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The therapeutic potential of metabotropic glutamate receptor modulation for schizophrenia

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Abstract

Accumulating evidence suggests that a dysregulation of the glutamatergic system exists in the brains of schizophrenia patients. The metabotropic glutamate (mGlu) receptors are being investigated as novel drug targets for this disease, and have shown promise in both preclinical and clinical studies. Activation of $mGlu_5$ receptors may be efficacious for several symptom domains (positive, negative, and cognitive) and the potential for targeting $mGlu_5$ receptors has been bolstered by recent research on mitigating toxicity profiles associated with $mGlu_5$ activation. Additionally, genetic profiling of schizophrenia patients suggests that genes encoding for $mGlu_1$ and $mGlu_3$ receptors are altered, prompting preclinical studies that have demonstrated potential antipsychotic and cognitive enhancing effects of agents that activate $mGlu_1$ and $mGlu_3$ receptors, respectively. Development of subtype-specific drugs for the mGlu receptors, such as allosteric modulators, could provide a path forward for more efficacious and tolerable therapeutics for schizophrenia.

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). It mediates cellular signaling between brain cells by binding both ionotropic (i.e. N-methyl-D-aspartate (NMDA), a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate) [1] and metabotropic glutamate (mGlu) receptors [2], thus contributing to information processing through neuronal network activity and synaptic plasticity [3]. Pharmacological modulation of the glutamatergic system is therefore poised to restore neuronal signaling and provide therapeutic benefit in neurological disease states. Schizophrenia, a neuropsychiatric disorder with a prevalence of around 1% of the world population [4], is one such psychiatric disorder that is highly amenable to glutamatergic modulation [5, 6]. Schizophrenia is clinically diagnosed in the United States according the criteria set by the current edition of the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-V) [7]. Of the three main symptom clusters found in schizophrenia

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patients, current typical and atypical antipsychotic medications that target the monoamine receptors have shown efficacy toward the positive (e.g., auditory and visual hallucinations, delusions), but not negative (e.g., social withdrawal, flat affect) nor cognitive (e.g., impairments in executive function, working memory and cognitive flexibility) symptoms [8]. Unfortunately, the efficacy of these medications is met with significant unwanted extrapyramidal side effects and weight gain, resulting in a significant unmet clinical need for improved pharmacological therapeutics.

Ongoing basic research into the biology of glutamate receptors has yielded significant knowledge that can be leveraged to improve drug discovery efforts for schizophrenia. Although the etiology of the disease is unknown, considerable evidence suggests that NMDA receptor hypofunction may contribute to the pathophysiology of schizophrenia [9, 10]. For example, administration of the NMDA receptor antagonist phencyclidine (PCP) causes schizophrenia-like symptoms in healthy individuals [11], and the NMDA receptor antagonist ketamine can exacerbate symptoms in individuals with schizophrenia [12]. These studies suggest an important role for NMDA receptor signaling in the pathology of schizophrenia; however, modulation of NMDA receptors using orthosteric agonists produces neuronal excitotoxicity and seizures, prohibiting direct NMDA receptor targeting as a viable therapeutic option. Alternatively, targeting the mGlu receptors pharmacologically may allow for regulation of glutamatergic neurotransmission and more precise tuning of the excitatory/inhibitory balance of the brain.

The mGlu receptors are G protein-coupled protein receptors that are sub-divided into three groups (Group I: $mGlu_1$ and $mGlu_5$; Group II: $mGlu_2$, $mGlu_3$; Group III: $mGlu_4$, $mGlu_6$, $mGlu_7$, $mGlu_8$), based on sequence homology, agonist selectivity and secondary signaling cascades [13]. As pharmacology efforts have advanced, the ability to attain subtype specificity of mGlu receptors has been accomplished through development of allosteric modulators. Positive allosteric modulators (PAMs) act to potentiate endogenous glutamate signaling, while negative allosteric modulators (NAMs) reduce the receptor responsiveness to glutamate [14]. In the context of CNS disorders, drug discovery efforts have elucidated beneficial modes of action for allosteric modulators that target subtypes within each of the three groups. Hence, several mGlu receptor subtypes represent novel therapeutic targets with potential utility for treatment of schizophrenia.

