Review

Metabotropic glutamate receptor 5 in the pathology and treatment of schizophrenia

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Abstract

Metabotropic glutamate receptor 5 (mGluR5) potentiates the NMDA receptor (NMDAR) in brain regions implicated in schizophrenia, making it a viable therapeutic target for the treatment of this disorder. mGluR5 positive allosteric modulators may represent a valuable novel strategy for schizophrenia treat- ment, given the favourable profile of effects in preclinical paradigms. However it remains unclear whether mGluR5 also plays a causal or epiphenomenal role in NMDAR dysfunction in schizophrenia. Animal and cellular data suggest involvement of mGluR5, whilst post-mortem human studies remain inconclusive. This review will explore the molecular, animal and human data to support and refute the involvement of mGluR5 in the pathology of schizophrenia. Furthermore, this review will discuss the potential of mGluR5 modulators in the therapy of schizophrenia as well as aspects of mGluR5 that require further characterisation.

1. Introduction

Schizophrenia is a neuropsychiatric disorder distinguished by a set of symptoms that typically emerge in early adulthood. Schizophrenia is characterised by hallucinations and delusions (positive symptoms), deficits in learning and memory (cognitive symptoms), depression and social isolation (negative symptoms), among many more (Lewis and Lieberman, 2000). Although the exact cause of schizophrenia is undetermined, studies suggest the disease is neurodevelopmental (for review see Arnold et al., 2004; Marenco and Weinberger, 2000; McGrath et al., 2003), with both genetic and environmental factors triggering a 'domino effect' by which cellular and neurotransmitter systems within the brain are compromised (Lang et al., 2007).

An imbalance in dopaminergic neurotransmission has been well documented in schizophrenia (Toda and Abi-Dargham, 2007). Accumulated evidence includes the ability of dopamine-reuptake inhibitors to induce hallucinations and delusions homologous to the positive symptoms of schizophrenia (Matthysse, 1974), in addition to the capability of dopamine D_2 receptor antagonists to successfully ameliorate some psychotic symptoms such as hallucinations and delusions (Andersson et al., 1998). However, dysfunction of the dopaminergic system does not account for the more discreet and debilitating symptoms seen in the disease, which have been attributed to disruptions in glutamatergic circuitry (Tsai and Coyle, 2002).

Glutamate has been linked to a myriad of processes surrounding cognition, memory and perception (Robbins and Murphy, 2006). Converging lines of evidence suggest dysfunction of the glutamatergic receptors is key to the aetiology of schizophrenia (Steele et al., 2012). Glutamate is an excitatory neurotransmitter present at the majority of synapses in the brain (Tsai and Coyle, 2002), and it is vital to neurodevelopment as well as synapse organisation and sensorimotor gating in adults (Arnold et al., 2004). Glutamate exerts effects through ionotropic and

metabotropic receptors. Ionotropic glutamate receptors, which include N-methyl-d-aspartate receptors (NMDAR), alpha-amino-3- hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPAR) and kainate receptors (Goff and Wine, 1997), are ligand-gated ion channels. Metabotropic glutamate receptors (mGluR) are G- protein-coupled receptors. Eight mGluRs (mGluR1-8) have been discovered and cloned thus far, and are grouped into three categories: Group 1 (mGluR1 and 5), Group 2 (mGluR2 and 3) and Group 3 (mGluR4, 6, 7 and 8) according to sequence homology, pharmacological properties and downstream activations (Niswender and Conn, 2010).

The glutamatergic hypothesis is a powerful explanatory model of schizophrenia. Of the proposed glutamatergic models, the NMDAR hypofunction model posits that dysregulation of glutamate is caused by reduced NMDAR function on GABAergic neurons in subcortical regions, leading to disinhibition of cortical glutamatergic efferents and a hyperglutamatergic state (Marek et al., 2010). This results in functional deficits in GABAergic interneurons, particularly parvalbumin-containing interneurons (Homayoun and Moghaddam, 2007; Nakazawa et al., 2012). This hypothesis is supported by the action of NMDAR antagonists, which are recognised precipitators of positive, negative and cognitive schizophrenia-like symptoms in humans and animals (Chartoff et al., 2005; Olney et al., 1999). These drugs also exacerbate symptoms of schizophrenia subjects (Javitt and Zukin, 1991), and adjunct treatment of schizophrenia subjects with glycine, a co-activator of NMDAR, improves aspects of schizophrenia symptomatology in some patients (Tsai and Coyle, 2002). This highlights dysfunction of glutamatergic signalling in schizophrenia.

