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Perspectives on the mGluR2/3 agonists as a therapeutic target for schizophrenia: still promising or a dead end?

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Abstract

Group II metabotropic glutamate receptor (mGluR2/3) agonists once showed promise as non-dopaminergic antipsychotic drugs because of their efficacy in alleviating symptoms of schizophrenia (SZ) in both animal models and human patients. However, the recent failure of Phase III clinical trials dealt a huge blow to the scientific community and the aftershock of the setback in mGluR2/3 research can be felt everywhere from grant support and laboratory studies to paper publication. An immediate question raised is whether mGluR2/3 is still a promising therapeutic target for schizophrenia. Answering this question is not easy, but apparently a new strategy is needed. This article provides a focused review of literature on the study of mGluR2/3 agonists, especially on mGluR2/3 agonists' mechanism of action and efficacy in both normal conditions and animal models of SZ, as well as clinical studies in human patients with the disease. We argue that the cellular and molecular actions of mGluR2/3 agonists, the distinct roles between mGluR2 and mGluR3, as well as their effects on different stages of the disease and different subpopulations of patients, remain incompletely studied. Until the mechanisms associated with mGluR2/3 are clearly elucidated and all treatment options are tested, it would be a great mistake to terminate the study of mGluR2/3 as a therapeutic target for schizophrenia. This review will thus shed light on the comprehensive features of the translational potential mGluR2/3 agonists as well as the need for further research into the more selective activation of mGluR2.

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Conflict of interest

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Keywords

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1. Introduction

Schizophrenia (SZ) is a chronic mental disorder with an incidence of about 0.3–1.0% in the human population (Howes and Kapur, 2009). Although the etiology of the disease remains unclear, SZ is believed to be a multifactorial disease, including genetics, environmental, psychological, and social factors. Symptoms of SZ include positive symptoms, negative symptoms, and cognitive deficits. The cognitive impairment is considered the most complicated dysfunction of SZ, and these deficits are present prior to the onset of psychosis and persist through development. There are no prominent molecular and cellular abnormalities, making diagnosis difficult, and development of successful therapeutics extremely challenging. The current treatment of SZ consists of primarily dopaminergic antipsychotic medications, which antagonize D2 receptors, combined with vocational and psychological counseling. These treatments, however, are only effective in positive symptoms, and the efficacy in negative and cognitive symptoms are very limited (Miyamoto et al., 2005). Recent progress has suggested a clinical potential in utilizing other pharmacological agents (Chaki et al., 2013, Durand et al., 2013, Niswender and Conn, 2010). Here we will focus on the studies of mGluR2/3 agonists as a potential antipsychotic drug for the treatment of SZ.

Based on the sequence homology, second messenger coupling, and pharmacological characteristics, mGluRs are classified into three major groups and eight subtypes: group I (mGluR1/5), group II (mGluR2/3), and group III (mGluR4/6/7/8) (Conn et al., 2009, Conn and Pin, 1997, Fell et al., 2012, Harrison et al., 2008, Mezler et al., 2010, Niswender and Conn, 2010, Schoepp et al., 1999).

The mGluR2/3 has long been linked to SZ (Moghaddam, 2004). Both type-2 and 3 metabotropic glutamate receptor gene (GRM 2 and 3) single nucleotide polymorphisms (SNPs) have been associated with cognitive performance and prefrontal cortex activity levels in SZ patients (Bishop et al., 2015, Chen et al., 2005, Egan et al., 2004, Harrison, Lyon, 2008, Joo et al., 2001, Kordi-Tamandani et al., 2013, Mossner et al., 2008). Administration of LY354740, a prototypical mixed mGlu2/mGlu3 agonist, effectively attenuated the disruptive effects of phencyclidine (PCP) on working memory, stereotypy, locomotion, and cortical glutamate efflux in the PCP model of SZ, at a dose that was without effects on spontaneous activity and corticolimbic dopamine neurotransmission (Moghaddam and Adams, 1998). LY354740 also reduced amphetamine (AMPH)-induced hyperlocomotion in rats (Cartmell et al., 1999). Subsequently, many other similar compounds have been developed, such as LY404039, LY404039's prodrug LY2140023, LY379268, etc. These drugs by activating mGluR2/3 offer promising therapeutic benefits to patients with SZ (Conn, Lindsley, 2009, Moghaddam, 2004, Moghaddam and Adams, 1998, Rotaru et al., 2011, Weinberger, 2007).

However, in 2012, mGluR2/3 agonist LY2140023 (pomaglumetad methionil) failed to meet the primary endpoint based on the positive and negative syndrome scale (PNASS) in Phase III clinical trials, questioning whether mGluR2/3 may be a therapeutic target for SZ. Despite this, we assert that with further research and new approaches, mGluR2/3 drugs may still be a viable clinical option. This review will focus on mGluR2/3 agonists' working mechanisms, the outcomes of *in vivo* animal studies and clinical trials, distinct functions of mGluR2 and mGluR3, the application status of newly selective mGluR2 agonists and positive allosteric modulators (PAM), as well as comparisons between mGluR2/3 agonists and current antipsychotics, in order to provide insights and future directions for research on mGluR2/3 agonists for SZ treatment.

2. Working mechanisms of mGluR2/3 agonists in the brain

GABAergic interneurons in the central nervous system are activated by the axon collaterals of excitatory neurons and exert a powerful inhibitory feedback to these excitatory cells. Based on the NMDA hypofunction hypothesis, the hyperglutamatergic condition results from the decreased action of NMDA receptors on GABAergic neurons, which in turn reduces inhibitory control of excitatory pyramidal neurons, leading to increased glutamate release and excessive stimulation of glutamatergic (e.g., AMPA/KA) receptors. This eventually results in excitotoxic damage and cognitive impairment (Lindsley et al., 2006, Lisman et al., 2008, Nakazawa et al., 2012, Olney and Farber, 1995, Olney et al., 1999, Snyder and Gao, 2013). mGluR2/3 agonists are proposed to decrease presynaptic glutamate release on excitatory neurons (Figure 1), which in turn reverses the hyperglutamatergic condition, and thus alleviates symptoms in SZ patients.

This heuristic hypothesis is obviously appealing, but how do mGluR2/3 agonists achieve this sophisticated action in such a delicate and even cell-type specific manner? It is widely believed that stimulation of presynaptically-localized mGluR2/3 modulates glutamate release through activation of $G_{\alpha i/o}$ pathway, as shown in Figure 1. It begins with adenylate cyclase (AC) catalyzing the conversion of cytosolic adenosine triphosphate (ATP) to cyclic-adenosine monophosphate (cAMP). In this pathway, activation of $G_{\alpha i/o}$ directly inhibits AC and thus decreases the production of cAMP. The level of cAMP determines the activity of various ion channels as well as members of the serine/threonine-specific protein kinase A (PKA) family. Therefore, the activation of mGluR2/3 leads to decreased glutamate release presynaptically by inhibiting AC-cAMP-PKA pathway (Anwyl, 1999, Cartmell and Schoepp, 2000, Moghaddam, 2004, Schoepp, Jane, 1999).

However, mGluR2/3 agonists also enhance postsynaptic excitatory receptor function, including both AMPARs and NMDARs, by regulating several intracellular pathways, as exhibited in Figure 2. Treatment of PFC slices with APDC, a highly selective and potent mGluR2/3 agonist, significantly increases the protein kinase C (PKC) activity and PKC-mediated phosphorylation of NMDA receptors (Tyszkiewicz et al., 2004). In addition, mGluR2/3 agonist LY379268 directly modulates NMDAR expression and function and reverses dizocilpine (MK-801)-induced NMDA dysfunction via activation of the Akt/glycogen synthase kinase 3β (GSK3β) pathway postsynaptically (Xi et al., 2011). In cultured prefrontal cortical neurons, LY379268 also increases the surface expression and function of

AMPA receptors through activating extracellular signal-regulated kinase1/2 (Erk1/2) and GSK3β signaling pathways (Wang et al., 2013). Moreover, activation of mGluR2/3 in the postsynaptic site can also inhibit AC-cAMP-PKA pathway, and thus indirectly activate Src signaling, resulting in an upregulation of NMDAR function (Trepanier et al., 2013). To elucidate the underlying mechanisms in this neuronal proccess, a recent study has identified several key molecules involved in the group II mGluR-induced potentiation of NMDAR exocytosis and function. Activation of mGluR2/3 by the agonist APDC increases Rab4 activity and the interaction between Rab4 and syntaxin 4, facilitating the formation of SNARE complex that is composed of SNAP-25, syntaxin 4 and vesicle-associated membrane protein (VAMP) at postsynaptic sites, which leads to the increased exocytosis of NMDARs (Cheng et al., 2013).