Group I mGlu receptors

The group I mGlu receptors consist of $mGlu_1$ and $mGlu_5$, both of which are coupled to signaling proteins that stimulate phosphoinositide hydrolysis and phospholipase C [2]. For many years, $mGlu_5$ has been considered an appealing therapeutic target due to its interaction with NMDA receptors through structural connections with scaffolding proteins such as Homer and Shank [15], as well as functionally by potentiation of NMDA receptor responses [16]. Correspondingly, positive allosteric modulation of $mGlu_5$ has been shown to enhance long-term plasticity (both long-term potentiation (LTP) and long-term depression (LTD)) in the hippocampus, and has pro-cognitive effects in healthy rodents [17]. When $mGlu_5$ is genetically deleted from mice, NMDA receptor-dependent plasticity and learning is impaired [18]. The $mGlu_5$-knockout mice have also been shown to display a disruption in

prepulse inhibition (PPI) [19], a model of sensory motor gating that is disrupted in schizophrenia patients, leading to the hypothesis that $mGlu_5$ may represent a therapeutic target for schizophrenia. Preclinical research has established that $mGlu_5$ PAMs could be efficacious for schizophrenia in assays with predictive validity [20–22]. Albeit promising, the development of compounds that target the $mGlu_5$ receptors for treatment of neurological disorders have been stymied by preclinical toxicology issues, possibly related to excessive NMDA receptor activation [23]. Mechanistic studies point to the possibility that subsets of $mGlu_5$ PAMs can be biased away from NMDA receptor current potentiation, thus mitigating excitotoxic/seizure-inducing profiles [24]. Interestingly, compounds such as VU0409551 that do not potentiate effects of $mGlu_5$ on NMDA receptor currents [25], retain their efficacy in rodent models, displaying antipsychotic-like and cognitive enhancing activity [26, 27]. These beneficial effects may be related to the ability of $mGlu_5$ PAMs to modify long-term plasticity through non-NMDA receptor related mechanisms such as enhanced excitability of pyramidal neurons [28], enhancement of long-term plasticity requiring protein synthesis [29], or possibly depression of inhibitory tone through local messengers such as cannabinoids [30]. Taken together, $mGlu_5$ represents a target that could be efficacious for positive, negative and cognitive symptoms of schizophrenia. However, this may be contingent on the potential to develop $mGlu_5$ PAMs without adverse side-effect liability.

While $mGlu_5$ has been heavily studied as a potential target for pharmacotherapy, $mGlu_1$ has received less attention. However, multiple mutations in the gene encoding for human $mGlu_1$ receptor, *GRM1*, have been identified in schizophrenia patients, raising the possibility that $mGlu_1$ may be dysregulated in schizophrenia [31]. This is supported by the finding that $mGlu_1$ mRNA expression is dysregulated in tissue of postmortem schizophrenia patients [32]. Interestingly, mutations that have been found to be associated with schizophrenia leads to a decrease in $mGlu_1$ signaling *in-vitro*, and a range of highly selective $mGlu_1$ PAMs can potentiate responses to activation of the mutant receptors [33], raising the possibility that $mGlu_1$ PAMs could reverse deficits in $mGlu_1$ signaling in schizophrenia patients that bear these mutations.

Preclinically, $mGlu_1$ knockout mice have a pathological phenotype that mirrors the symptomology of schizophrenia, such as deficits in PPI [34]. Given the hyperdopaminergic state of the schizophrenic brain [35, 36], drugs that antagonize the dopamine system have been a mainstay of the therapeutic treatment. Therefore, production of new drugs that act to dampen dopaminergic efflux would be predicted to have antipsychotic efficacy. It was demonstrated that group I mGlu activation depresses dopamine release in the dorsal striatum of mice using fast-scan cyclic voltammetry *ex-vivo*; an effect likely attributable specifically to $mGlu_1$ activation, as the presence of $mGlu_5$ antagonist or using $mGlu_5$–null mice did not affect group I mGlu agonist-evoked dopamine release [37]. Indeed, administration of a selective $mGlu_1$ PAM, VU6004909, causes dopamine release to be significantly attenuated in the dorsal striatum after electrical stimulation of the medial forebrain bundle in rats [38]. Incongruently, $mGlu_1$ NAMs are also beneficial in preclinical assays such as methamphetamine induced-hyperlocomotion and disruption of PPI [39]. Therefore, more research is necessary to elucidate the precise mechanisms by which $mGlu_1$ modulation shows efficacy in these assays. These data also highlight the important fact that underlying

individual pathology such as the presence of *GRM1* mutations may promote the utility of $mGlu_1$ specific drugs.