2. Metabotropic glutamate receptor 5

Although the NMDAR is widely implicated in glutamatergic dysfunction associated with schizophrenia, it is unlikely that it is the solitary aetiological factor. Still, evidence suggests that many schizophrenia risk factors converge on the NMDAR rendering it of primary concern (Kantrowitz and Javitt, 2010). As excitatory glutamatergic neurotransmission is also modulated by mGluRs, it is possible that dysfunction within this aspect of glutamatergic circuitry may exist. In particular, Groups 1 and 2 mGluRs are currently under scrutiny in relation to schizophrenia. However, unique inter- connections between the NMDAR and mGluR5 cause this glutamate receptor subtype to be of special interest.

Within the central nervous system, mGluR5 is expressed in the cerebral cortex, hippocampus, nucleus accumbens, lateral septum, striatum, hypothalamus and some regions of the amygdala, as well as on non-neuronal cells such as astrocytes, oligodendrocytes, microglia and stemprogenitor cells (Balázs et al., 1997; Melchiorri et al., 2007; Pietraszek et al., 2005; Tasker et al., 1998; Van Den Pol et al., 1995). mGluR5 is most abundantly expressed post-synaptically on pyramidal cells and interneurons of the cortex (Marek et al., 2010; Niswender and Conn, 2010; Nyilas et al., 2009). Some evidence suggests presynaptic expression of mGluR5 may also exist (Romano et al., 1995).

mGluRs are complex in signalling and structure, though studies spanning over 25 years have elucidated numerous details regarding their pathways, effectors and interactions. Positive coupling of Group 1 mGluRs to G_q/G_{11} initiates stimulation of phospholipase C (PLC) and production of inositol 1,4,5-triphosphate (IP_3) as well as downstream activation of protein kinase C (PKC), cyclic adenosine monophosphate response element-binding (CREB) and brain-derived neurotrophic factor (BDNF) (Fig. 1). Signalling in Group 1 mGluRs is unlike mGluR Groups 2 and 3, which couple to $G_{i/o}$ and affiliated downstream pathways (Vinson and Conn, 2012).

mGluR5 is anchored to the cell membrane by a 7- transmembrane (7TM) domain that contains

the binding site of most allosteric modulators and is responsible for activation of the connecting G-protein and subsequent effectors (Francesconi and Duvoisin, 1998). Joining the 7TM and N-terminal is a highly conserved cysteine rich domain (CRD) (Rondard et al., 2006). mGluR5a/b, the most common splice variants, also possess long C-termini, which allow their interaction with scaffolding proteins (Tu et al., 1999).

Additional mechanisms that modulate mGluR5 have recently emerged. Evidence exists that mGluR5 is desensitised by G protein- coupled receptor kinase 2 and 3 (GRK2 and GRK3), kinases which regulate the desensitisation of G protein-coupled receptors including those of mGluR5 (Sorensen and Conn, 2003). G_q/G_{11} phosphorylation is mediated by the huntingtin-binding protein, optineurin (Anborgh et al., 2005). Also, Norbin (neurochondrin) (Wang et al., 2009), Tamalin (GRP-1-associated scaffold protein) (Kitano et al., 2002) and calmodulin (Lee et al., 2008) have been shown to bind directly to the C-terminus of mGluR5 to modulate surface expression and trafficking. These proteins ultimately modulate mGluR5 desensitisation, endocytosis and recycling.

mGluR5 contains three possible splice variants. mGluR5a is highly expressed in the postnatal rat brain and therefore thought to be involved in early development (Minakami et al., 1995). mGluR5b differs to mGluR5a as it contains an additional 32 amino- acid segment in the cystoplasmic tail of the 7TM domain and is more abundant in the adult brain (Romano et al., 1996). A lesser- known subtype is mGluR5d, present in the human cerebellum and hippocampus, this splice-variant has a shorter C-terminus and therefore possibly less interactions with scaffolding proteins and intracellular proteins than mGluR5a and mGluR5b (Malherbe et al., 2002).

2.1. Implication of the mGluR5/NMDAR complex in schizophrenia

mGluR5 is hypothesised to be implicated in schizophrenia due to overwhelming evidence of its association with the NMDAR (Marino and Conn, 2002). The anchoring proteins Homer, SH_3 and multiple ankyrin repeat domains (SHANK), guanylate-kinase-associated (GKAP, also known as SAPAP) and post-synaptic density 95 (PSD- 95) form a physical link between NMDAR and mGluR5 (Tu et al., 1999) (Fig. 1). mGluR5a/b interact with Homer via the long C- terminus. There is increasing evidence that the Homer1a isoform is critical to mGluR5 activation and the triggering of its downstream effectors, thereby affecting NMDAR function (Kammermeier and Worley, 2007; Ronesi and Huber, 2008). Recently, the multi- scaffolding protein Preso1 has been shown to modulate the activity of this link (Hu et al., 2012).