The postsynaptic effects of mGluR2/3 agonists on glutamatergic receptors however, are contradictory to the hypothesis of reversing hyperglutamatergic state via presynaptic action of reducing glutamate release. At this point, it remains unclear how to reconcile these seemingly discordant findings and determine what the net effects of mGluR2/3 activation are on brain function, particularly cognition and behavior. It appears that the presynaptic action is an immediate and direct effect of mGluR2/3 activation, whereas activation of mGluR2/3 in the postsynaptic site engages an indirect and slower effect on intracellular signaling pathways to modulate the glutamate receptors. It is possible that through presynaptically reduced glutamate release and postsynaptically enhanced glutamate receptor function, mGluR2/3 agonists are able to modulate synaptic transmission, and reset the balance of synaptic activity to a new “normal” condition, consequently alleviating the hyperglutamatergic condition in SZ individuals. Still, how exactly this paradoxical action of a presynaptic decrease of glutamate and postsynaptic increase of receptor function results in a net effect that could treat the disease remains to be explored.

Further, understanding mGluR2/3’s interactions with dopaminergic, serotoninergic and GABAergic systems will allow for a better understanding of mGluR2/3 agonists’ roles in brain function and behavior, as well as their potential for SZ treatment. Current studies have demonstrated that elevated dopamine function is associated with glutamatergic dysfunction in SZ (Pauli et al., 2013), and serotonin regulates both dopamine and glutamate neurotransmission in cortical and sub-cortical regions (de Bartolomeis et al., 2013). A fundamental question is whether activation of mGluR2/3 can directly affect dopamine D2 receptors to achieve the necessary antipsychotic action without targeting the glutamate system, as argued by Seeman et al. (Seeman et al., 2008, Seeman and Guan, 2009, Seeman and Guan, 2008). However, a recent study provides both *in vitro* and *in vivo* evidence for a lack of interaction with dopamine D2 receptors by the mGlu2/3 receptor agonists LY354740 and LY379268 (Fell et al., 2009). Interestingly, a direct 5-HT2AR-mGluR2 interaction between the receptor complex seems to be involved in the altered cortical processes of SZ, providing a promising target for the treatment of psychosis (Fribourg et al., 2011, Gonzalez-Maeso et al., 2008). Further, glutamate and GABA are the major excitatory and inhibitory neurotransmitters that are critical for normal neuronal signaling. Some crucial intracellular signaling pathways, such as the Akt/GSK-3β signaling pathway, which is closely relevant to the psychotic condition, has been reported to be significantly influenced by interactions of

dopamine, serotonin, GABA and glutamate transmission (de Bartolomeis, Buonaguro, 2013, Li et al., 2011, Li and Gao, 2011, Li et al., 2012, Li et al., 2009, Xi, Li, 2011). As a result, it is important to take different systems' interactions into account when evaluating each drug's efficiency. It is possible and likely, during the progression of SZ, glutamatergic dysfunction presents first in the early stage with cognitive impairment, which in turn, affects the dopamine and serotonin system, as well as GABAergic inhibition in the later stages with negative symptoms and psychosis, as proposed by Howes and Kapur in the revised dopamine hypothesis (Howes and Kapur, 2009). Given this, patients' complete medication history should be considered when selecting research subjects for clinical trials or prescribing new medications.

3. Differential role of mGluR2 and mGluR3 in antipsychotic and neuroprotective actions

Despite the joint action of mGluR2/3 agonists, there is evidence indicating that mGluR2 and mGluR3 may exhibit different actions in normal brain function and in the abnormal condition of SZ (Table 1). First, mGluR2 and mGluR3 show distinct regional distributions in the central nervous system (Marek, 2010). Using a tritiated LY459477, a selective and structurally novel mGlu2/3 receptor agonist, the distribution of mGluR2 and mGluR3 was studied in transgenic mice lacking either mGluR2, mGluR3, or both receptors. The data show that brain regions enriched in mGluR2 include the medial prefrontal cortex, selected hippocampal regions such as CA1 and dental gyrus, the medial mammillary nucleus, the medial habenula, and the cerebellar granular cell layer, whereas regions enriched in mGluR3 are the dorsolateral entorhinal cortex, the hippocampal CA1 field, the piriform cortex, the substantia nigra, the thalamic reticular nucleus, and primary sensory thalamic nuclei (Wright et al., 2013).

Second, mGluR2 and mGluR3 are expressed in different cells. While both mGluR2 and mGluR3 are localized to neurons, only mGluR3 is expressed in astrocytes (Petralia et al., 1996, Tamaru et al., 2001). These studies also suggest that populations of mGluR2 and mGluR3 receptors are localized differentially in synapses, i.e. those in and near the presynaptic and postsynaptic membranes and in glial wrappings of synapses, in several regions of the brain. Specifically, mGluR2 is expressed in both pre- and postsynaptic elements, having no close association with synapses, whereas the vast majority of mGluR3 in presynaptic elements is not closely associated with glutamate and GABA release sites in the striatum and thalamus, respectively. However, in the spines of the dentate granule cells, the highest receptor density was found in perisynaptic sites. These results indicate that the localization of mGluR3 in the postsynaptic elements has a unique functional role in glutamatergic neurotransmission (Petralia, Wang, 1996, Tamaru, Nomura, 2001). Thus, mGluR2 and mGluR3 receptors are found in various combinations of presynaptic, postsynaptic and glia localizations that may reflect differential modulation of synaptic transmission.

Third, evidence suggests that mGluR2 plays an important role in mediating antipsychotic activity in SZ (Fell et al., 2008, Woolley et al., 2008), while mGluR3 is crucial in exerting neuroprotective effects (Durand, Carniglia, 2013). Using mGluR2- and mGluR3-deficient

mice, two independent studies investigated the relative contribution of mGluR2 and mGluR3 in mediating the antipsychotic profile of LY404039, a potent mGluR2/3 agonist, in PCP and AMPH models of psychosis. The antipsychotic-like effects of LY404039 (10 mg/kg i.p.) on PCP and AMPH-evoked behavioral activation (i.e., increased ambulation, increased distance, and reduced time spent at rest) only exists in mGluR3-deficient mice but not in mGluR2- or mGluR2/3-deficient mice, indicating that activation of mGlu2, but not mGlu3 receptors, is responsible for the antipsychotic-like effect of LY404039 (Fell, Svensson, 2008, Woolley, Pemberton, 2008). In contrast, in cultured astrocytes, which lack mGluR2 subunits, mGluR2/3 agonist LY379268 exhibited no neuroprotective actions, suggesting that the neuroprotective effect of mGlu2/3 agonists is mostly derived from activation of mGluR3 in astrocytes (Corti et al., 2007). Apparently, mGluR3's antipsychotic effects remain to be characterized, but its specific role in neuroprotection through promoting the release of neurotrophic factors in astrocytes (Bruno et al., 1998, Bruno et al., 2001, Bruno et al., 1997) and ameliorating both the induction and progression of neuronal degeneration (Nicoletti et al., 1996) have been well characterized (Durand, Carniglia, 2013).

