a novel approach for the treatment of all major symptom domains (positive, negative, and cognitive) of this disorder. Although the discovery of selective agonists of these receptors is a challenge, there have been recent advances in the discovery of highly selective positive allosteric modulators (PAMs) of mGluR2 and mGluR5. These mGlu receptor-selective PAMs have properties needed for optimization as clinical candidates and have robust effects in animal models that predict efficacy in treatment of schizophrenia.

Introduction

Schizophrenia is a devastating psychiatric illness that afflicts 1% of the population worldwide. The core symptoms observed in schizophrenic patients comprise positive symptoms (thought disorder, delusions, hallucinations, paranoia), negative symptoms (social withdrawal, anhedonia, apathy, paucity of speech) and cognitive impairments, including deficits in perception, attention, learning, short- and long-term memory and executive function. The cognitive deficits in schizophrenia are one of the major disabilities associated with the illness and are considered a reliable predictor of long-term disability and treatment outcome [1–3]. Currently available antipsychotics effectively treat the positive symptoms, but provide only modest effects on the negative symptoms and cognitive impairments. Furthermore, some patients are unresponsive to current antipsychotic treatments and several of these agents are associated with adverse side effects, including disturbances in motor function, weight gain, and sexual dysfunction [1,3,4]. Thus, there is a need for new treatment strategies for this disorder that provide major improvements in efficacy across multiple symptom clusters and have fewer adverse effects.

A major challenge in developing novel therapeutic approaches for treatment of schizophrenia is the absence of clear molecular or cellular neuropathological changes responsible for this disorder. Until recently, the dominant hypothesis has been that excessive dopaminergic transmission in the forebrain is a key causative factor for the pathophysiology

underlying schizophrenia (see Refs. [5,6] for reviews). This hypothesis is based primarily on the observation that clinically effective antipsychotic drugs have substantial antagonist activity at dopamine D₂ receptors, and that the therapeutic efficacy of these compounds is highly correlated with their affinity for striatal D₂ receptors. In addition, the psychotomimetic properties of indirect dopamine agonists and alterations in striatal dopamine release in schizophrenic patients support the involvement of dopamine in the pathophysiology of schizophrenia. Although compelling, the limitations in efficacy and adverse effects of currently available antipsychotics have led researchers to look for additional neurochemical or neurophysiological alterations that might contribute to the pathophysiology of this disorder.

Disruption of cortical and midbrain circuits in schizophrenia

Although the underlying pathophysiology of schizophrenia remains unknown, accumulating evidence points to disruptions in multiple neurotransmitter systems that modulate neural circuits important for normal affect, sensory processing, and cognition (see Refs. [7–9] for reviews). In particular, early clinical findings demonstrated that changes in glutamatergic transmission produced by antagonists of the N-methyl-D-aspartate (NMDA) subtype of ionotropic glutamate receptors, including phencyclidine (PCP), result in a state of psychosis in humans that is similar to that observed in schizophrenic patients [10–12]. These studies suggest that agents that increase NMDA receptor function have potential as therapeutics for the treatment of all major symptom clusters (positive, negative, cognitive) of the disease [10–13]. More recently, studies indicate that reduced NMDA receptor function induces complex changes in transmission through cortical and subcortical circuits that involve both glutamatergic and GABAergic synapses and include downstream increases in transmission at glutamatergic synapses in the prefrontal cortex [14–16]. Importantly, these circuit changes might share common features with changes in brain circuit activities that occur in schizophrenia patients [7]. One hypothesis is that NMDA receptors involved in these symptoms might reside at glutamatergic synapses on GABAergic projection neurons in midbrain regions as well as GABAergic interneurons and glutamatergic projection neurons in key cortical and limbic regions [10–13]. For example, as shown in Figure 1, under normal conditions the activation of NMDA receptors localized on GABAergic projection neurons in subcortical regions, such as the nucleus accumbens, provides inhibitory control on excitatory glutamatergic thalamocortical neurons that project to pyramidal neurons in the prefrontal cortex (PFC). Hypofunction or blockade of these NMDA receptors on midbrain inhibitory GABAergic neurons (Figure 1a) could result in a disinhibition of glutamatergic thalamocortical inputs to pyramidal neurons in the PFC (Figure 1b). This disinhibition would lead to a subsequent increased activity of glutamatergic thalamic neurons and increased activity mediated by the DL-a-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) subtype of glutamate receptors at thalamocortical synapses in the PFC (Figure 1c,d). Based on this model, manipulations that enhance NMDA receptor function, such as activation of metabotropic glutamate receptor subtype 5 (mGluR5) located on GABAergic neurons, have potential as a novel approach to the treatment of schizophrenia. An alternative approach might be to reduce excitatory glutamatergic transmission at key synapses, such as thalamocortical synapses in the PFC, by activation of metabotropic glutamate receptor subtypes 2 and 3 (mGluR2 and mGluR3) presynaptically located in these synapses [6,10,12,13,17,18]. Although other viable models of circuit changes associated with schizophrenia exist, this hypothesis provides one possible framework within which to consider effects of ligands at mGlu receptors that might be relevant to schizophrenia.