NMDAR and mGluR5 are co-localised in many parts of the brain including the hippocampus, striatum and the neocortex (Alagarsamy et al., 2002; Henry et al., 2002; Luccini et al., 2007), all of which are highly implicated in schizophrenia. A large body of evidence has shown mGluR5 activation to potentiate NMDAR currents (Attucci et al., 2001; Awad et al., 2000; Doherty et al., 1997; Benquet et al., 2002; Mannaioni et al., 2001; Pisani et al., 2001; Ugolini et al., 1999). This occurs through downstream stimulation of PKC, acti- vating a divergent sequence involving stimulation of cell adhesion kinase ß/proline-rich tyrosine kinase (CAKß/Pyk2) and subsequent phosphorylation of the Src protein (Fig. 1). In turn, Src directly potentiates the NMDAR (Groveman et al., 2012; Huang et al., 2001; Lu et al., 1999). A reciprocal relationship is evident, with the NMDAR able to modulate mGluR5 function. Calcium ions entering through the NMDAR activate protein phosphatase 2B/calcineurin (PP2B/CaN), which directly dephosphorylates mGluR5 (Alagarsamy et al., 2005) (Fig. 1). This modulation may be dose-dependent, as low concentrations of NMDA, the NMDAR agonist, increase mGluR5 function, whilst high concentrations of NMDA inhibit NMDAR activation of mGluR5 (Alagarsamy et al.,

2002).

In addition to the physiological link between the NMDAR/mGluR5 complex, the physical link between these receptors may have functional implications for associated signalling pathways. Homer proteins have been shown to modulate mGluR5 trafficking (Ango et al., 2002), and there is increasing evidence that mGluR5-mediated modulation of the NMDAR may be affected by alterations of PSD scaffolding proteins (Thomas, 2002). Alterations in these processes could result in uncoupling of the NMDAR/mGluR5 complex in the pathological state. It is unclear whether alterations in PSD scaffolding proteins are causal or epiphenomal in the pathology of schizophrenia. Nonetheless, these studies indicate that mGluR5-mediated signalling may be impaired in schizophrenia.

A more intricate relationship with mGluR5 and NMDAR has also been exposed. Matta et al. (2011) recently found evidence that mGluR5 stimulates the developmental NMDAR NR2 subunit switch within the hippocampus and visual cortex. Using mGluR5 knock out (KO) mice, this study demonstrated that NMDAR and mGluR5 drive the NR2B to NR2A subunit switch via the downstream signalling cascade of these receptors illustrated in Fig. 1. Furthermore, this switch is deficient in mGluR5 KO mice. This is significant as NR2A and NR2B subunits have differing localisations and activate differing survival pathways (Hardingham et al., 2002). Of particular importance, NR2A containing receptors play a critical role in the development and maturation of GABAergic circuits, particularly parvalbumin-containing interneurons (Kinney et al., 2006; Zhang and Sun, 2010), which are deficient in schizophrenia. Therefore, an imbalance of NR2A and NR2B subunits is implicated in schizophrenia (Geddes et al., 2011). Furthering evidence of the relationship between NMDARs and mGluR5, this suggests that mGluR5 could be involved in pathological changes of NMDAR subunit composition and the developmental aetiology of disorders such as schizophrenia. Nevertheless, future studies are required to determine the extent of these findings and the presence of this mGluR5-mediated subunit switch in other brain regions involved in schizophrenia symptomatology. Consolidation of this evidence with the molecular findings listed above insinuates a fundamental role of mGluR5 in the development of schizophrenia.

2.2. Is mGluR5 involved in the pathology of schizophrenia? Evidence from rodent studies

Investigations of mGluR5 KO mice support involvement of mGluR5 in the aetiology of schizophrenia. Genetic deletion of mGluR5 triggers behaviours that are analogous to behavioural manifestations induced by glutamate hypofunction models as well as observed schizophrenia phenotypes, such as decreased sensorimotor gating, decreased short-term spatial memory and sensitivity to locomotor deficits induced by NMDAR antagonists (Brody et al., 2004; Chiamulera et al., 2001; Gray et al., 2009; Lu et al., 1997). It is likely that genetic abolition of mGluR5 impedes normal NMDAR development, producing the reported behavioural alterations.