4. In vivo studies of mGluR2/3 agonists in animal models of SZ

There are different types of animal models for SZ, including pharmacological, developmental (e.g. methylazoxymethanol acetate) and genetic models (e.g. DISC1) (Carpenter and Koenig, 2008). However, studies of mGluR2/3 agonists' effects on developmental and genetic SZ models are severely limited, and to our knowledge, there is no available literature exploring this important research question. One model that has been used extensively is the AMPH-induced SZ-like model (Table 2). AMPH works by increasing dopaminergic and noradrenergic activity in mesolimbic brain regions and produces acute SZ-like psychotic symptoms, usually with the presentation of hyperlocomotion (Auclair et al., 2002). With treatment of 10 mg/kg LY404039, AMPH-induced increases in ambulation and travel distance were reversed (Fell, Svensson, 2008). Other mGluR2/3 agonists such as LY354740 and LY379268 were found to have similar effects in regulating AMPH-induced psychosis and certain behavioral effects as LY404039 (Cartmell, Monn, 1999, Cartmell et al., 2000b, Galici et al., 2005, Woolley, Pemberton, 2008).

Another commonly used pharmacological model targets at the glutamate system, with NMDAR antagonists like PCP, ketamine and MK-801. In the PCP model, mGluR2/3 agonists (e.g., LY379268, LY354740, LY544344) were reported to effectively reverse certain behavioral phenotypes such as locomotor activity and prepulse inhibition (Cartmell et al., 2000a, Profaci et al., 2011, Rorick-Kehn et al., 2006, Swanson and Schoepp, 2002). LY379268 also resulted in a significant reduction in ketamine-induced hyperactivity (Imre et al., 2006, Lorrain et al., 2003b) and MK-801-induced hyperlocomotion (Chartoff et al., 2005, Xi, Li, 2011). However, when Cartmell et al. tested LY354740 and LY379268's effects on both PCP- and AMPH-induced SZ animal models, they found that administration of either LY354740 or LY379268 led to a marked reduction in PCP-evoked behavioral changes but had minimal effects on AMPH-evoked hyperlocomotion. This demonstrates mGluR2/3 agonists' specificity in targeting the glutamate system and the absence of effects on the dopaminergic signaling (Cartmell, Monn, 1999).

An intriguing unanswered question concerns the effects of mGluR2/3 agonists on cognition and negative symptoms. Previous studies on the effects of mGluR2/3 stimulation on cognitive function produced conflicting results. Recent studies indicated that mGluR2/3 agonist LY379268 is effective in reversing post-weaning social isolation-induced recognition memory deficits (Jones et al., 2011) and in correcting a SZ-like phenotype induced by prenatal stress (Matrisciano et al., 2012). Selective mGluR2-PAM LY487379 also promotes cognitive flexibility and inhibitory behavioral control (Nikiforuk et al., 2010) and facilitates responses to sensory stimulation (Copeland et al., 2012) and social discrimination in rats that have been administered PCP (Harich et al., 2007). However, Schlumberger et al. reported that mGluR2/3 agonist LY354740 (3–10 mg/kg) did not modify PCP-induced working memory deficits assessed in a spontaneous alternation task and had no effect on PCP-evoked amnesia in the passive avoidance test (Schlumberger et al., 2009).

SZ is a neurodevelopmental disorder, and a failure to correct the synaptic disruption with treatment immediately following symptom onset would miss a critical treatment or prevention window for SZ. Because NMDAR dysfunction may occur during the early stage of the disease, early treatment would possibly be more effective. Indeed, targeting mGluRs in 1-month-old young mice is efficacious in reversing fragile X syndrome (Michalon et al., 2012), and cognitive training in adolescence prevents adult deficits in a neonatal ventral hippocampal lesion model of SZ (Lee et al., 2012). Therefore, it is critical to address the important concept of whether early-stage (juvenile period) treatment is able to reverse or prevent the progression of SZ, especially for cognitive deficits. Additionally, studies on mGluR2/3 agonist's dose-dependent effects and function under both normal and disease conditions are still limited. Galici et al. reported that LY379268 induced dose-dependent reductions in PCP- and AMPH-induced hyperlocomotor activity, but chronic treatment with LY379268 failed to replicate this effect (Galici, Echemendia, 2005). Given that drugs utilized in clinical populations are primarily administered chronically, an important question raised is whether the acute effects reported in most of the animal studies can be used as a reliable indicator for potential clinical efficacy and also whether chronic treatment with mGluR2/3 agonists will result in issues with tolerance. Finally, although mGluR2/3 agonists reversed certain cognitive deficits induced by NMDAR blockade (Moghaddam and Adams, 1998, Nikiforuk, Popik, 2010), in normal animals these agents had either no effects or even impaired cognition (Aultman and Moghaddam, 2001, Higgins et al., 2004, Schlumberger, Schafer, 2009). These findings are consistent with the hypothesis that the utility of mGluR2/3 agonists on cognitive function may be limited to conditions associated with NMDAR dysfunction or the disease state (Nikiforuk, Popik, 2010). All of these questions require more experiments to determine the most effective therapeutic window of mGluR2/3 agonists during different developmental periods, disease stages, or other conditions.

5. The rise and fall of mGluR2/3 agonists in clinical trials for treatment of SZ

In an early clinical attempt, Patil et al. in Eli Lilly compared the mGluR2/3 agonist LY2140023 with olanzapine, an atypical antipsychotic, for treatment of SZ with bipolar

disorder as an active control in a small population of patients in a randomized, double-blind, placebo-controlled study. This first Phase II clinical trial was an immediate success and promising. Patients with 40 mg LY2140023 administered twice daily showed significant improvements in both positive and negative symptoms, but not in cognitive symptoms compared to the placebo (Patil et al., 2007) (Table 2).

However, in August 2012, Eli Lilly and Company suddenly announced their decision to stop Phase III development as their more complete Phase III clinical trial of mGluR2/3 agonist LY2140023 failed to meet its primary endpoint based on the unaltered PANSS scale (Adams et al., 2013, Adams et al., 2014). The cause of failure was multifaceted. One possibility could be that the patients used in the study may not respond to glutamate-based treatment due to their previous treatment history. It is likely that patients in the trial may have had prior exposure to other antipsychotics that block either D2 receptors, 5-HT_{2A} receptors, or both. Moreover, those patients with a history of a hyperdopaminergic condition will have more influential reactions to the drugs targeting dopaminergic receptors rather than glutamatergic receptors (Howes and Kapur, 2014). In fact, no significant difference in total mGluR2/3 density was identified in the prefrontal cortex (Frank et al., 2011, Ghose et al., 2009) and anterior cingulate cortex (Matosin et al., 2014) in SZ patients compared with healthy controls, although there was a negative correlation between mGluR2/3 density and age (Frank, Newell, 2011). It is therefore likely that mGluR2/3 alteration or glutamatergic dysfunction only occurs in the early stage of the disease. Another possibility could be that researchers choose to measure the PANSS instead of a cognitive-based endpoint. As Downing et al. mentioned, LY2140023 did not show significant improvement compared to placebo on PANSS total scores in SZ patients (Downing et al., 2014). However, Krystal et al. demonstrated that LY354740 produced a significant dose-related improvement in working memory in healthy human subjects who had been administered ketamine (Krystal et al., 2005). Although these results were contradictory to what Patil et al. reported (Patil, Zhang, 2007), a clinical trial evaluating cognitive improvement is definitely warranted, especially for those patients not responsive to dopaminergic antipsychotics. Therefore, more attention should be given to patient inclusion criteria and in understanding mGluR2/3 agonists' distinct effects on positive, negative and cognitive symptoms.