mGluR5 as a novel target for the treatment of schizophrenia

Based on the studies outlined above, it is possible that compounds that specifically potentiate NMDA receptor currents could ameliorate the symptoms of schizophrenia. Interestingly, the mGluR5 has emerged as a closely associated signaling partner with the NMDA receptor and might play an integral role regulating NMDA receptor function in a variety of forebrain regions. A large number of cellular studies suggest that activation of mGluR5 potentiates NMDA receptor function in forebrain regions [13,19–24]. In addition, the NMDA component of excitatory postsynaptic potentials in the hippocampus is reduced in mGluR5-knockout mice, and these animals exhibit deficits in NMDA-dependent plasticity and learning [25,26]. NMDA receptors physically interact with mGluR5 via binding to scaffolding proteins [27] and functionally interact via a reciprocal positive-feedback system in which mGluR5 potentiates NMDA receptor currents and NMDA receptors regulate responses to activation of mGluR5 through activation of the protein phosphatase calcineurin or a protein kinase [28,29]. Thus, mGluR5 and NMDA receptors are closely associated signaling partners and a selective agonist of mGluR5 might provide a viable approach to increasing NMDA receptor function for treatment of schizophrenia. Consistent with this hypothesis, mGluR5 receptor-knockout mice display a disruption in prepulse inhibition (PPI) [30,31], a model of sensory motor gating that is disrupted in schizophrenic patients. Furthermore, the selective mGluR5 antagonist 2-methyl-6-(phenylethyl)-pyridine (MPEP) potentiates the psychotomimetic and cognition impairing effects of PCP in animal models [30–32]. Taken together, these findings are consistent with the hypothesis that mGluR5 might represent a novel target for the development of antipsychotics.

Discovery of novel allosteric potentiators of mGluR5 The studies outlined above provide strong support for the hypothesis that activators of mGluR5 might provide a novel approach for the treatment of schizophrenia. Over the last decade, two important strategies have been utilized to develop highly selective activators of mGluR5 through targeting either the orthosteric or allosteric regions of the receptor. By definition, orthosteric agonists of mGluR5 bind and act at the endogenous agonist-binding or orthosteric site of the receptor. By contrast, allosteric agonists or potentiators of mGluR5 do not bind to the orthosteric ligand binding site, but bind and act at other sites termed allosteric sites, to either activate the receptor or potentiate activation of the receptor by its natural ligand (see Ref. [33] for review). Unfortunately, efforts to develop highly selective orthosteric agonists of mGluR5 that have properties suitable for use as drugs have failed. The glutamate binding site is highly conserved across mGlu receptor subtypes [34], making it difficult to develop highly selective orthosteric agonists. Also, mGluR5 orthosteric agonists are analogs of glutamate and do not possess suitable pharmacokinetic properties and brain penetration to allow them to be useful as drugs. Finally, there are several problems associated with the use of agonists as drugs, including adverse effects associated with excessive receptor activation and profound receptor desensitization. To circumvent these problems, we and others have now developed highly selective allosteric potentiators or positive allosteric modulators (PAMs) of mGluR5 [3,35]. These mGluR5 PAMs do not activate the receptor directly but act at allosteric sites to potentiate the response of the receptor to activation by glutamate. The mGlu receptors contain three major domains, a large extracellular N-terminal domain, a heptahelical domain containing seven transmembrane regions linked by short loops, and an intracellular C-terminal domain (Figure 2). Glutamate binds to the N-terminal extracellular domain of mGluR5, whereas the mGluR5 PAMs bind at sites in the seven transmembrane spanning regions.