Group II mGlu receptors

The group II mGlu receptors, consisting of $mGlu_2$ and $mGlu_3$, couple to G-protein subunits that inhibit adenylate-cyclase activity [2]. Activation of these receptors by group II mGlu receptor orthosteric agonists has been shown to enhance the function of NMDA receptors [40], as well as regulate LTD and LTP in the prefrontal cortex and the hippocampus, respectively [41–43]. Furthermore, activation of group II mGlu receptors reduces excessive activity at glutamatergic synapses in the PFC that is induced by hallucinogens such as the 5-HT_2A receptor agonist DOI or administration of NMDA receptor antagonists [44, 45]. Therefore, these receptors are prime targets for the treatment of schizophrenia where NMDA receptor dysregulation and plasticity impairments are thought to be occurring in these brain areas. Indeed, seminal work testing target viability of the group II receptors for schizophrenia was conducted in rats and revealed that the $mGlu_{2/3}$ agonist, LY354740, was capable of rescuing deficits in stereotypy, locomotion, spatial working memory and cortical glutamate efflux induced by the NMDA-receptor antagonist PCP [46]. This finding was strengthened by the translation of $mGlu_{2/3}$ agonist efficacy in attenuating NMDA receptor-induced deficits in working memory within human subjects [47]. Clinically, the $mGlu_{2/3}$ agonist LY2140023, developed by Eli Lilly and Company, entered a double blind-placebo controlled phase II clinical trial and showed safety and tolerability; without weight gain or extrapyramidal side effects seen with typical antipsychotics. Most importantly, there was also a significant improvement in positive and negative symptoms of schizophrenia compared to placebo [48]. However, the effects of LY2140023 were washed out by a large placebo effect in a follow-up phase II study [49]. Combined with a subsequent placebo controlled study where the atypical antipsychotic risperidone improved scores on the Positive and Negative Symptom Scale, the $mGlu_{2/3}$ agonist LY2140023 failed to show efficacy [50]. While the reasons for clinical failure can be manifold, the importance of dose-response was exemplified by a recent non-human primate study that demonstrated $mGlu_{2/3}$ agonist enhancement of working memory follows an inverted-U dose-response, where low doses improve working memory but higher doses have varied effects [51]. Nonetheless, given the mixed results from these trials and others, Eli Lilly terminated the further development of this compound as a clinical candidate. While these trials were not successful, the fact that the drug did have benefit in some patients suggests that perhaps $mGlu_2$ or $mGlu_3$ specific drugs could yield better results clinically.

Selective $mGlu_2$ PAMs have been heavily pursued as drug candidates for schizophrenia given that preclinical data suggest that $mGlu_2$ primarily mediates the antipsychotic-like effects of $mGlu_{2/3}$ agonists in animal models. This is evidenced by the finding that the $mGlu_{2/3}$ agonist, LY314582, fails to reduce NMDA receptor-antagonist induced hyper-locomotion in $mGlu_2$ KO mice [52]. Several $mGlu_2$ PAMs, including LY487379 and biphenyl-indanone A (BINA), have shown efficacy in preclinical animal models of schizophrenia [53, 54] (for in-depth review see [55]). This research paved the way for $mGlu_2$ PAM testing in clinical trials. However, a proof of principle phase II study of AstraZeneca's $mGlu_2$ PAM AZD8529 did not demonstrate efficacy of the drug candidate compared to

placebo, while the atypical antipsychotic risperidone demonstrated significant efficacy [56]. These results taken together illustrate the difficulty of translating preclinical research findings, and highlight the potential shortcomings in animal modeling approaches. Certainly, the underlying pathology within clinical populations of schizophrenia patients is heterogeneous and disease etiology is likely to be multifaceted; possibly making activation of a single target insufficient to provide therapeutic benefit for a wide population sample. Therefore, the ability to stratify patient population based on biomarkers or genotype may enable pharmacotherapy to be tailored and boost efficacy for individual patients.

Mutations in *GRM3*, the gene encoding for $mGlu_3$, have been shown to be associated with schizophrenia and deficits in cognitive function [57, 58]. The generation of knockout mice and development of specific $mGlu_3$ tool compounds has enabled researchers to begin to uncover the basic functions of $mGlu_3$ in the CNS. Within the prefrontal cortex (PFC), an area of the brain important for working memory and cognition, $mGlu_3$ functions postsynaptically to induce long-term depression (LTD) of excitatory transmission as well as induce calcium mobilization [41] and increase pyramidal cell excitability through inhibition of postsynaptic cAMP-K^+ channel actions [51]. Furthermore, $mGlu_3$ modulates plasticity within the hippocampus, a declarative memory center that is altered in schizophrenia [59]. $mGlu_3$ is required for induction of LTD in the dentate gyrus subregion [60], and facilitates LTP through post-synaptic mechanisms in the CA1 subregion [43]. However, under some conditions activation of $mGlu_3$ can inhibit induction of LTP. Specifically, activation of $mGlu_3$ in hippocampal astrocytes, during corresponding beta-adrenergic receptor activation leads to an attenuation of LTP enhancement through a novel form of glial-neuronal communication [42], suggesting that $mGlu_3$ modulates plasticity differently depending on the activity of the network.

Behaviorally, $mGlu_3$ alterations could contribute to phenotypes associated with schizophrenia given that $mGlu_3$ knockout mice show hyperactivity as well as deficits in reference memory and working memory tests [61], paralleling some known functions of the group I mGlu, $mGlu_5$. Interestingly, recent preclinical evidence uncovered intriguing interactions of $mGlu_3$ and $mGlu_5$, where activation of $mGlu_3$ potentiates $mGlu_5$ signaling. Furthermore, $mGlu_3$-dependent LTD in the PFC was shown to be dependent on $mGlu_5$ activity [62]. Combined with the fact that $mGlu_3$ may provide neuroprotection in response to NMDA receptor-mediated toxicity [63], a drug activating $mGlu_3$ may reduce the risk for cytotoxicity while improving excitatory signaling. Therefore, $mGlu_3$ represents a novel target for cognitive dysfunction in schizophrenia patients, and development of specific $mGlu_3$ potentiators could provide valuable adjunct therapy options.