6. Overview of more selective mGluR2/3 agonists: potentials of compounds as mGluR2 agonist/mGluR3 antagonist, mGluR2 positive allosteric modulator (PAM), and selective mGluR2 agonist

As discussed above, mGluR2 and mGluR3 may play a different role in regulating neuronal and synaptic function. Therefore, it has been hypothesized that a more selective and potent mGluR2 agonist may exert a more specific antipsychotic action. Although the discovery of selective agonists of mGluR2 is a challenge, there have been recent advances in developing the highly selective mGluR2 agonist/mGluR3 antagonist LY395756 and positive allosteric modulators (PAMs) such as LY487379, JNJ-42153605, JNJ-40068782, and biphenylindanone A (BINA) (Dhanya et al., 2011, Niswender and Conn, 2010).

When comparing mGluR2/3 agonist LY379268 with mGluR2 PAM LY487379 in the AMPH- and PCP-induced SZ model, unlike LY379268, LY487379 could reverse AMPH-induced disruption of prepulse inhibition (PPI) of the acoustic startle reflex, indicating a potential role in cognitive fragmentation (AMPH- and PCP-induced hyperlocomotion were unaffected) (Galici, Echemendia, 2005). With stronger metabolic stability, another PAM, JNJ-42153605 effectively reversed PCP-induced hyperlocomotion (Cid et al., 2012). In addition, it has been reported that JNJ-40068782 was able to potentiate the binding of mGluR2/3 agonists (Lavreysen et al., 2013). However, one of the most important obstacles in the development of a mGluR2 PAM for potential clinical use is that most of the compounds, such as BINA, are not water soluble, directly limiting their applicability in animal models to assess effects on mitigating behavioral deficits.

A promising mGluR2 PAM that may shed light onto PAMs' therapeutic value in clinical populations is ADX71149 (Addex Company). Recently, Addex announced in a press release that ADX71149 has passed a Phase IIa clinical study that demonstrated that ADX71149 not only met the primary criterion of safety and tolerability, but also affected patients with negative symptoms (Hopkins, 2013). Although promising results of ADX71149 in clinical studies have been demonstrated, its Phase III clinical trial results have not been released. Research about PAMs remains insufficient, and more laboratory and clinical researches are needed to obtain a better understanding of PAMs' comprehensive properties. Further clinical investigations comparing mGluR2/3 agonists and mGluR2 PAMs, as well as a selective agonist of mGluR2, are still necessary.

7. Advantages and disadvantages in application of mGluR2/3 agonists

Compared to other typical and atypical antipsychotic drugs, mGluR2/3 agonists have many advantages that warrant further investigation. The mechanisms of mGluR2/3 agonists and most of the current antipsychotic medications are distinct. While typical (e.g. haloperidol) and atypical (e.g. clozapine and olanzapine) antipsychotics both target the dopamine system, atypical antipsychotics exert effects on the serotonin system as well. Typical antipsychotics are associated with a higher rate of extrapyramidal symptoms (EPS) which can be explained by specific inhibition of dopamine receptors (Miyamoto, Duncan, 2005, Tamminga, 1997), whereas atypical antipsychotics display fewer EPS and more weight gain, diabetes, and risk of metabolic syndrome (Schultz et al., 2007, Tandon et al., 2008).

In contrast, patients treated with mGluR2/3 agonists did not display the side effects commonly associated with current dopaminergic antipsychotics. For example, LY2140023 was generally well tolerated and appeared to have a low association with adverse events related to dopamine D2 receptor antagonism (e.g., EPS) (Mezler, Geneste, 2010). A potential association of LY2140023 treatment and seizure events has been identified, although an accurate and reliable understanding of the incidence of these events requires further clinical testing (Kinon and Gomez, 2013). In addition, in patients treated with LY2140023 or placebo, Ayan-Oshiodi et al. reported no clear trends for increased treatment-emergent adverse events (TEAEs) incidence occurring with higher doses of LY2140023 in both single-dose and multiple-dose treatment groups. The TEAEs with the highest incidence were gastrointestinal and nervous system events, but no serious adverse events occurred, and

most TEAEs were mild in severity and transient in nature. There were also no clinically significant changes in electroencephalograms in subjects receiving LY2140023, and it was generally well tolerated in healthy subjects (Ayan-Oshodi et al., 2012). Furthermore, there was no evidence of withdrawal symptoms in subjects with the abrupt discontinuation of 4-week LY2140023 administration (Stauffer et al., 2014).

The safety, tolerability and potential therapeutic effects of JNJ-40411813/ADX-71149, a mGluR2 PAM (NCT01323205), are also being investigated in patients with SZ (Chue and Lalonde, 2014). The field is waiting for the outcome, although preliminary Phase IIa results suggest potential in the treatment of negative symptoms; a trend toward separation from placebo was observed after 1 month at moderate doses of the investigational drug used as an adjunct to antipsychotics (Chue and Lalonde, 2014) (see De Boer P, Sinha V, Hoeben E, et al. Characterization of the clinical effect of a positive allosteric modulator of the metabotropic glutamate receptor-2 [poster #998]. Presented at the 68th Annual Conference of the Society of Biological Psychiatry; May 16–18, 2013; San Francisco, CA).

Despite the low side effects, mGluR2/3 agonists' efficacy in SZ patients did not seem to be better than current antipsychotics, at least as a monotherapy. LY2140023 failed to bring a more significant improvement on either positive or negative symptoms compared with other standard antipsychotics (Adams, Kinon, 2013, Adams, Zhang, 2014, Stauffer et al., 2013). In a long-term, phase 2 comparative safety study of LY2140023 versus atypical antipsychotic standard of care (SOC: olanzapine, risperidone, or aripiprazole) in patients with SZ, Adams et al (Adams, Kinon, 2013) reported that there was no statistically significant difference between LY2140023 and SOC for time to discontinuation due to lack of tolerability. The incidence of serious adverse events was comparable between groups. LY2140023-treated patients reported significantly more TEAEs of vomiting, agitation, and dyspepsia, while SOC-treated patients reported significantly more akathisia and weight gain. Improvement in PANSS total score over the initial 6 to 8 weeks of treatment was similar between groups, but improvement was significantly greater in the SOC group at 24-week endpoint. LY2140023 and SOC groups had comparable negative symptom improvement at 24-week endpoint. In another 24-week, multicenter, randomized, double-blind, Phase 3 study, they compared LY2140023 with aripiprazone, an atypical antipsychotic, on efficacy and various safety measures, including serious adverse events (SAEs), discontinuation due to adverse events (AEs), TEAEs, EPS, and suicide-related thoughts and behaviors. Consistently, LY2140023 also showed a significantly lower change in PANSS total scores, significantly higher incidences of SAEs and discontinuation due to AEs compared with aripiprazole. No statistically significant differences in the incidence of TEAEs, EPS, or suicidal ideation or behavior were noted between treatment groups (Adams, Zhang, 2014). It should be noted that patients in both studies were not selected per Howes and Kapur criteria (Howes and Kapur, 2014). It would be interesting to see whether mGluR2/3 agonists are more effective after the patients are grouped and analyzed by dopamine-drug responders versus non-responders.

8. Potential of using mGluR2/3 agonist as adjunctive to antipsychotics and the promise for pharmacogenomic treatment

As discussed above, LY2140023 is an mGluR2/3 full agonist that initially appeared promising (Patil, Zhang, 2007), but ultimately provided disappointing results as a monotherapy in acute psychosis (Downing, Kinon, 2014). Given that mGluR2/3 agonists fail to generate persistent antipsychotic effects in different experiments, mGluR2/3 agonists might not be an optimal candidate as a solitary treatment for SZ, at least for those patients in late stage with clear psychosis at a hyperdopaminergic state. However, the drug may be effective as an adjunct (such as d-serine, glycine, glycine transporter 1 inhibitor, electroconvulsive therapy, etc.) therapy to currently approved antipsychotics (Chue and Lalonde, 2014). Stauffer et al tested this idea, but found no significant difference with LY2140023 as an adjunctive treatment for patients with prominent negative symptoms of SZ compared to placebo (Stauffer, Millen, 2013). As a result, the development program of this compound has been terminated. It should be pointed out that a growing number of studies have investigated the efficacy of novel, adjunctive pharmacotherapies for treatment of cognitive deficits in SZ with conflicting results (Choi et al., 2013). The lack of efficacious pharmacological treatments for the negative and cognitive symptoms certainly represents a significant unmet need, especially considering the importance of these symptoms on patient outcomes. Hence, further research to identify and characterize novel pharmacological treatments (such as the potential of mGluR2 agonist and PAM) for negative and cognitive symptoms is greatly needed (Chue and Lalonde, 2014).