Three distinct series of mGluR5 PAMs are represented by (1E,2E)-1,2-bis(3-fluorobenzylidene)hydrazine (DFB), N-{5-chloro-2-[(1,3-dioxoisindolin-2-

yl)methyl]phenyl]-2-hydroxybenzamide (CPPHA), and 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) (Figure 3) [36–40]. In general, these mGluR5 PAMs do not activate mGluR5 when added alone but increase the sensitivity of mGluR5 to orthosteric agonists (Figure 3b), and shift the concentration response curve of orthosteric agonists to the left (Figure 3c). DFB, the first identified mGluR5 PAM [37], is highly selective for mGluR5 and has little activity at other mGlu receptor subtypes. DFB provided a breakthrough in demonstrating the viability of this approach for increasing mGluR5 activity. However, the poor potency, efficacy and solubility of this compound limit its use in native preparations or in vivo [37]. Another advance came with discovery of CPPHA [38]. Similar to DFB, CPPHA has no agonist activity but potentiates mGluR5 activation by glutamate with EC₅₀ values in the submicromolar range. CPPHA shifts mGluR5 glutamate concentration-response curve fivefold to tenfold to the left. Importantly, CPPHA potentiates mGluR5-mediated enhancement of NMDA receptor currents in hippocampal slices [38]. The effect on mGluR5-mediated potentiation of NMDA receptor currents is especially encouraging given the central role of this effect in the potential utility of mGluR5 PAMs in the treatment of schizophrenia. However, CPPHA is not adequately soluble in appropriate vehicles for in vivo studies and does not have pharmacokinetic properties and blood-brain barrier penetration for behavioral studies.

The next advance came with discovery of a third series of mGluR5 PAMs, represented by CDPPB, which has higher potency and solubility than both DFB and CPPHA [36,39,41–43]. CDPPB induces a robust potentiation of mGluR5-mediated responses with EC₅₀ values of 25–100 nM. At 1 mM, CDPPB shifts mGluR5 agonist concentration response curves nine fold to the left. Furthermore, the activity of CDPPB was tested against a panel of 175 receptors, transporters, ion channels and enzymes and had no submicromolar activities at any of these known receptors [39].

Interestingly, these three classes of mGluR5 PAMs, DFB, CPPHA and CDPPB, act by interactions at at least two allosteric binding sites on mGluR5. Extensive molecular pharmacology studies suggest that mGluR5 PAM activity of DFB and CDPPB is mediated by binding to the same site in the 7TM domain of the receptor as a well-characterized allosteric antagonist of mGluR5 termed MPEP [37,41]. By contrast, CPPHA does not interact with the MPEP site but is likely to act by interactions with another site in the 7TM domain of mGluR5 [44]. In addition to differences in mechanisms of action of these PAMs on mGluR5 responses, recent studies suggest that members of these different structural classes have the potential of differentially regulating different signaling pathways coupled to mGluR5. For instance, CPPHA induces parallel leftward shifts of the concentration-response curves of 3,5-dihydroxyphenylglycine DHPG and glutamate-induced calcium transients in cortical astrocytes but significantly inhibits maximal mGluR5-mediated increases in ERK1/2 phosphorylation in cortical astrocytes [45].

Another advance represented by the discovery of CDPPB relative to the previous mGluR5 PAMs is that this compound provided the first mGluR5 PAM suitable for in vivo studies. Interestingly, CDPPB has robust activity in reversing amphetamine-induced increases in locomotor activity and amphetamine-induced disruption of PPI in rats, two models commonly used to predict antipsychotic efficacy [39]. These results demonstrate that mGluR5 PAMs produce significant efficacy in at least two animal models that predict efficacy in treatment of positive symptoms of schizophrenia. In addition, CDPPB and other mGluR5 PAMs enhance hippocampal synaptic plasticity, which is thought to be important for cognitive function [46], reverse effects of NMDA receptor antagonists on neuronal firing in the prefrontal cortex [47], and reverse deficits in set-shift task performance induced by NMDA receptor antagonists [48]. These data suggest that mGluR5 PAMs might also have efficacy in the treatment of cognitive disturbances in patients with schizophrenia.

Although CDPBB offers a significant advance, it is important to note that CDPBB is still suboptimal for in vivo studies in that it is not readily soluble in vehicles that are most useful for animal dosing. After these initial reports with CDPBB, investigators at Addex Pharmaceuticals reported a distinct mGluR5 PAM chemotype, represented by (S)-(4-fluorophenyl){3-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]piperidin-1-yl}methanone (ADX47273), which also produced efficacy in preclinical behavioral models that predict efficacy in treatment of both positive symptoms and cognitive disturbances in patients with schizophrenia [49]. Although the properties of ADX47273 have not been reported in detail, this compound might provide a further improvement for use in vivo. Together, these findings provide direct support for the hypothesis that mGluR5 PAMs have potential utility as novel antipsychotic and cognition-enhancing agents.