Group III mGlu receptors

The group III receptors are coupled to signaling cascades that inhibit adenylate cyclase activity, and thus primarily function as presynaptic autoreceptors. Aside from $mGlu_6$, which is restricted to the retina, $mGlu_4$, $mGlu_7$, and $mGlu_8$ are all potential targets to normalize glutamatergic tone within the CNS of schizophrenia patients [13]. Basic research in the field is in its early stages of validating these receptors as specific targets, however, group III agonists such as ACPT-I possess antipsychotic-like effects in animal models by reducing

PCP-induced hyperlocomotion in rodents [64]. In addition, the selective $mGlu_4$ PAM, ADX88178, can improve indicators of all three symptom clusters preclinically [65]. Evidence that $mGlu_4$ could heterodimerize with $mGlu_2$ *in vivo* [66] supports the possibility of targeting this $mGlu_{2/4}$ complex to provide even greater subtype selectivity; although the antipsychotic efficacy of such a drug has yet to be tested experimentally. While $mGlu_7$ and $mGlu_8$ both play a role in cognitive functions [67, 68] and glutamatergic signaling in the hippocampus [69, 70], direct evidence for these receptors as targets for schizophrenia is lacking. In fact, current data may suggest that $mGlu_7$ PAMs could exacerbate positive symptoms [71]. More research is certainly required using more extensive preclinical modeling before the value of these targets can be ruled out, especially as more advanced selective compounds become available.

Conclusion

The fact that the negative and cognitive symptom domains of schizophrenia are often insufficiently controlled in the clinical setting substantiates the need for new pharmacotherapies for this disorder. The mGlu receptors represent several novel targets for the treatment of schizophrenia, with receptors from each of the three mGlu sub-groups showing promise. Based on preclinical data, $mGlu_5$ PAMs that are devoid of toxicity and seizure liability could yield effective treatment for all three symptom domains. Furthermore, the genetic alterations in the genes encoding $mGlu_1$ and $mGlu_3$ within the schizophrenia patient population support recent preclinical data suggesting potential antipsychotic and cognitive enhancing attributes of drugs targeting these receptors. It will be of interest to see how future investigations expound upon this data. Together, the studies outlined in this review illuminate the ongoing basic and clinical research that will undoubtedly drive discovery efforts to make safer and more efficacious mGlu targeted drugs for this disorder.

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References

1. Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ, Dingledine R. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev. 2010; 62(3):405–96. [PubMed: 20716669]
2. Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. Annu Rev Pharmacol Toxicol. 1997; 37:205–37. [PubMed: 9131252]
3. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993; 361(6407):31–9. [PubMed: 8421494]
4. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008; 30:67–76. [PubMed: 18480098]
5. Noetzel MJ, Jones CK, Conn PJ. Emerging approaches for treatment of schizophrenia: modulation of glutamatergic signaling. Discov Med. 2012; 14(78):335–43. [PubMed: 23200065]
6. Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology. 2012; 37(1):4–15. [PubMed: 21956446]

7. Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, Malaspina D, Owen MJ, Schultz S, Tsuang M, et al. Definition and description of schizophrenia in the DSM-5. Schizophr Res. 2013; 150(1):3–10. [PubMed: 23800613]
8. Li P, Snyder GL, Vanover KE. Dopamine Targeting Drugs for the Treatment of Schizophrenia: Past, Present and Future. Curr Top Med Chem. 2016; 16(29):3385–3403. [PubMed: 27291902]
9. Javitt DC. Glutamatergic theories of schizophrenia. Isr J Psychiatry Relat Sci. 2010; 47(1):4–16. [PubMed: 20686195]
10. Coyle JT. NMDA receptor and schizophrenia: a brief history. Schizophr Bull. 2012; 38(5):920–6. [PubMed: 22987850]
11. Domino, E., Luby, ED. Abnormal mental states induced by phencyclidine as a model of schizophrenia, Phencyclidine: Historical and Current Perspectives. NPP Books; Ann Arbor, MI: 1981. p. 401-418.
12. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 1994; 51(3):199–214. [PubMed: 8122957]
13. Niswender CM, Conn PJ. Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol. 2010; 50:295–322. [PubMed: 20055706]
14. Conn PJ, Christopoulos A, Lindsley CW. Allosteric modulators of GPCRs: a novel approach for the treatment of CNS disorders. Nat Rev Drug Discov. 2009; 8(1):41–54. [PubMed: 19116626]
15. Tu JC, Xiao B, Naisbitt S, Yuan JP, Petralia RS, Brakeman P, Doan A, Aakalu VK, Lanahan AA, Sheng M, et al. Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. Neuron. 1999; 23(3):583–92. [PubMed: 10433269]
16. Awad H, Hubert GW, Smith Y, Levey AI, Conn PJ. 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(21):7871–9. [PubMed: 11050106]
17. Ayala JE, Chen Y, Banko JL, Sheffler DJ, Williams R, Telk AN, Watson NL, Xiang Z, Zhang Y, Jones PJ, et al. mGluR5 positive allosteric modulators facilitate both hippocampal LTP and LTD and enhance spatial learning. Neuropsychopharmacology. 2009; 34(9):2057–71. [PubMed: 19295507]
18. Jia Z, Lu Y, Henderson J, Taverna F, Romano C, Abramow-Newerly W, Wojtowicz JM, Roder J. Selective abolition of the NMDA component of long-term potentiation in mice lacking mGluR5. Learn Mem. 1998; 5(4–5):331–43. [PubMed: 10454358]
19. Brody SA, Dulawa SC, Conquet F, Geyer MA. Assessment of a prepulse inhibition deficit in a mutant mouse lacking mGlu5 receptors. Mol Psychiatry. 2004; 9(1):35–41. [PubMed: 14699440]
20. Kinney GG, O'Brien JA, Lemaire W, Burno M, Bickel DJ, Clements MK, Chen TB, Wisnoski DD, Lindsley CW, Tiller PR, 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(1):199–206. [PubMed: 15608073]
21. Kinney GG, Burno M, Campbell UC, Hernandez LM, Rodriguez D, Bristow LJ, Conn PJ. Metabotropic glutamate subtype 5 receptors modulate locomotor activity and sensorimotor gating in rodents. J Pharmacol Exp Ther. 2003; 306(1):116–23. [PubMed: 12660307]
22. Gastambide F, Cotel MC, Gilmour G, O'Neill MJ, Robbins TW, Tricklebank MD. Selective remediation of reversal learning deficits in the neurodevelopmental MAM model of schizophrenia by a novel mGlu5 positive allosteric modulator. Neuropsychopharmacology. 2012; 37(4):1057–66. [PubMed: 22129780]
23. Parmentier-Batteur S, Hutson PH, Menzel K, Uslaner JM, Mattson BA, O'Brien JA, Magliaro BC, Forest T, Stump CA, Tynebor RM, et al. Mechanism based neurotoxicity of mGlu5 positive allosteric modulators--development challenges for a promising novel antipsychotic target. Neuropharmacology. 2014; 82:161–73. [PubMed: 23291536]
24. Rook JM, Noetzel MJ, Pouliot WA, Bridges TM, Vinson PN, Cho HP, Zhou Y, Gogliotti RD, Manka JT, Gregory KJ, et al. Unique signaling profiles of positive allosteric modulators of metabotropic glutamate receptor subtype 5 determine differences in in vivo activity. Biol Psychiatry. 2013; 73(6):501–9. [PubMed: 23140665]

25•. Rook JM, Xiang Z, Lv X, Ghoshal A, Dickerson JW, Bridges TM, Johnson KA, Foster DJ, Gregory KJ, Vinson PN, et al. Biased mGlu5-Positive Allosteric Modulators Provide In Vivo Efficacy without Potentiating mGlu5 Modulation of NMDAR Currents. Neuron. 2015; 86(4): 1029–40. A manuscript detailing the discovery that biased $mGlu_5$ PAMs activate unique signalling pathways and exclude NMDA receptor modulation and excitotoxicity in rodents. [PubMed: 25937172]

26••. Balu DT, Li Y, Takagi S, Presti KT, Ramikie TS, Rook JM, Jones CK, Lindsley CW, Conn PJ, Bolshakov VY, et al. An mGlu5-Positive Allosteric Modulator Rescues the Neuroplasticity Deficits in a Genetic Model of NMDA Receptor Hypofunction in Schizophrenia. Neuropsychopharmacology. 2016; 41(8):2052–61. An elegant study demonstrating $mGlu_5$ positive allosteric modulation in correcting plasticity impairments in a mouse model of schizophrenia. [PubMed: 26741285]

27. Ghoshal A, Moran SP, Dickerson JW, Joffe ME, Grueter BA, Xiang Z, Lindsley CW, Rook JM, Conn PJ. Role of mGlu5 receptors and inhibitory neurotransmission in M1 dependent muscarinic LTD in the prefrontal cortex: implications in schizophrenia. ACS Chem Neurosci. 2017

28. Mannaioni G, Marino MJ, Valenti O, Traynelis SF, Conn PJ. Metabotropic glutamate receptors 1 and 5 differentially regulate CA1 pyramidal cell function. J Neurosci. 2001; 21(16):5925–34. [PubMed: 11487615]