In line with what has been observed in the mGluR5 KO studies, adult rats treated with mGluR5 selective negative allosteric modulators, MPEP (2-methyl-6-(phenylethynyl)-pyridine) or MTEP (3- [(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine), displayed social interaction deficits, impaired working memory, reduced instrumental learning, as well as intensification of the detrimental effects induced by NMDAR antagonists (Campbell et al., 2004; Henry et al., 2002; Homayoun et al., 2004; Pietraszek et al., 2005; Vales et al., 2010; Vollenweider et al., 1998; Zou et al., 2007). Homayoun and Moghaddam (2007) further observed cortical neurons in the prefrontal cortex (PFC) of awake rats, where MPEP decreased spontaneous burst activity of these neurons and augmented the effects of the non-competitive NMDAR antagonist, MK-801, on spontaneous neuron activity. Additionally, mGluR5 is altered on a molecular level in response to NMDAR

antagonist treatment, as a study in adult rats detected a decrease in mGluR5 mRNA expression in subcortical regions and the hippocampal formation 1 h following an injection of the NMDAR antagonist phencyclidine (PCP) (Abe et al., 2001). Homer 1a has also been reported to be altered following NMDAR antagonist treatment (Cochran et al., 2002; Iasevoli et al., 2007), which may indicate a possible alteration in the coupling between NMDAR and mGluR5 in this model. It is unknown whether this coupling is altered during key developmental periods of relevance to schizophrenia, such as adolescence, which may have implications for mGluR5-targeted therapeutics.

Under certain conditions, mGluR5 blockade by MPEP administration has also been shown to interfere with sensorimotor gating, a process that is diminished in schizophrenia sufferers (Henry et al., 2002; Zou et al., 2007). mGluR5 was demonstrated to modulate conditioning of the sensorimotor gating process, with Zou et al. (2007) demonstrating that MPEP blocked the enhancing effect of fear conditioning on prepulse inhibition (PPI). Furthermore, MPEP has been shown to potentiate the PCP-induced deficits in PPI (Henry et al., 2002). Interestingly, MPEP alone induced no effect on PPI (Henry et al., 2002; Zou et al., 2007). It is unclear then, why mGluR5 and Norbin knockout mice display deficits in PPI (Gray et al., 2009; Wang et al., 2009). Although these studies indicate that mGluR5 may play a critical role in the filtering of extraneous information in normal sensory processing, this may be mediated through the NMDAR as PPI deficits can be induced by NMDAR blockade (Bakshi and Geyer, 1995; Bakshi et al., 1999; Corbett et al., 1995; Wiseman Harris et al., 2003).

Another collection of studies in rodents suggests mGluR5 is crucial for proper learning and memory, which are processes disrupted in many schizophrenia patients. Long-term depression (LTD) and long-term potentiation (LTP) are two opposing forms of synaptic plasticity, which when imbalanced, can cause cognitive deficits. Disruptions to mGluR5-related signalling (such as mGluR5 KO and application of mGluR5 antagonists) has been shown to cause impaired LTP and LTD, hence suggesting mGluR5 plays a critical role in cognition. These studies have previously been reviewed extensively (Vinson and Conn, 2012).

2.3. Is mGluR5 involved in the pathology of schizophrenia? Evidence from human studies

Genetics studies have implicated mGluR5 and its effectors in the pathophysiology of schizophrenia. One study reported an increase in allele frequency distribution of the microsatellite G64931 present in the mGluR5 gene, GRM5, in schizophrenia subjects in a large case–control Scottish population (Devon et al., 2001). Whilst this has been the only genetic evidence directly implicating mGluR5 in schizophrenia aetiology, other genes that indirectly effect mGluR5 should be noted. For example, several studies have reported that RGS4 is a susceptibility gene in schizophrenia (Large, 2007; Shao et al., 2010; Tarazi et al., 1996), a gene that negatively modulates G_q protein-mediated signalling, including that of mGluR5. Additionally, the genes encoding for postsynaptic scaffolding proteins Homer, SHANK, GKAP and PSD95 have been shown to be of importance in some populations (Ting et al., 2012). Collectively, these studies provide support for the possibility of genetic mutations affecting mGluR5 signalling in schizophrenia.

Whilst the cellular, animal and genetic studies presented implicate mGluR5 and/or its effectors in the development and pathology of schizophrenia, little alteration has been reported directly within the post-mortem schizophrenia brain (Table 1). Several of these investigations have observed mGluR5 using mRNA and protein studies. mGluR5 mRNA levels were found to be unaltered in the thalamus, hippocampus, PFC and striatum of patients with schizophrenia (Gupta et al., 2005; Ohnuma et al., 2000; Richardson- Burns et al., 2000; Volk et al., 2010). A similar study by

Ohnuma et al. (1998) reported that mGluR5 mRNA expression in the PFC, specifically Brodmann's Area (BA) 11, was significantly increased only in layer 3 of the cortex. Also, glutamate transporter expression was significantly decreased, pointing towards less functional glutamate and decreased glutamate transmission.

Limited studies have examined mGluR5 protein in various cortical and subcortical brain regions of schizophrenia patients and no changes were found (Corti et al., 2011; Gupta et al., 2005) (Table 1). In accordance, we have recently found no change in mGluR5 protein or binding in the dorsolateral prefrontal cortex (DLPFC) of schizophrenia subjects, although alterations may be sub- diagnosis dependent (Matosin et al., unpublished observations).