Group II mGlu receptor agonists and mGluR2 PAMs for treatment of schizophrenia

A large number of preclinical and clinical studies provide strong evidence that agonists of mGluR2 and mGluR3 (group II mGlu receptors) also have potential as a novel approach to the treatment of schizophrenia. Group II mGlu receptor agonists such as (1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) and related compounds (Figure 4) that are highly selective for mGluR2 and mGluR3 have robust activity in animal models that have been used to predict efficacy of potential antipsychotic agents [3,50]. Consistent with the animal studies, clinical studies reveal that a highly selective agonist of group II mGlu receptors has robust efficacy in improving ratings for positive and negative symptoms in patients with schizophrenia [51]. Unlike currently marketed antipsychotic agents, there were no major adverse events reported for the mGluR2/3 agonist in the clinical studies to date. However, further clinical studies will be required to fully establish safety of these compounds after long-term dosing in schizophrenic patients, as well as assess possible efficacy on the cognitive impairments in these patients. Taken together, these findings represent an important breakthrough and could ultimately lead to introduction of group II mGlu receptor activators as a fundamentally novel approach to the treatment of schizophrenia.

As mentioned above, animal studies reveal that the psychotomimetic agents increase activity of glutamatergic synapses in the PFC, and hyperactivity of glutamate neurotransmission in the PFC and limbic structures has been postulated to play a critical role in the pathophysiology of schizophrenia [12,15,52]. Interestingly, effects of psychotomimetic agents on glutamatergic transmission in the PFC are blocked by group II mGlu receptor agonists [15,52,53]. Although it is not yet clear whether this action of group II mGlu receptor agonists is mechanistically related to the antipsychotic actions of these compounds, these actions fit well with current models of disruptions in subcortical and cortical circuits that might be involved in the psychotomimetic effects of NMDA receptor antagonists and the range of symptoms observed in schizophrenia patients (see Figure 1).

Despite advances in development of group II mGlu receptor agonists, it is not yet clear whether orthosteric agonists of these receptors will reach the market for broad clinical use. To date, the discovery and development of mGluR2/3 agonists have been accomplished with only one major chemical scaffold, and it is unlikely that further improvements involving a significant departure from the structures of these compounds will be possible. Moreover, long-term administration of group II mGlu receptor agonists induces robust tolerance in at least one rodent model that has been used to predict antipsychotic efficacy [54]. These orthosteric agonists also activate both mGluR2 and mGluR3 and do not provide insights into which of these group II mGlu receptor subtypes is most important for clinical efficacy. Although, recent findings demonstrate that the antipsychotic-like effects of mGlu2/3

receptor agonists, such as LY404039 [4-amino-2-thiabicyclo(3.1.0)hexane-4,6-dicarboxylic acid] are absent in mGluR2-knockout, but not mGluR3-knockout, mice [55,56]. Thus, it is possible that positive allosteric modulators of mGluR2 might be an alternative approach that could provide greater selectivity and other potential advantages to orthosteric agonists.

Multiple novel compounds have now been identified that act as allosteric potentiators of mGluR2. Most of these novel molecules are structurally related to two prototypical mGluR2 PAMs, termed LY487379 {2,3,2-trifluoro-N-[4-(2-methoxyphenoxy)phenyl]-N-(pyridine-3-ylmethyl)ethane-sulfonamide} [54,57] and 4' [(2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy)methyl]biphenyl-4-carboxylic acid (BINA) [15,58–61] (Figure 4). These compounds are highly selective for mGluR2 and do not potentiate responses to activation of mGluR3 or other mGlu receptor subtypes. In most systems, these compounds have no agonist activity at mGluR2 but induce a leftward shift of the concentration-response curve to glutamate. Mutation analysis has identified three amino acids in the 7TM domain that are critical for actions of mGluR2 PAMs [61,62]. The mGluR2 PAMs have robust effects in potentiating responses to group II mGlu receptor agonists at several identified synapses glutamatergic synapses [57,59,61,63,64], including excitatory synaptic responses in the PFC that are thought to be relevant to actions of psychotomimetic agents [63]. Furthermore, multiple structurally distinct mGluR2-selective PAMs have efficacy in animal models that predict antipsychotic activity that are very similar to those observed with the mGluR2/3 orthosteric agonists [54,57,59,60,63,65]. Taken together with the clinical studies establishing efficacy of group II mGlu receptor agonists in the treatment of schizophrenia, these studies raise the possibility that selective mGluR2 PAMs might provide a novel approach to the treatment of these disorders that is devoid of the adverse effects associated with currently available drugs.