29. Huber KM, Roder JC, Bear MF. Chemical induction of mGluR5- and protein synthesis--dependent long-term depression in hippocampal area CA1. J Neurophysiol. 2001; 86(1):321–5. [PubMed: 11431513]

30. Xu J, Antion MD, Nomura T, Kraniotis S, Zhu Y, Contractor A. Hippocampal metaplasticity is required for the formation of temporal associative memories. J Neurosci. 2014; 34(50):16762–73. [PubMed: 25505329]

31. Ayoub MA, Angelicheva D, Vile D, Chandler D, Morar B, Cavanaugh JA, Visscher PM, Jablensky A, Pfleger KD, Kalaydjieva L. Deleterious GRM1 mutations in schizophrenia. PLoS One. 2012; 7(3):e32849. [PubMed: 22448230]

32. Volk DW, Eggan SM, Lewis DA. Alterations in metabotropic glutamate receptor 1alpha and regulator of G protein signaling 4 in the prefrontal cortex in schizophrenia. Am J Psychiatry. 2010; 167(12):1489–98. [PubMed: 20889653]

33•. Cho HP, Garcia-Barrantes PM, Brogan JT, Hopkins CR, Niswender CM, Rodriguez AL, Venable DF, Morrison RD, Bubser M, Daniels JS, et al. Chemical modulation of mutant mGlu1 receptors derived from deleterious GRM1 mutations found in schizophrenics. ACS Chem Biol. 2014; 9(10):2334–46. The novel $mGlu_1$ PAMs described here partially rescue receptor function caused by deleterious *GRM1* mutations found in schizophrenic patients. [PubMed: 25137254]

34. Brody SA, Conquet F, Geyer MA. Disruption of prepulse inhibition in mice lacking mGluR1. Eur J Neurosci. 2003; 18(12):3361–6. [PubMed: 14686909]

35. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol Psychiatry. 1999; 46(1):56–72. [PubMed: 10394474]

36. Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, Bramon-Bosch E, Valmaggia L, Johns L, Broome M, et al. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. Arch Gen Psychiatry. 2009; 66(1):13–20. [PubMed: 19124684]

37. Zhang H, Sulzer D. Glutamate spillover in the striatum depresses dopaminergic transmission by activating group I metabotropic glutamate receptors. J Neurosci. 2003; 23(33):10585–92. [PubMed: 14627643]

38. Yohn SECD, Foster DJ, Garcia-Barrantes PM, Joffe ME, Cheer JP, Lindsley CW, Conn PJ. Regulation of Striatal Dopamine Release by Metabotropic Glutamate Receptor Subtype 1 via an Endocannabinoid-Dependent Mechanism: Implications for the Treatment of Schizophrenia. Abstract, Society for Neuroscience. 2017

39. Satow A, Suzuki G, Maehara S, Hikichi H, Murai T, Kawagoe-Takaki H, Hata M, Ito S, Ozaki S, Kawamoto H, et al. Unique antipsychotic activities of the selective metabotropic glutamate receptor 1 allosteric antagonist 2-cyclopropyl-5-[1-(2-fluoro-3-pyridinyl)-5-methyl-1H-1,2,3-triazol-4-yl]-2,3-dih ydro-1H-isoindol-1-one. J Pharmacol Exp Ther. 2009; 330(1):179–90. [PubMed: 19359526]

40. Tyszkiewicz JP, Gu Z, Wang X, Cai X, Yan Z. Group II metabotropic glutamate receptors enhance NMDA receptor currents via a protein kinase C-dependent mechanism in pyramidal neurones of rat prefrontal cortex. J Physiol. 2004; 554(Pt 3):765–77. [PubMed: 14645456]

41. Walker AG, Wenthur CJ, Xiang Z, Rook JM, Emmitte KA, Niswender CM, Lindsley CW, Conn PJ. Metabotropic glutamate receptor 3 activation is required for long-term depression in medial prefrontal cortex and fear extinction. Proc Natl Acad Sci U S A. 2015; 112(4):1196–201. [PubMed: 25583490]

42••. Walker AG, Sheffler DJ, Lewis AS, Dickerson JW, Foster DJ, Senter RK, Moehle MS, Lv X, Stansley BJ, Xiang Z, et al. Co-Activation of Metabotropic Glutamate Receptor 3 and Beta-Adrenergic Receptors Modulates Cyclic-AMP, Long-Term Potentiation, and Disrupts Memory Reconsolidation. Neuropsychopharmacology. 2017 An investigation of hippocampal $mGlu_3$ signialling in astrocytes and its role in plasticity and cognition, providing target validation for cognitive domains.