We found preliminary evidence of a sub-diagnostic decrease in mGluR5, specifically in schizoaffective subjects of depressive subtype. In line with these results, patients with major depression have been reported to have reduced mGluR5 (Deschwanden et al., 2011). Whilst we are cautious with our findings due to insufficient power (n = 4), these findings highlight the differing underlying bio- chemistries in the subtypes of schizophrenia. Further studies are required to determine if there is a diagnostic-specific alteration in mGluR5, as this has implications for novel drugs that target this receptor.

The role of mGluR5 in the pathology of schizophrenia remains unclear. Indirect evidence from animal manipulation studies (i.e. mGluR5 KO and mGluR5 antagonism) suggests involvement of mGluR5, however this may be due to indirect effects of the model on the NMDAR, such as through the anchoring PSD proteins. Conversely, data from post-mortem human studies suggest that mGluR5 is not altered in schizophrenia. These negative findings may be explained by alteration of mGluR5 function, rather than expression. For example, both Homer 1 gene (Spellmann et al., 2011) and protein (Engmann et al., 2011) may be altered in schizophrenia. As Homer1 is critical for mGluR5/NMDAR coupling (Iasevoli et al., 2007; Thomas, 2002) mGluR5 function may be altered, despite that mGluR5 mRNA and protein appear unaltered in schizophrenia. Nonetheless, the functional relationship between mGluR5 and NMDAR may provide a therapeutic mechanism to indirectly modulate NMDAR activity. In this case, unaltered levels of mGluR5 in schizophrenia are beneficial, as this would mean an unhindered therapeutic target. It is unknown whether NMDAR/mGluR5 coupling is altered in schizophrenia; however, intrinsic factors such as age of disease onset, the stage of disease progression or schizophrenia risk factors (such as cannabis, stress, and pubertal hormones) may affect this complex. This may have direct influences on the efficiency of mGluR5-targeted therapeutics.

3. The effect of current antipsychotic drugs on mGluR5

Antipsychotic drugs (APDs) are currently the primary form of treatment for schizophrenia patients. Whilst both first, second and third generation APDs competitively antagonise dopamine D_2 receptors, second and third generation antipsychotics have a much more complex mode of action with various affinities for dopaminergic, serotonergic, muscarinic, adrenergic and histamatergic receptors (Coward, 1992; Seeman, 2002). Despite being widely efficacious for positive schizophrenia symptoms, APDs dis- play minimal benefits for negative and cognitive symptom profiles for many patients (Heresco-Levy, 2003). In addition, APDs cause a large array of adverse effects, including obesity, metabolic syndrome, sedation and motor dysfunction among more (Kane, 2011).

There are limited studies investigating the involvement of mGluR5 in the mechanisms of current antipsychotics. Chronic administration of clozapine in mGluR5 KO mice was shown to reverse sensorimotor gating deficits and ameliorate hyperactivity, although it did not improve memory

deficits (Gray et al., 2009). This suggests that clozapine may exert indirect effects on mGluR5 signalling and therefore may have consequences for the co-administration of mGluR5-targeted therapeutics with current therapeutics.

We have recently shown that acute, subchronic and chronic treatments with typical (haloperidol) and atypical (olanzapine) antipsychotics do not influence mGluR5 binding density in the rat PFC, hippocampus or striatum (Matosin et al., unpublished observations). Another study however has shown that mGluR5 mRNA expression is increased by typical (haloperidol) and atypical (sertinadole) APD treatment (Iasevoli et al., 2010). Despite the discrepancy, it must be noted that mRNA levels do not denote corresponding changes in protein expression (Greenbaum et al., 2003). In addition, treatments with haloperidol and atypical antipsychotics quetiapine and clozapine, but not sertindole, have been shown to increase Homer1a expression, although this may be brain region dependent (Polese et al., 2002). As antipsychotic drugs have also been shown to affect Homer1a gene expression, this may be a critical link in the APD-induced effects on mGluR5.

It remains unclear whether mGluR5 is affected by current APDs, however, another study suggests that interactions do occur between mGluR5 and D_2 receptors, a major target of most APDs. mGluR5 protein expression was reported to be decreased in the PFC following chronic adolescent treatment with the potent dopamine agonist, apomorphine (Shao et al., 2010). This mechanism of action may be attributable to "receptor mosaics", a term coined by the Agnati/Fuxe group, whereby receptors may be coupled physically resulting in diverging and more complex signalling pathways (Fuxe et al., 2008). This group reported that D_2 and mGluR5 form heterodimers in the striatum, particularly at the corticostriatal glutamate synapse, raising the possibility that mGluR5 was altered by apomorphine via this pathway (Agnati et al., 2010). Additionally, a direct linkage between the NR2B subunit of the NMDAR and D_2 receptor has been observed, whereby stimulation of D_2 reduces phosphorylation of NR2B (Liu et al., 2006). This could indirectly exert effects on mGluR5 due to the close relationship it has with the NMDAR.