Conclusions

Over the past decade, new data from animal and clinical studies suggest that ligands at metabotropic glutamate receptors might provide a novel approach to the treatment of multiple CNS disorders. This includes compelling evidence that selective increases in activity of two mGlu receptor subtypes, mGluR2 and mGluR5, could provide a novel approach to the treatment of schizophrenia. Although development of traditional orthosteric agonists might provide a viable approach for activating these receptors, major advances have also been made in establishing selective PAMs of both mGluR2 and mGluR5. Selective mGluR2 and mGluR5 PAMs have now been optimized for use in animal models and have robust effects in animal models that predict efficacy in treatment of both positive symptoms and possibly cognitive disturbances in schizophrenia patients. These advances are providing a fundamental advance in our approaches to regulating GPCRs as drug targets and might provide a novel approach to the treatment of schizophrenia.

References

1. Meltzer HY. Treatment of schizophrenia and spectrum disorders: pharmacotherapy, psychosocial treatments, and neurotransmitter interactions. *Biol Psychiatry* 1999;46:1321–1327. [PubMed: 10578448]
2. Tan HY, et al. Dysfunctional and compensatory prefrontal cortical systems, genes and the pathogenesis of schizophrenia. *Cereb Cortex* 2007;17 (Suppl 1):i171–i181. [PubMed: 17726000]
3. Conn PJ, et al. Schizophrenia: moving beyond monoamine antagonists. *Mol Interv* 2008b;8:99–107. [PubMed: 18403654]
4. Nikam SS, Awasthi AK. Evolution of schizophrenia drugs: a focus on dopaminergic systems. *Curr Opin Investig Drugs* 2008;9:37–46.

5. Toda M, Abi-Dargham A. Dopamine hypothesis of schizophrenia: making sense of it all. *Curr Psychiatry Rep* 2007;9:329–336. [PubMed: 17880866]
6. Carlsson A, et al. Neurotransmitter aberrations in schizophrenia: new perspectives and therapeutic implications. *Life Sci* 1997;61:75–94. [PubMed: 9217267]
7. Lisman JE, et al. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci* 2008;31:234–242. [PubMed: 18395805]
8. Carlsson A. The neurochemical circuitry of schizophrenia. *Pharmacopsychiatry* 2006;39 (Suppl 1):S10–S14. [PubMed: 16508890]
9. Lewis DA, Moghaddam B. Cognitive dysfunction in schizophrenia: convergence of gamma-aminobutyric acid and glutamate alterations. *Arch Neurol* 2006;63:1372–1376. [PubMed: 17030651]
10. Coyle JT. Glutamate and schizophrenia: beyond the dopamine hypothesis. *Cell Mol Neurobiol* 2006;26:365–384. [PubMed: 16773445]
11. Lindsley CW, et al. Progress towards validating the NMDA receptor hypofunction hypothesis of schizophrenia. *Curr Top Med Chem* 2006;6:771–785. [PubMed: 16719816]
12. Chavez-Noriega LE, et al. Novel potential therapeutics for schizophrenia: focus on the modulation of metabotropic glutamate receptor function. *Curr Neuropharmacol* 2005;3:9–34.
13. Marino MJ, Conn PJ. Direct and indirect modulation of the N-methyl D-aspartate receptor. *Curr Drug Targets CNS Neurol Disord* 2002;1:1–16. [PubMed: 12769631]
14. Liu J, Moghaddam B. Regulation of glutamate efflux by excitatory amino acid receptors: evidence for tonic inhibitory and phasic excitatory regulation. *J Pharmacol Exp Ther* 1995;274:1209–1215. [PubMed: 7562490]
15. Lorrain DS, et al. Effects of ketamine and N-methyl-D-aspartate on glutamate and dopamine release in the rat prefrontal cortex: modulation by a group II selective metabotropic glutamate receptor agonist LY379268. *Neuroscience* 2003;117:697–706. [PubMed: 12617973]
16. Moghaddam B, et al. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 1997;17:2921–2927. [PubMed: 9092613]
17. Aghajanian GK, Marek GJ. Serotonin model of schizophrenia: emerging role of glutamate mechanisms. *Brain Res Brain Res Rev* 2000;31:302–312. [PubMed: 10719157]
18. Sharp FR, et al. Psychosis: pathological activation of limbic thalamocortical circuits by psychomimetics and schizophrenia? *Trends Neurosci* 2001;24:330–334. [PubMed: 11356504]
19. Ugolini A, et al. Potentiation of NMDA and AMPA responses by the specific mGluR5 agonist CHPG in spinal cord motoneurons. *Neuropharmacology* 1999;38:1569–1576. [PubMed: 10530818]
20. Awad H, et al. Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. *J Neurosci* 2000;20:7871–7879. [PubMed: 11050106]
21. Doherty AJ, et al. A novel, competitive mGlu(5) receptor antagonist (LY344545) blocks DHPG-induced potentiation of NMDA responses but not the induction of LTP in rat hippocampal slices. *Br J Pharmacol* 2000;131:239–244. [PubMed: 10991916]
22. Attucci S, et al. Activation of type 5 metabotropic glutamate receptors enhances NMDA responses in mice cortical wedges. *Br J Pharmacol* 2001;132:799–806. [PubMed: 11181420]
23. Mannaioni G, et al. Metabotropic glutamate receptors 1 and 5 differentially regulate CA1 pyramidal cell function. *J Neurosci* 2001;21:5925–5934. [PubMed: 11487615]
24. Pisani A, et al. Metabotropic glutamate receptor 5 mediates the potentiation of N-methyl-D-aspartate responses in medium spiny striatal neurons. *Neuroscience* 2001;106:579–587. [PubMed: 11591458]
25. Jia Z, et al. Selective abolition of the NMDA component of long-term potentiation in mice lacking mGluR5. *Learn Mem* 1998;5:331–343. [PubMed: 10454358]
26. Lu YM, et al. Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP. *J Neurosci* 1997;17:5196–5205. [PubMed: 9185557]