43••. Rosenberg N, Gerber U, Ster J. Activation of Group II Metabotropic Glutamate Receptors Promotes LTP Induction at Schaffer Collateral-CA1 Pyramidal Cell Synapses by Priming NMDA Receptors. J Neurosci. 2016; 36(45):11521–11531. This paper demonstrates an important role for $mGlu_3$ in promoting LTP through NMDA receptor-dependent mechanisms in the hippocampus, suggesting potential cognitive enhancing effects of $mGlu_3$ pharmacological targeting. [PubMed: 27911756]

44. Homayoun H, Jackson ME, Moghaddam B. Activation of metabotropic glutamate 2/3 receptors reverses the effects of NMDA receptor hypofunction on prefrontal cortex unit activity in awake rats. J Neurophysiol. 2005; 93(4):1989–2001. [PubMed: 15590730]

45. Klodzinska A, Bijak M, Tokarski K, Pilc A. Group II mGlu receptor agonists inhibit behavioural and electrophysiological effects of DOI in mice. Pharmacol Biochem Behav. 2002; 73(2):327–32. [PubMed: 12117586]

46. Moghaddam B, Adams BW. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science. 1998; 281(5381):1349–52. [PubMed: 9721099]

47. Krystal JH, Abi-Saab W, Perry E, D'Souza DC, Liu N, Gueorguieva R, McDougall L, Hunsberger T, Belger A, Levine L, et al. Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology (Berl). 2005; 179(1):303–9. [PubMed: 15309376]

48. Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, Avedisova AS, Bardenstein LM, Gurovich IY, Morozova MA, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat Med. 2007; 13(9):1102–7. [PubMed: 17767166]

49. Kinon BJ, Zhang L, Millen BA, Osuntokun OO, Williams JE, Kollack-Walker S, Jackson K, Kryzhanovskaya L, Jarkova N. A multicenter, inpatient, phase 2, double-blind, placebo-controlled dose-ranging study of LY2140023 monohydrate in patients with DSM-IV schizophrenia. J Clin Psychopharmacol. 2011; 31(3):349–55. [PubMed: 21508856]

50. Downing AM, Kinon BJ, Millen BA, Zhang L, Liu L, Morozova MA, Brenner R, Rayle TJ, Nisenbaum L, Zhao F, et al. A Double-Blind, Placebo-Controlled Comparator Study of LY2140023 monohydrate in patients with schizophrenia. BMC Psychiatry. 2014; 14:351. [PubMed: 25539791]

51••. Jin LE, Wang M, Yang ST, Yang Y, Galvin VC, Lightbourne TC, Ottenheimer D, Zhong Q, Stein J, Raja A, et al. mGluR2/3 mechanisms in primate dorsolateral prefrontal cortex: evidence for both presynaptic and postsynaptic actions. Mol Psychiatry. 2016An elegant study showing mGlu2/3 agonists demonstrate an inverted-U dose response on working memory in non-human primates, providing mechanistic insight into prefrontal cortex modulation by group II mGlu agonists

52. Spooren WP, Gasparini F, van der Putten H, Koller M, Nakanishi S, Kuhn R. 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(1):R1–2. [PubMed: 10844118]

53. Galici R, Echemendia NG, Rodriguez AL, Conn PJ. 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(3): 1181–7. [PubMed: 16123306]

54. Galici R, Jones CK, Hemstapat K, Nong Y, Echemendia NG, Williams LC, de Paulis T, Conn PJ. 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(1):173–85. [PubMed: 16608916]

55. Maksymetz J, Moran SP, Conn PJ. Targeting metabotropic glutamate receptors for novel treatments of schizophrenia. Mol Brain. 2017; 10(1):15. [PubMed: 28446243]

56. Litman RE, Smith MA, Doherty JJ, Cross A, Raines S, Gertsik L, Zukin SR. AZD8529, a positive allosteric modulator at the mGluR2 receptor, does not improve symptoms in schizophrenia: A proof of principle study. Schizophr Res. 2016; 172(1–3):152–7. [PubMed: 26922656]

57••. Egan MF, Straub RE, Goldberg TE, Yakub I, Callicott JH, Hariri AR, Mattay VS, Bertolino A, Hyde TM, Shannon-Weickert C, et al. Variation in GRM3 affects cognition, prefrontal glutamate, and risk for schizophrenia. Proc Natl Acad Sci U S A. 2004; 101(34):12604–9. Clinical study in which the $mGlu_2$ PAM, AZD8529, was shown not to have efficacy in a schizophrenic population. [PubMed: 15310849]

58••. Saini SM, Mancuso SG, Mostaid MS, Liu C, Pantelis C, Everall IP, Bousman CA. Meta-analysis supports GWAS-implicated link between GRM3 and schizophrenia risk. Transl Psychiatry. 2017; 7(8):e1196. This paper identifies a link between *GRM3* genetic variation and risk for schizophrenia through a genome-wide association study. [PubMed: 28786982]