These two linkages (mGluR5-D_2 , NR2B-D_2) provide evidence of an interaction between glutamatergic and dopaminergic transmission. Dysfunctions within these neurochemical systems are reflective of positive, negative and cognitive symptomatology. Therefore, mGluR5-targeted therapeutics may treat all symptom profiles through the direct links between glutamatergic and dopaminergic receptors. Nonetheless, more studies are needed to clearly characterise and understand this mechanism in order to manipulate it therapeutically.

4. mGluR5 as a therapeutic target for schizophrenia

As the NMDAR cannot be directly agonised as a therapy for schizophrenia due to the risk of excitotoxicity, indirect modulation of NMDAR through mGluR5 shows promise as mGluR5 is primarily distributed in brain regions relevant to schizophrenia. Consistent with mGluR5 antagonist effects discussed earlier, mGluR5 agonists have been shown to ameliorate cognitive impairments induced by NMDAR antagonists (Lecourtier et al., 2007; Stefani and Moghaddam, 2010; Vales et al., 2010). Additionally, Kinney et al. (2006) showed that mGluR5 agonism attenuated NMDAR antagonist induced deficits in parvalbumin. However, due to cytotoxic effects associated with direct agonism, positive allosteric modulators (PAMs) are the preferred candidate for development. PAMs do not activate receptors directly, rather they act on an allosteric site to potentiate activation by glutamate (Conn et al., 2009).

PAMs of mGluR5, the majority acting at the MPEP allosteric binding site, reverse a wide-range

of positive, negative and cognitive schizophrenia-like behaviours induced in both dopaminergic (i.e. amphetamine) and glutamatergic (i.e. MK-801/PCP) animal models of schizophrenia (Table 2). mGluR5 PAMs have also been reported not to cause sedation (Gilmour et al., 2013; Parmentier- Batteur et al., 2012), or other unwanted behavioural side effects (Balschun et al., 2006), although "very mild" catalepsy has been reported at high doses (Liu et al., 2008; Schlumberger et al., 2010). Whilst a variety of behavioural studies have examined the effects of mGluR5 PAMs (Table 2), many of these studies involved acute pre-treatment with these agents (prior to a dopamine or NMDA challenge), rather than an analysis of their therapeutic proper- ties in combatting already induced schizophrenia-like behaviours. The therapeutic potential of these agents in an established animal model of schizophrenia should therefore be scrutinised.

As can be seen from Table 2, there has been little investigation into the chronic use of these potential therapeutics. This is highly relevant as the long-term therapeutic potential and side-effect profile must be characterised in order for these agents to move forward into the clinical setting. It is only recently that the use of mGluR5 PAMs has been studied beyond a single acute injection (Clifton et al., 2012; Horio et al., in press; Parmentier-Batteur et al., 2012). Importantly, these studies showed behaviourally favourable effects of chronic mGluR5 PAM treatment, however, both Clifton et al. (2012) and Horio et al. (in press) reported that chronic treatment, as opposed to an acute injection, was required to treat PCP-induced cognitive deficits. Further, Horio et al. (in press) showed that chronic (14 days) mGluR5 PAM treatment did not cause antipsychotic tolerance to PCP-induced deficits. Parmentier-Batteur et al. (2012), however, reported changes in mGluR5 densities in an amphetamine model, suggesting tolerance may occur. Whilst Clifton et al. (2012) did not examine molecular alterations indicative of tolerance, they found that chronic treatment with mGluR5 PAM CDPPB was able to continue to exert effects long after the treatment had ceased. It therefore remains unclear whether these agents generate tolerance to antipsychotic actions, but in light of the results reported by Clifton et al. (2012) and Horio et al. (in press), this is unlikely.

Molecular findings in these models report that mGluR5 PAMs cause phosphorylation of NR1/NR2B NMDAR subunits both in vitro (Uslaner et al., 2009) and in vivo (Parmentier-Batteur et al., 2012), consequently affecting NMDAR-mediated currents, channel opening properties and receptor trafficking (Uslaner et al., 2009). This indicates that mGluR5 PAMs mediate these behaviours through their relationship with the NMDAR, though in vivo studies suggest this is treatment-duration and brain-region dependent and possibly NMDAR subunit specific (Parmentier-Batteur et al., 2012). No other studies have examined if mGluR5 levels themselves are altered by these modulators.