27. Ehlers MD. Synapse structure: glutamate receptors connected by the shanks. *Curr Biol* 1999;9:R848–R850. [PubMed: 10574750]
28. Alagarsamy S, et al. Activation of NMDA receptors reverses desensitization of mGluR5 in native and recombinant systems. *Nat Neurosci* 1999;2:234–240. [PubMed: 10195215]
29. Alagarsamy S, et al. NMDA-induced potentiation of mGluR5 is mediated by activation of protein phosphatase 2B/calcineurin. *Neuropharmacology* 2005;49 (Suppl 1):135–145. [PubMed: 16005030]
30. Brody SA, et al. Assessment of a prepulse inhibition deficit in a mutant mouse lacking mGlu5 receptors. *Mol Psychiatry* 2004;9:35–41. [PubMed: 14699440]
31. Kinney GG, et al. Metabotropic glutamate subtype 5 receptors modulate locomotor activity and sensorimotor gating in rodents. *J Pharmacol Exp Ther* 2003;306:116–123. [PubMed: 12660307]
32. Campbell UC, et al. The mGluR5 antagonist 2-methyl-6- (phenylethynyl)-pyridine (MPEP) potentiates PCP-induced cognitive deficits in rats. *Psychopharmacology (Berl)* 2004;175:310–318. [PubMed: 15024550]
33. Conn PJ, et al. Allosteric modulators of GPCRs as a novel approach for treatment of CNS disorders. *Nat Rev Drug Discov.* (in press).
34. Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. *Annu Rev Pharmacol Toxicol* 1997;37:205–237. [PubMed: 9131252]
35. Chen Y, Conn PJ. mGluR5 positive allosteric modulators. *Drugs Future* 2008;33:355–360.
36. Lindsley CW, et al. Discovery of positive allosteric modulators for the metabotropic glutamate receptor subtype 5 from a series of N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamides that potentiate receptor function in vivo. *J Med Chem* 2004;47:5825–5828. [PubMed: 15537338]
37. O'Brien JA, et al. A family of highly selective allosteric modulators of the metabotropic glutamate receptor subtype 5. *Mol Pharmacol* 2003;64:731–740. [PubMed: 12920211]
38. O'Brien JA, et al. A novel selective allosteric modulator potentiates the activity of native metabotropic glutamate receptor subtype 5 in rat forebrain. *J Pharmacol Exp Ther* 2004;309:568–577. [PubMed: 14747613]
39. Kinney GG, et al. A novel selective positive allosteric modulator of metabotropic glutamate receptor subtype 5 has in vivo activity and antipsychotic-like effects in rat behavioral models. *J Pharmacol Exp Ther* 2005;313:199–206. [PubMed: 15608073]
40. Zhao Z, et al. Challenges in the development of mGluR5 positive allosteric modulators: the discovery of CPPHA. *Bioorg Med Chem Lett* 2007;17:1386–1391. [PubMed: 17210250]
41. Chen Y, et al. Interaction of novel positive allosteric modulators of metabotropic glutamate receptor 5 with the negative allosteric antagonist site is required for potentiation of receptor responses. *Mol Pharmacol* 2007;71:1389–1398. [PubMed: 17303702]
42. de Paulis T, et al. Substituent effects of N-(1,3-diphenyl-1 H-pyrazol-5-yl) benzamides on positive allosteric modulation of the metabotropic glutamate-5 receptor in rat cortical astrocytes. *J Med Chem* 2006;49:3332–3344. [PubMed: 16722652]
43. Rodriguez A, et al. A close structural analog of 2-methyl-6- (phenylethynyl)-pyridine acts as a neutral allosteric site ligand on metabotropic glutamate receptor subtype 5 and blocks the effects of multiple allosteric modulators. *Mol Pharmacol* 2005;68:1793–1802. [PubMed: 16155210]
44. Chen Y, et al. N-{4-Chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl}-2-hydroxybenzamide (CPPHA) acts through a novel site as a positive allosteric modulator of group 1 metabotropic glutamate receptors. *Mol Pharmacol* 2008;73:909–918. [PubMed: 18056795]
45. Zhang Y, et al. Allosteric potentiators of metabotropic glutamate receptor subtype 5 have differential effects on different signaling pathways in cortical astrocytes. *J Pharmacol Exp Ther* 2005;315:1212–1219. [PubMed: 16135701]
46. Ayala JE, et al. Group III mGluR regulation of synaptic transmission at the SC-CA1 synapse is developmentally regulated. *Neuropharmacology* 2008;54:804–814. [PubMed: 18255102]
47. Lecourtier L, et al. Positive allosteric modulation of metabotropic glutamate 5 (mGlu5) receptors reverses N-methyl-D- aspartate antagonist-induced alteration of neuronal firing in prefrontal cortex. *Biol Psychiatry* 2007;62:739–746. [PubMed: 17511968]