Another consideration for the SZ treatment is the evaluation technique. The most widely used methods to assess mGluR2/3 agonists' outcome of SZ treatment is behavioral testing. It is well known that results of behavioral tests can be subjective and variable, and this may partially explain the contradictory results performed by different groups. Given that SZ is such a heterogeneous disease with great varieties in terms of etiology, risk factors, pathological processes, onset time, and disease stages and symptoms, more objective indicators of mGluR2/3 agonists' efficacy in SZ is urgently needed. Responding to this need for objective measures of individual differences in drug responses are pharmacogenetics. These studies aid in discovering the DNA determinants of which influence drug efficacy and tolerability. Given that both type-2 and 3 metabotropic glutamate receptor gene (GRM 2 and 3) single nucleotide polymorphisms (SNPs) have been associated with cognitive performance and prefrontal cortex activity in SZ patients (Bishop, Reilly, 2015, Egan, Straub, 2004, Harrison, Lyon, 2008, Joo, Shibata, 2001, Kordi-Tamandani, Dahmardeh, 2013, Mossner, Schuhmacher, 2008), it would be valuable to use pharmacogenomics to aid in finding the proper treatments for individual patients with different genetic profiles. In fact, a recent study examined the pharmacogenetic relationships between GRM3 and selected variants in relevant dopamine genes with changes in spatial working memory and SZ symptoms after treatment. Interestingly, they found that working memory performance worsened after antipsychotic risperidone treatment. The worsening was associated with GRM3 rs1468412, but the negative symptom improvement was associated with GRM3 rs6465084. In contrast, there were no pharmacogenetic associations between DRD2/ANKK1 and COMT with working memory changes or symptom response to treatment (Bishop,

Reilly, 2015). This study provided direct pharmacogenetic associations of the GRM3 gene with working memory and the clinical response to antipsychotics in first-episode SZ. This information is useful in identifying patients susceptible to adverse cognitive outcomes associated with antipsychotic treatment and suggests that glutamatergic mechanisms contribute to such effects. However, other studies have not provided such a promising outcome in SZ pharmacogenomics. A recent pharmacogenetic analysis of the mGlu2/3 agonist LY2140023 in the treatment of SZ reported that 23 SNPs were associated with a change in PANSS in response to LY2140023 at 28 days in SZ patients, and 16 of these SNPs were located in the serotonin 2A receptor (HTR2A), suggesting a genetic association exists between SNPs in several genes and LY2140023 treatment (Liu et al., 2012). Moreover, in an assessment of SZ endophenotypes, patients of the AA genotype performed poorly in the digit symbol test, a measure of attention. This study provides further evidence for the potential importance of the glutamate receptor GRM3 in SZ, and indicates that the novel antipsychotic LY2140023 may actually be targeting a pathogenic pathway of SZ (Mossner, Schuhmacher, 2008). At this point, therapeutic outcomes of several psychotropic drugs have been weakly linked to specific genetic variants without independent replication (Hamilton, 2015). Additional clinical trials are needed to establish replication of these results.

9. Conclusion and Insights

This review summarizes mGluR2/3 agonists' mechanisms of action, mGluR2 and mGluR3's distinct properties and roles in neuropsychiatry and neuroprotection. It also analyzes the potential and status of targeting mGluR2/3 for SZ treatment.

Despite the progress that has been made, many questions still exist, including the effective and safe window of mGluR2/3 agonists in different developmental periods, the difference between mGluR2/3 agonists and more selective mGluR2 agonists and PAMs, as well as the comparison between mGluR2/3 agonists and other antipsychotic drugs. More specifically, it is unknown whether the opposite effects of mGluR2/3 on pre- and postsynaptic sites could explain the failed action in improving SZ symptoms in clinical trials. Are the effects of mGluR2/3 agonist cell-type (excitatory pyramidal neurons versus inhibitory GABAergic interneurons) and brain region (PFC, hippocampus, ventral tegmental area, and other limbic areas) specific? Are the effects of mGluR2/3 agonist age- and/or SZ stage-dependent? Answering these questions in the future will certainly not only enhance our understanding of the mGluR2/3 effects in brain function but also provide better insights into the development of novel compounds targeting mGluR2/3 for clinical intervention of SZ. Only by solving these mechanistic puzzles can we put mGluR2/3 agonists into clinical trials and provide the optimal therapeutic benefit for individuals afflicted with SZ or other related psychiatric disorders.

In summary, as a potential non-dopaminergic "antipsychotic" drug, pharmacological activation of mGluR2 or mGluR3 still holds promise in alleviating symptoms of SZ. Especially, given the low side effects and high tolerability profile, selective mGluR2 agonist and mGluR2 PAM are still considered promising candidates for pharmacogenomic treatment or as an adjunct to current antipsychotic drugs in the treatment of SZ, particularly

for cognitive and negative symptoms. The failure of current clinical trials should not be interpreted as a default termination of all potential studies on group II mGluRs because as discussed above, the precise manner of the execution of a clinical trial can have profound consequences for the ultimate outcome of the trial. Based on the literature review, we argue that until the mechanisms associated with mGluR2 or mGluR3, individually or jointly as mGluR2/3, are clearly elucidated, it is important to continue the study of mGluR2/3 as a therapeutic target for SZ.

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Abbreviations

3,5-DHPG	3,5-dihydroxyphenylglycine
5-HT	5-hydroxytryptamine or serotonin
AC	adenylate cyclase
ACPD	1-amino-1,3-dicarboxycyclopentane
alpha-MPT	alpha-methyl-DL-p-tyrosine methyl ester
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPH	amphetamine
APDC	dihydroxyphenylglycine
ASST	attentional set-shifting task
ATP	cytosolic adenosine triphosphate
BINA	biphenylindanone A
cAMP	cyclic-adenosine monophosphate
Csk	c-terminal of Src kinase
DA	dopamine
DCG-IV	(2S,1′R,2′ R,3′R)-2-(2,3-dicarboxycyclopropyl) glycine
DIV	days in vitro
DOI	2,5-dimethoxy-4-iodoamphetamine
DRL72	differential reinforcement of a low-rate 72 s
DTI	diffusion tensor imaging
Erk1/2	Extracellular signal-regulated kinase1/2
fEPSP	field excitatory post-synaptic potential
GABA	gama-aminobutyric acid

Gsk-3β	glycogen synthase kinase 3β
HSP	heat shock protein
i.c.v	intracerebroventricular
I.P	intraperitoneal
KO	knock out
LTD	long term depression
LTP	long term potentiation
MAPH	methamphetamine
mGluRs	metabotropic glutamate receptors
MK-801	dizocilpine
NMDA	N-methyl-D-aspartate
NSF	N-ethylmaleimide-sensitive factor
P.O	per os
PAMs	positive allosteric modulators
PCP	phencyclidine
PCPA	DL-p-chlorophenylalanine
PD	parkinson’s disease
PKA	protein kinase A
PKC	protein kinase C
PVT	paraventricular thalamic nucleus
s.c	subcutaneous
SLM	stratum lacunosum moleculare
SNAP	soluble NSF activating protein
SNARE	soluble NSF activating protein receptor
SNP	single nucleotide polymorphism
SZ	schizophrenia
TAP	temporo-ammonic path
VAMP	vesicle-associated membrane protein