59. Tamminga CA, Stan AD, Wagner AD. The hippocampal formation in schizophrenia. Am J Psychiatry. 2010; 167(10):1178–93. [PubMed: 20810471]

60. Poschel B, Wroblewska B, Heinemann U, Manahan-Vaughan D. The metabotropic glutamate receptor mGluR3 is critically required for hippocampal long-term depression and modulates long-term potentiation in the dentate gyrus of freely moving rats. Cereb Cortex. 2005; 15(9):1414–23. [PubMed: 15635057]

61. Fujioka R, Nii T, Iwaki A, Shibata A, Ito I, Kitaichi K, Nomura M, Hattori S, Takao K, Miyakawa T, et al. Comprehensive behavioral study of mGluR3 knockout mice: implication in schizophrenia related endophenotypes. Mol Brain. 2014; 7:31. [PubMed: 24758191]

62. Di Menna L, Joffe ME, Iacovelli L, Orlando R, Lindsley CW, Mairesse J, Gressens P, Cannella M, Caraci F, Copani A, Bruno V, Battaglia G, Conn PJ, Nicoletti F. Functional partnership between mGlu3 and mGlu5 metabotropic glutamate receptors in neurons. Pharmacology. 2017 in press.

63. Corti C, Battaglia G, Molinaro G, Riozzi B, Pittaluga A, Corsi M, Mugnaini M, Nicoletti F, Bruno V. The use of knock-out mice unravels distinct roles for mGlu2 and mGlu3 metabotropic glutamate receptors in mechanisms of neurodegeneration/neuroprotection. J Neurosci. 2007; 27(31):8297–308. [PubMed: 17670976]

64. Palucha-Poniewiera A, Klodzinska A, Stachowicz K, Tokarski K, Hess G, Schann S, Frauli M, Neuville P, Pilc A. Peripheral administration of group III mGlu receptor agonist ACPT-I exerts potential antipsychotic effects in rodents. Neuropharmacology. 2008; 55(4):517–24. [PubMed: 18619473]

65. Kalinichev M, Le Poul E, Bolea C, Girard F, Campo B, Fonsi M, Royer-Urios I, Browne SE, Uslaner JM, Davis MJ, et al. Characterization of the novel positive allosteric modulator of the metabotropic glutamate receptor 4 ADX88178 in rodent models of neuropsychiatric disorders. J Pharmacol Exp Ther. 2014; 350(3):495–505. [PubMed: 24947466]

66. Yin S, Noetzel MJ, Johnson KA, Zamorano R, Jalan-Sakrikar N, Gregory KJ, Conn PJ, Niswender CM. Selective actions of novel allosteric modulators reveal functional heteromers of metabotropic glutamate receptors in the CNS. J Neurosci. 2014; 34(1):79–94. [PubMed: 24381270]

67. Holscher C, Schmid S, Pilz PK, Sansig G, van der Putten H, Plappert CF. Lack of the metabotropic glutamate receptor subtype 7 selectively impairs short-term working memory but not long-term memory. Behav Brain Res. 2004; 154(2):473–81. [PubMed: 15313036]

68. Gerlai R, Adams B, Fitch T, Chaney S, Baez M. Performance deficits of mGluR8 knockout mice in learning tasks: the effects of null mutation and the background genotype. Neuropharmacology. 2002; 43(2):235–49. [PubMed: 12213278]

69. Klar R, Walker AG, Ghose D, Grueter BA, Engers DW, Hopkins CR, Lindsley CW, Xiang Z, Conn PJ, Niswender CM. Activation of Metabotropic Glutamate Receptor 7 Is Required for Induction of Long-Term Potentiation at SC-CA1 Synapses in the Hippocampus. J Neurosci. 2015; 35(19): 7600–15. [PubMed: 25972184]

70. Zhai J, Tian MT, Wang Y, Yu JL, Koster A, Baez M, Nisenbaum ES. Modulation of lateral perforant path excitatory responses by metabotropic glutamate 8 (mGlu8) receptors. Neuropharmacology. 2002; 43(2):223–30. [PubMed: 12213276]

71. Wieronska JM, Stachowicz K, Acher F, Lech T, Pilc A. Opposing efficacy of group III mGlu receptor activators, LSP1-2111 and AMN082, in animal models of positive symptoms of schizophrenia. Psychopharmacology (Berl). 2012; 220(3):481–94. [PubMed: 21952670]

Highlights

- $mGlu_5$ PAMs are efficacious for positive, negative, and cognitive symptoms in animal models
- Clinical trials for $mGlu_2$ PAMs have not been successful
- Genetic studies have identified *GRM1* and *GRM3* as dysregulated in the schizophrenic brain
- $mGlu_1$ PAMs reduce dopamine release in preclinical studies and could be potentially beneficial for positive symptoms
- $mGlu_3$ activation appears to be pro-cognitive and neuroprotective preclinically