48. Darrah JM, et al. Interaction of N-methyl-D-aspartate and group 5 metabotropic glutamate receptors on behavioral flexibility using a novel operant set-shift paradigm. *Behav Pharmacol* 2008;19:225–234. [PubMed: 18469540]
49. Epping-Jordan MP, et al. In vivo characterization of mGluR5 positive allosteric modulators as novel treatments for schizophrenia and cognitive dysfunction. *Neuropharmacology* 2005;49 (Suppl 1):243. [PubMed: 15993446]
50. Schoepp DD, Marek GJ. Preclinical pharmacology of mGlu2/3 receptor agonists: novel agents for schizophrenia? *Curr Drug Targets CNS Neurol Disord* 2002;1:215–225. [PubMed: 12769628]
51. Patil ST, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. *Nat Med* 2007;13:1102–1107. [PubMed: 17767166]
52. Moghaddam B, Adams BW. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. *Science* 1998;281:1349–1352. [PubMed: 9721099]
53. Marek GJ, et al. Physiological antagonism between 5- hydroxytryptamine (2A) and group II metabotropic glutamate receptors in prefrontal cortex. *J Pharmacol Exp Ther* 2000;292:76–87. [PubMed: 10604933]
54. Galici R, et al. A selective allosteric potentiator of metabotropic glutamate (mGlu) 2 receptors has effects similar to an orthosteric mGlu2/3 receptor agonist in mouse models predictive of antipsychotic activity. *J Pharmacol Exp Ther* 2005;315:1181–1187. [PubMed: 16123306]
55. Fell MJ, et al. Evidence for the role of metabotropic glutamate (mGlu)2 not mGlu3 receptors in the preclinical antipsychotic pharmacology of the mGlu2/3 receptor agonist (–)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY404039). *J Pharmacol Exp Ther* 2008;326:209–217. [PubMed: 18424625]
56. Spooren WP, et al. Lack of effect of LY314582 (a group 2 metabotropic glutamate receptor agonist) on phencyclidine-induced locomotor activity in metabotropic glutamate receptor 2 knockout mice. *Eur J Pharmacol* 2000;397:R1–R2. [PubMed: 10844118]
57. Johnson MP, et al. Discovery of allosteric potentiators for the metabotropic glutamate 2 receptor: synthesis and subtype selectivity of N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine. *J Med Chem* 2003;46:3189–3192. [PubMed: 12852748]
58. Cube RV, et al. 3-(2-Ethoxy-4-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}phenyl)propanoic acid: a brain penetrant allosteric potentiator at the metabotropic glutamate receptor 2 (mGluR2). *Bioorg Med Chem Lett* 2005;15:2389–2393. [PubMed: 15837331]
59. Galici R, et al. Biphenyl-indanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype 2, has antipsychotic- and anxiolytic-like effects in mice. *J Pharmacol Exp Ther* 2006;318:173–185. [PubMed: 16608916]
60. Pinkerton AB, et al. Allosteric potentiators of the metabotropic glutamate receptor 2 (mGlu2). Part 3: Identification and biological activity of indanone containing mGlu2 receptor potentiators. *Bioorg Med Chem Lett* 2005;15:1565–1571. [PubMed: 15745798]
61. Schaffhauser H, et al. Pharmacological characterization and identification of amino acids involved in the positive modulation of metabotropic glutamate receptor subtype 2. *Mol Pharmacol* 2003;64:798–810. [PubMed: 14500736]
62. Rowe BA, et al. Transposition of three amino acids transforms the human metabotropic glutamate receptor (mGluR)-3 positive allosteric modulation site to mGluR2, and additional characterization of the mGluR2 positive allosteric modulation site. *J Pharmacol Exp Ther* 2008;326:240–251. [PubMed: 18430863]
63. Bennyworth M, et al. A selective positive allosteric modulator of metabotropic glutamate receptor subtype 2 blocks a hallucinogenic drug model of psychosis. *Mol Pharmacol* 2007;72:477–484. [PubMed: 17526600]
64. Poisik O, et al. Metabotropic glutamate receptor 2 modulates excitatory synaptic transmission in the rat globus pallidus. *Neuropharmacology* 2005;49:135–145.
65. Govek SP, et al. Benzazoles as allosteric potentiators of metabotropic glutamate receptor 2 (mGluR2): efficacy in an animal model for schizophrenia. *Bioorg Med Chem Lett* 2005;15:4068–4072. [PubMed: 16005222]