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Highlights

- mGluR2/3 as a therapeutic target for schizophrenia
- Working mechanisms of mGluR2/3 agonists in the brain
- Differential role of mGluR2 and mGluR3 in antipsychotic and neuroprotective action
- Studies of mGluR2/3 agonists in animal models of schizophrenia
- mGluR2/3 agonist as adjunct to antipsychotics and promise of pharmacogenomics

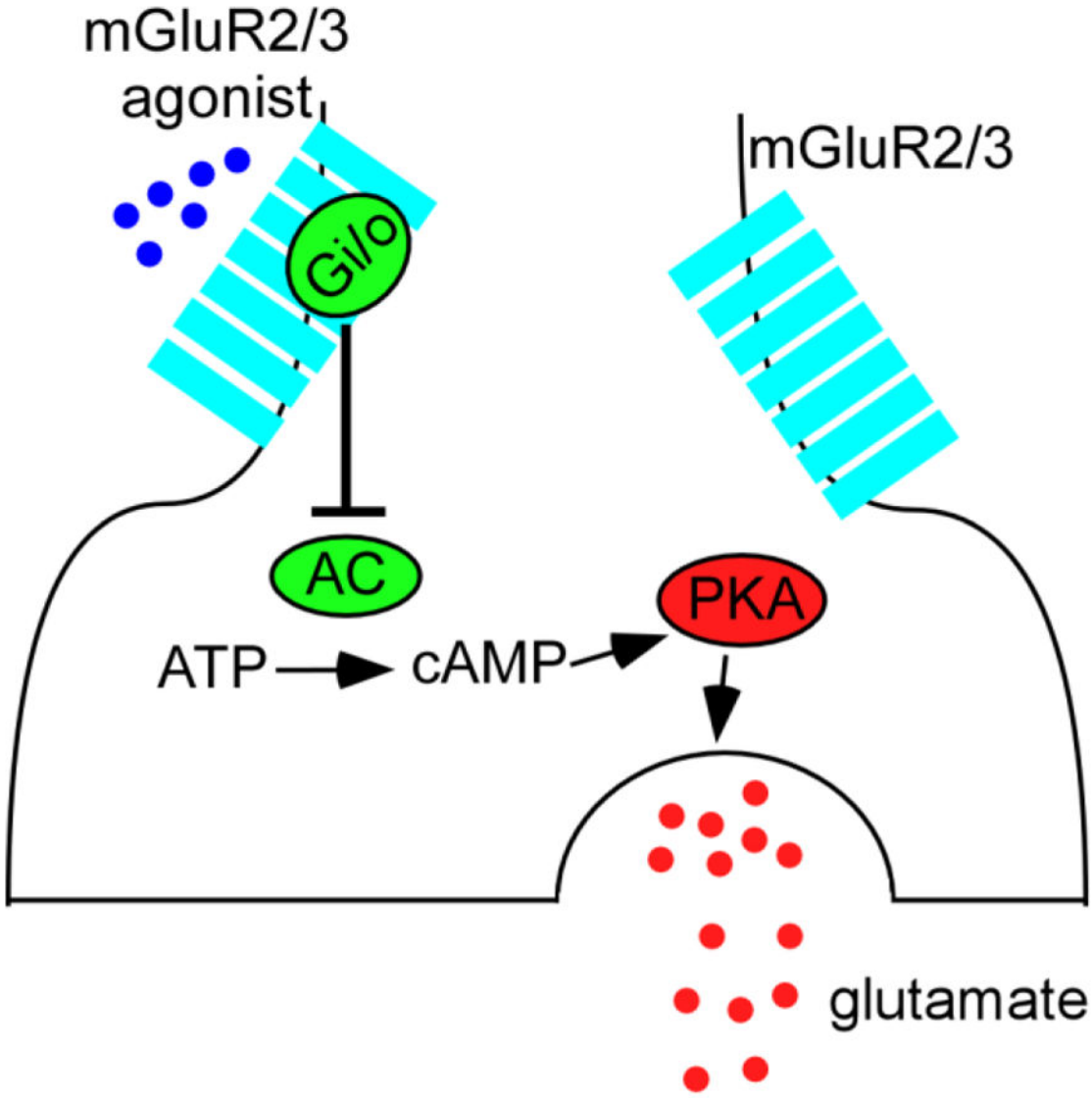

Figure 1.
A schematic summary graph shows that mGluR2/3 agonists reduce glutamate release at presynaptic site by inhibiting AC-cAMP-PKA signaling pathway.

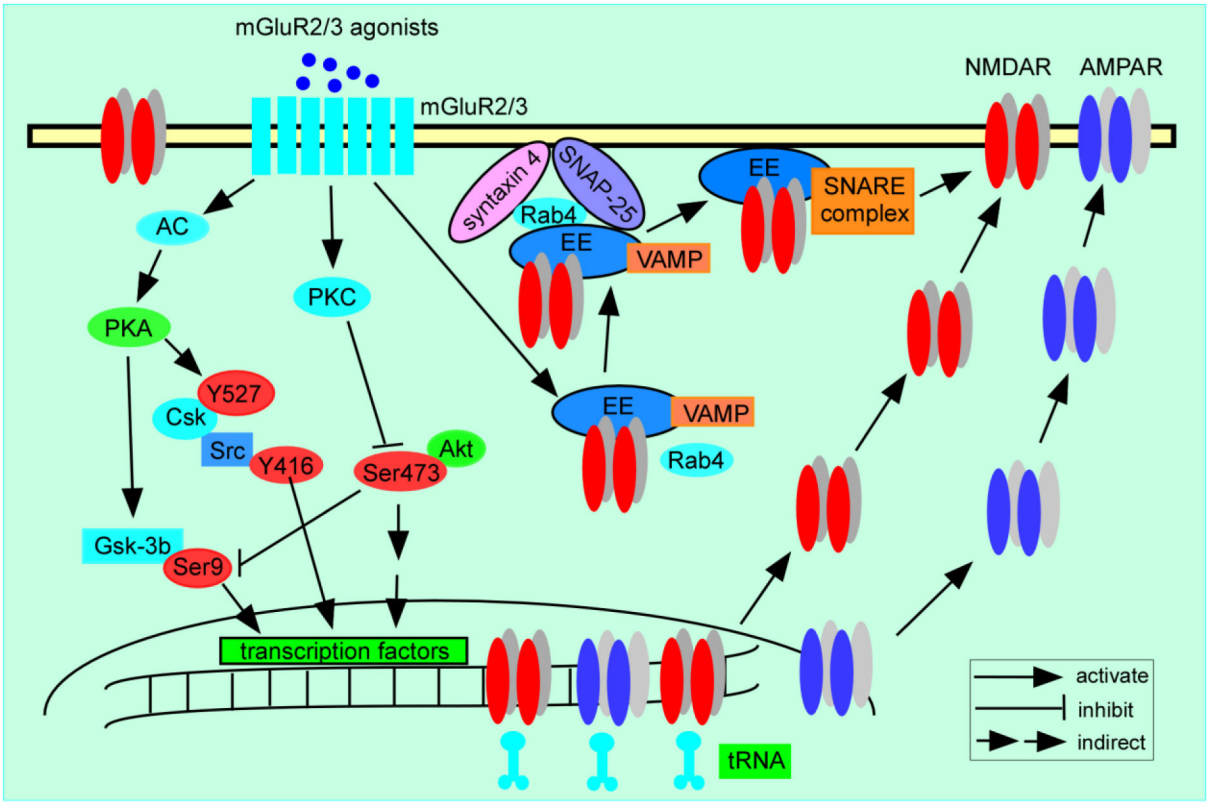

Figure 2.