As schizophrenia is classified as a neurodevelopmental disorder (Rapoport et al., 2005), it is important to characterise these agents' potential during critical neurodevelopmental phases such as adolescence. It has been shown that dopamine and glutamate systems mature during this time period and assaults during this phase may result in effects to brain maturation, potentially causing severe abnormalities in the adult brain, leading to schizophrenia (Spear, 2000). Treatment with mGluR5 PAMs during this period may also prove a possible prevention measure in individuals with a high risk of developing schizophrenia, particularly as studies so far show encouraging results when pre-treating with an mGluR5 PAM (Table 2). Further experimentation in models that have relevance to schizophrenia may be beneficial to assess this potential. In particular, NR1 knockdown (Ramsey, 2009) and perinatal NMDAR antagonist models (Du Bois and Huang, 2007) are practical models of developmentally derived NMDAR hypofunction. These models display behavioural and neurochemical changes analogous to schizophrenia, and have demonstrated predictive-validity. Therefore, they will be instrumental in assessing the potential of novel drugs to attenuate developmental NMDAR hypofunction-derived alterations in behaviour

and neurochemistry. However, it must be kept in mind that any animal model will have limitations due to the inherent human nature of schizophrenia and the species differences for disease development.

Despite that other mGluRs modulate glutamatergic neurotransmission, studies point towards mGluR5 as a superior target for the treatment of schizophrenia due to its ability to directly modulate the NMDAR (Harrison et al., 2008; Vinson and Conn, 2012). mGluR2/3 have also been of focus, however, phase II clinical trials with mGluR2/3 agonist LY404039 are so far inconclusive. One study found the drug as efficacious as olanzapine (Patil et al., 2007), whilst the other found no therapeutic benefit of either therapeutic compared to placebo (Kinon et al., 2011). It was shown in an animal model that agonising or positively modulating mGluR5, but not mGluR2/3, reverses MK-801-induced cognitive deficits (Vales et al., 2010). Furthermore, a collection of molecular studies has shown that activation of NMDAR is exclusive to mGluR5 and not mGluR1 (Awad et al., 2000; Doherty et al., 1997, 2000; Jia et al., 1998; Mannaioni et al., 2001; Pisani et al., 2001), although this could be brain region dependent (Benquet et al., 2002). Furthering this, Pietraszek et al. (2005) showed that antagonising mGluR5, but not mGluR1, potentiated the effects of MK-801. Together, these reports suggest a unique potential of mGluR5 specifically, although clinical trials will confirm this notion.

In face of the popularity of mGluR5 modulators in preclinical studies conducted all over the world, mGluR5 PAMs have not yet reached clinical trials. In 2008, Merck & Co., Inc. licensed rights to preclinical trials with ADX63365, an mGluR5 PAM, for the treatment of schizophrenia. A major issue inhibiting mGluR5 PAMs was their solubility and oral bioavailability, although the orally active analogue VU0360172 (Rodriguez et al., 2010) and Lilly compounds LSN2463359 and LSN2814617 (Gilmour et al., 2013) now exist. Of note, the latter two show very promising results, having 87% and 99% receptor occupancy in the hippocampus following oral administration. In addition, these compounds show favourable in vitro and in vivo properties (Gastambide et al., 2012, 2013; Gilmour et al., 2013). However, these studies provide preliminary evidence that mGluR5-targeted PAMs are unable to reverse hyperlocomotion, analogous to positive schizophrenia-like behaviours; nonetheless, previous results have shown therapeutic potential in this area, therefore, the ability for mGluR5 to mediate positive aspects of schizophrenia can not be ruled out.

Other modulators of mGluR5 have successfully broken into the clinical phases for the treatment of various pathologies. For example, mGluR5 antagonists AFQ056 (Novatis) and RO4917523 (Roche) are currently under Phase IIb/III testing for sufferers of fragile X and major depression respectively (see clinicaltrials.gov). Despite this, mGluR5 antagonists have been shown to exacerbate schizophrenia-like symptoms induced by NMDAR antagonists (Homayoun and Moghaddam, 2006). Although these agents appear beneficial in antidepressant and anxiolytic models (Brodkin et al., 2002; Busse et al., 2004; Inta et al., 2012; Pałucha et al., 2005; Tatarczyn´ska et al., 2001) and fragile X syndrome (Gürkan and Hagerman, 2012), they appear to be detrimental in schizophrenia. It is not clear why blockade of mGluR5 can induce schizophrenia- like symptoms in animal models, however they are therapeutic in models of depression, anxiety and fragile X, among more.

5. Future directions and final remarks

Although the involvement of mGluR5 in the pathological process of schizophrenia is uncertain, a growing body of evidence supports its ability to modulate the neurochemical dysfunction attributable to the disorder. Indeed, a lack of change of this receptor in schizophrenia is beneficial from a pharmacotherapy aspect, as its ability to modulate the NMDAR is potentially unhindered.