Figure 1.

A Model of microcircuitry underlying the NMDA receptor hypofunction hypothesis of schizophrenia. (a) Under normal conditions, activation of NMDA receptors localized on GABAergic projection neurons (as shown in orange) in subcortical regions, such as the nucleus accumbens, provides inhibitory control on excitatory glutamatergic thalamocortical neurons (as shown in green) that project to pyramidal neurons in the PFC. (b) Hypofunction or blockade of these NMDA receptors on midbrain inhibitory GABAergic neurons, which are normally under excitatory control from glutamatergic afferents, results in decreased excitation of GABAergic inhibitory neurons. (c) This decreased excitation of GABAergic inhibitory neurons leads to disinhibition of thalamocortical glutamatergic neurons that

normally provide excitatory input to pyramidal neurons in the PFC. (d) This disinhibition of glutamatergic neurons in the thalamus results in an enhanced release of glutamate, excessive activation of non-NMDA glutamate receptors, and enhanced excitability in postsynaptic structures in the PFC, including pyramidal neurons. mGluR5 and mGluR2/3 receptors are expressed in key regions for the potential modulation of this altered circuitry.

Figure 2.

Schematic Illustration of metabotropic glutamate receptor structure. mGlu receptors share no sequence homology with any other GPCRs. As shown, mGlu receptors possess a large N-terminal extracellular domain that contains the orthosteric binding site of the endogenous ligand glutamate, seven putative transmembrane domains separated by short intra- and extracellular loops, and a cytoplasmic carboxyl-terminal domain variable in length.

Figure 3.

Representative positive allosteric modulators of mGluR5 and their activities on responses to glutamate. (a) Representative chemical structures of four different series of mGluR5 PAMs, including DFB, CPPHA, CDPPB, and ADX47273. (b) Schematic representation of effect of a representative allosteric potentiator on the mGluR5 calcium mobilization response to an EC_{20} concentration of glutamate. The responses to an EC_{20} concentration of glutamate in the presence of vehicle (blue trace) and PAM (green trace) are shown. Also shown is the response to a maximally effective concentration of glutamate (red trace). (c) In the presence of an mGluR5 PAM, the concentration response curve of the group I mGluR5 orthosteric agonist DHPG for activation of mGluR5 is shifted to left.

Figure 4. Representative chemical structures of Group II mGlu receptor agonist LY354740 and mGluR2 PAMs LY487379 and BINA.