A schematic summary graph shows the postsynaptic effects of mGluR2/3 agonists on the regulation of both AMPA and NMDA receptors. The mGluR2/3 agonist APDC significantly increases PKC-mediated phosphorylation of NMDA receptors (Tyszkiewicz, Gu, 2004). APDC also increases the interaction between Rab4 and syntaxin 4, which facilitates the formation of soluble SNARE complexes that is composed of SNAP-25, syntaxin 4 and VAMP at postsynaptic sites, leading to the increased exocytosis of NMDARs (Cheng, Liu, 2013). Moreover, activation of mGluR2/3 inhibits the AC-cAMP-PKA pathway and thereby activates Src-mediated upregulation of NMDAR functions (Trepanier, Lei, 2013). In addition, LY379268 increases the surface expression of AMPA receptors through activating ERK1/2 and GSK-3β signaling pathways (Wang, Li, 2013), directly modulates NMDAR expression and function, as well as reverses MK801-induced NMDAR dysfunction via activation of Akt/Gsk-3β pathway (Xi, Li, 2011).

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Table 1

Distinct function of mGluR2 and mGluR3

Model	Pharmacology	Methods	Effects	Reference
Wild type (WT) C57Bl/6J mice and generated mGluR2 and mGluR3 knockout (KO) mice	LY379268 (0.3–10 mg/kg, SC) PCP (1–5 mg/kg, I.P.) AMPH (1–10 mg/kg, I.P.)	Circling, falling, stereotypy, ataxia and locomotor activity	LY379268 reversed PCP- and AMPH- evoked hyperactivity and behavioral alterations in WT and mGluR3 KO mice but not in mice lacking mGluR2	(Woolley, Pemberton, 2008)
mGluR2 and mGluR3 KO mice versus WT mice	LY541850: a selective orthosteric mGlu2 agonist and mGlu3 antagonist DCG-IV: mGluR2/3 agonist	Test the field excitatory post-synaptic potentials (fEPSPs) evoked by stimulation of the temporo-ammonic path (TAP) input to CA1 stratum lacunosum moleculare (SLM); Locomotor activity	fEPSPs were inhibited by LY541850 in mGlu3−/− mice and wild-type littermates, but were not significantly affected in mGlu2−/− mice. Systemic administration of LY541850 to wild-type mice, reduced the increase in locomotor activity following both PCP and AMPH administration	(Hanna et al., 2013)
WT and mGluR 2-deficient mice	LY404039: a potent mGluR2/3 agonist (3–30 mg/kg, I.P.) PCP (7.5 mg/kg, I.P.) AMPH (5 mg/kg, I.P.)	Ambulations, distance traveled, and reduced time spent at rest	The antipsychotic-like effects of LY404039 on PCP- and AMPH-evoked behavioral activation were absent in mGluR2 and mGluR2/3 but not in mGluR3-deficient mice, indicating that the activation of mGluR2, but not mGluR3 is responsible for the antipsychotic-like effects of the mGluR2/3 agonist	(Fell, Svensson, 2008)
mGluR2 KO mice	N/A	Histological changes Paired-pulse facilitation Tetanus-induced LTP and LTD at the mossy fiber-CA3 synapse Water maze learning task	LTD induced by low-frequency stimulation was almost fully abolished in these mGluR2 KO mice. The presynaptic mGluR2 is essential for inducing LTD at the mossy fiber-CA3 synapses	(Yokoi et al., 1996)
WT control mice and mGluR2 KO mice	LY314582: mGluR2/3 agonist (20 mg/kg, i.p.) PCP (2.5 mg/kg, s.c.)i.p.)	Spontaneous and PCP-induced locomotor activity	LY314582 attenuated spontaneous and PCP-induced locomotor activity in wild-type control mice, but inhibited neither spontaneous nor PCP-induced locomotor activity in mGluR2 KO mice	(Spooren et al., 2000)
MK-801 animal schizophrenia model	LY379268: an mGluR2/3 agonist MK-801 BINA: mGluR2 potentiator	Social memory impairment	Both LY379268 and BINA improved social memory impairment induced by MK-801, indicating the stimulation of mGlu2R could be an effective approach for the treatment of certain cognitive dysfunctions	(Hikichi et al., 2013)
mGluR3 KO and WT mice	MK-801	Spontaneous alternation in a T-maze test Y-maze novelty discrimination test Rewarded alternation T-maze test	The mGluR3 KO mice show a working memory defect and an enhanced response to MK-801 in the T- and Y-maze tests, indicating a cognitive disturbance and left-right asymmetry in certain behavioral responses of mGluR3-KO mice	(Lainiola et al., 2014)
mGluR3 KO mice and WT mice	Methamphetamine (MAPH)	Comprehensive behavioral analyses LTP in the CA1 region in the hippocampus In vivo microdialysis measurements of extracellular dopamine	The mGluR3 KO mice showed hyperactivity in the open field, impaired reference memory for stressful events in the Porsolt forced swim test, impaired contextual memory in cued and contextual fear conditioning test, and impaired working memory in the T-Maze forced alternation task test. No difference in LTP but enhancement in the methamphetamine-induced release of dopamine in the KO mice	(Fujioka et al., 2014)

Model	Pharmacology	Methods	Effects	Reference
Cultures from WT, and mGluR2 KO and mGluR3 KO mice	LY379268	NMDA induction of excitotoxic neuronal death	LY379268 was equally neuroprotective in neuron cultures from WT, mGluR2 KO, mGluR3 KO mice, but was abolished in cultured mGluR3 KO astrocytes	(Corti, Battaglia, 2007)
Cultures containing both neurons and astrocytes from P14–16 mice	NAAG	Brief exposure to NMDA (10 min) Phase-contrast microscopy to assess neuronal injury	The medium collected from cultured astrocytes 2 to 20 hours after a brief exposure to mGlu3 receptor agonists is highly neuroprotective against NMDA toxicity	(Bruno, Sureda, 1997)
Cultures containing both neurons and astrocytes from P14–16 mice	DCG-IV	NMDA pulse Phase-contrast microscopy to assess neuronal injury	mGluR3 in astrocytes leads to an increased formation and release of TGFβ, which produced the neuroprotective function	(Bruno, Battaglia, 1998)

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Table 2

In vivo effects of mGluR2/3 agonists on animal models and human subjects

Model	Animals/Patients	Pharmacology	Effects	Reference
In animal models				
Phencyclidine (PCP)- and amphetamine (AMPH)-induced schizophrenia (SZ) model	Male C57B1/6J mice P70–P90	LY379268 (0.3–10 mg/kg S.C.) PCP (1–5 mg/kg, I.P.) AMPH (1–10 mg/kg, I.P.)	LY379268 was able to reverse PCP- and AMPH-evoked hyperactivity and PCP- induced behavioral alterations	(Woolley, Pemberton, 2008)
PCP- and AMPH-induced SZ model	Male Sprague-Dawley rats P70–P90 (250–300 g)	LY354740 (1–10 mg/kg, s.c.) LY379268 (0.3–3 mg/kg, s.c.) PCP (5 mg/kg, s.c.) AMPH (3 mg/kg, s.c.)	LY354740 (1–10 mg/kg s.c.) and LY379268 (0.3–3 mg/kg s.c.) reversed the increases in ambulations, fine motor (nonambulatory) movements, and decreased time at rest evoked by PCP- but had minimal effects on AMPH-evoked motor activities	(Cartmell, Monn, 1999)
AMPH-induced SZ model	Male Sprague-Dawley rats (250–300 g)	LY379268 (1 mg/kg, s.c.)	LY379268 attenuated AMPH-induced ambulations and rearing, but did not alter AMPH-evoked fine motor movements	(Cartmell, Monn, 2000b)
PCP-induced SZ model	Male Sprague-Dawley rats (250–300 g)	LY379268 (1 mg/kg, s.c.)	LY379268 reduced PCP-induced falls and turns, completely abolished backpedaling, but didn't affect PCP-evoked forepaw treading	(Cartmell, Monn, 2000a)
PCP- and AMPH-induced SZ-like model	Male C57BL6/J mice 2- to 5- month	LY379268 (0.3, 1, and 3 mg/kg i.p.) AMPH (3.2 mg/kg s.c.) PCP (5.6 mg/kg s.c.)	LY379268 resulted in a significant reduction in PCP- and AMPH-induced hyperlocomotor activity but did not alter spontaneous locomotor activity. Chronic LY379268 treatment failed to block PCP- and AMPH- induced hyperlocomotor activity	(Galici, Echemendia, 2005)
PCP-induced psychotic conditions	Male Sprague-Dawley rats 200g for all experiments except 280 g for PPI experiments	LY354740 (1–10 mg/kg, I.P.) PCP (2mg/kg subcutaneous)	LY354740 induced anxiolytic-like effects at doses of 3 and 10 mg/kg but not 1 mg/kg. A dose of 10 mg/kg LY354740 attenuated PCP-induced locomotor activity. All doses of LY354740 had no effects on PPI and PCP-induced working memory deficits and amnesia	(Schlumberger, Schafer, 2009)
PCP- and D-AMPH- induced SZ-like model	C56BL/6 and DBA/2 mice (6–8 weeks)	LY354740 (1–10 mg/kg, I.P.) PCP (6 mg/kg, I.P.) AMPH (6 mg/kg for C57BL mice and 10 mg/kg for DBA2 mice, I.P.)	LY354740 (5 and 10 mg/kg) moderated the effects of PCP on prepulse inhibition of acoustic startle in DBA/2 but not C57BL/6 mice. This suggested effects of mGluR2/3 agonists are strain-specific	(Profaci, Krolikowski, 2011)
PCP-induced psychotic activity (impaired discrimination)	Juvenile male Wistar rats (3 weeks old)	LY354740 (1–10 mg/kg, I.P.) PCP (10 mg/kg, s.c.)	Acute pretreatment with LY-354740 (1–10 mg/kg) facilitated social discrimination impaired with PCP administration, but had no effects in total time spent in social interaction	(Harich, Gross, 2007)
PCP- and MK- 801-induced NMDA hypofunction model	Dopamine-deficiency mice and control mice (2–3 weeks)	LY379268 (10 mg/kg, I.P.) PCP (5 mg/kg, I.P.) MK-801 (0.75 mg/kg, I.P.)	LY37 effectively blocked PCP- and MK-801-induced hyperlocomotion activity in both DD mice and control mice	(Chartoff, Heusner, 2005)

Model	Animals/Patients	Pharmacology	Effects	Reference
PCP-induced SZ models	Male Sprague-Dawley rats (250–350 g)	LY354740 (10, 30, 100 mg/kg, s.c.) LY544344 (10, 30, 100 mg/kg, P.O.)	LY544344 and LY 354740 of 30 or 100 mg/kg dose-dependently inhibited PCP-induced hyperlocomotor activity, whereas LY354740 did not significantly reverse PCP-mediated behaviors at doses up to 100 mg/kg	(Rorick-Kehn, Perkins, 2006)
MK-801-induced SZ model	Female Sprague-Dawley rats (250–278g)	LY379268 (0.3 or 3.0 mg/kg, I.P.)	LY379268 significantly reduced MK-801-induced total activity and enhanced NMDAR functions postsynaptically	(Xi, Li, 2011)
Ketamine-evoked SZ models	Adult male Wistar rats (200–250g)	LY379268 (1–3 mg/kg, I.P.) Ketamine (4–12 mg/kg, I.P.)	LY379268 reduced ketamine-evoked hyperlocomotion but could not restore ketamine-evoked PPI deficit that is due to ketamine-induced changes in monoamine transmission. A low dose of LY37 (1 mg/kg) produced anxiolytic effects, while a higher dose (3 mg/kg) appeared to be anxiogenic	(Imre, Salomons, 2006)
Ketamine-evoked SZ models	Male Sprague-Dawley rats (300–350 g)	LY379268 systemic (3 mg/kg, s.c.) or local (1 mM, in the probe) Ketamine (18 mg/kg, s.c., 1 mM in the probe)	Both systemic and local treatment of LY379268 blocked ketamine-evoked glutamate, but not DA release. Local ketamine increased DA release, but not glutamate release in the mPFC. Ketamine acted outside of the mPFC to enhance glutamate, but within the mPFC to enhance DA release	(Lorrain et al., 2003a)
Ketamine-induced SZ models	Male Sprague-Dawley rats (250–300 g)	LY379268 (0.3–10 mg/kg, I.P.) Ketamine (25 mg/kg, I.P.)	LY379268 dose-dependently inhibited ketamine-evoked NE release in the ventral hippocampus and reduced ketamine-induced hyperactivity	(Lorrain, Schaffhauser, 2003b)
PCP-induced SZ model	Male Sprague-Dawley rats (250–300 g)	LY379268 (3.0 mg/kg s.c.) PCP (10 mg/kg, I.P.) α-MPT (400 mg/kg, I.P.) PCPA (300 mg/kg, I.P.)	LY379268 blocked PCP-evoked ambulatory activity and fine movements in control, alpha-MPT-, and PCPA-treated animals, suggesting LY37 was effective in regulating catecholamine and serotonin-depleted animal models	(Swanson and Schoepp, 2002)
PCP- and LSD- induced SZ models	Male Fischer rats (6 weeks)	LY379268 (0.3–10 mg/kg, I.P.) PCP (3.0 mg/kg, I.P.) LSD (0.1 mg/kg, I.P.)	LY379268 significantly diminished PCP training dose and stimulus control by LSD	(Winter et al., 2004)
DOI-induced SZ models	Male Albino-Swiss mice (24–26 g)	LY354740 (0.025–1 mg/kg, I.P.) LY379268 (0.125–2.5 mg/kg, I.P.) DOI (2.5 mg/kg, I.P.)	LY354740 and LY379268 inhibited DOI-induced head twitches in mice in a dose-dependent manner. LY379268 suppressed an increase in the frequency of sEPSP induced by bath-applied DOI in the mPFC	(Klodzinska et al., 2002)
In human subjects				
N/A	19 healthy human subjects with ketamine infusion as a cognitive impairment model	LY354740, placebo (100 mg, 400 mg, p.o.) ketamine (bolus of 0.26 mg/kg over 1 min, infusion of 0.65 mg/kg per hour for 100 min)	LY354740 did not have a significant effect on working memory on the placebo, but produced a significant dose-related improvement in working memory during ketamine infusion	(Krystal, Abi-Saab, 2005)
N/A	SZ patients	LY2140023 Olanzapine as active control placebo	Treatment with LY2140023, like treatment with olanzapine showed statistically significant	(Patil, Zhang, 2007)

Model	Animals/Patients	Pharmacology	Effects	Reference
			improvements in both positive and negative symptoms in SZ patients compared to placebo	
improvements in both positive and negative symptoms in SZ patients compared to placebo				
N/A	1013 adult patients (ages 18–65) with SZ who had experienced an exacerbation of symptoms within 2 weeks prior to study	placebo, LY2140023 40 mg twice daily (BID), LY2140023 80 mg BID	Neither LY2140023 dose showed significant improvement compared to placebo on the PANSS total in either population	(Downing, Kinon, 2014)
N/A	678 SZ patients	LY2140023 aripiprazole	Change in PANSS total scores for aripiprazole was significantly greater than for LY21400231	(Adams, Zhang, 2014)
N/A	261 SZ patients with prominent negative symptom evidence of functional impairment	LY2140023 (40 mg twice daily) standard of care (SOC: olanzapine, risperidone, or aripiprazole)	Improvement in PANSS total score over the initial 6 to 8 weeks of treatment was similar between groups, but improvement was significantly greater in the SOC group at 24-week endpoint; LY2140023 and SOC groups had comparable negative symptom improvement in 24-week endpoint	(Adams, Kinon, 2013)
N/A	352 SZ patients who were receiving standard of care (SOC) therapy	LY2140023 (20mg twice daily) Continued SOC	This study found no benefit of adjunctive LY2140023 versus SOC for negative symptoms in patients with SZ receiving treatment with SOC before	(Stauffer, Millen, 2013)