Promising new data indicates that mGluR5 PAMs may be a valuable alternative or additional approach to treating schizophrenia, however, preliminary data suggests that current schizophrenia therapeutics may affect mGluR5, which may therefore have implications for the adjunct use of mGluR5 PAMs with current therapeutics. Additionally, the long-term effects of mGluR5 positive modulation should be assessed in order to characterise the benefits and side-effect profile of these agents so as to move for- ward into clinical trials. mGluR5 therapeutics are highly relevant due to their reported abilities to treat all facets of schizophrenia- like symptomatology in animals. Their actions in combination with other neuropharmacological agents should also be explored, especially due to the heterogeneous nature of schizophrenia. Until then, mGluR5 remains a promising target for regulating glutamatergic neurotransmission in schizophrenia.

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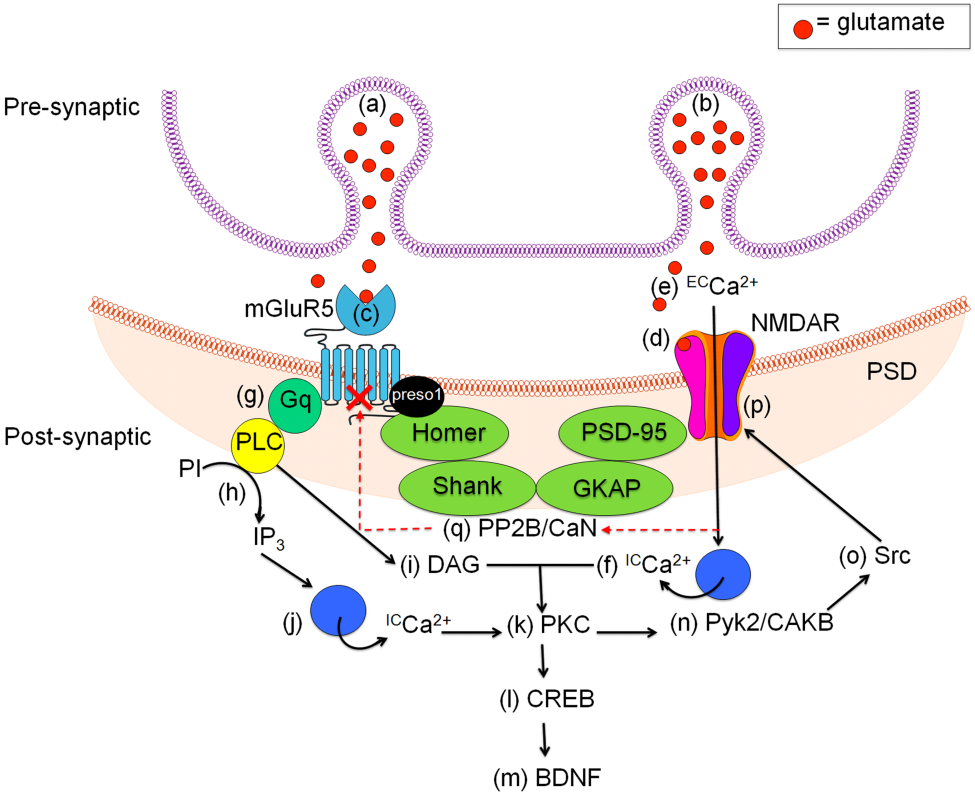

Figure 1 Schematic of mGluR5 and NMDAR signalling pathway. mGluR5 and NMDAR are physically linked by the scaffolding proteins Homer (*via* Preso1), SH_3 and multiple ankyrin repeat domains (SHANK), guanylate-kinase-associated (GKAP, also known as SAPAP) and post-synaptic density 95 (PSD-95) in the post-synaptic density (PSD). (*a*) (*b*) Glutamate-containing vesicles are exocytosed into the synaptic cleft. Glutamate binds to both (*c*) mGluR5 and (*d*) NMDAR. (*e*) Extra-cellular calcium ion ($^{EC}Ca^{2+}$) influx occurs through phosphorylated NMDAR ion channel and (*f*) triggers further release of calcium from intracellular stores ($^{IC}Ca^{2+}$). (*g*) Phosphorylation of mGluR5 by glutamate activates the G-protein $G_{q/11}$, subsequently activating phospholipase C (PLC). (*h*) PLC initiates conversion of phosphoinositide (PI) to inositol 1,4,5-triphosphate (IP_3) and subsequent activation of (*i*) diacylglycerol (DAG). (*j*) IP_3 causes release of intracellular calcium. The combination of DAG with intracellular calcium released due to (*f*) NMDAR activation, initiates phosphorylation of (*k*) protein-kinase C (PKC). Here pathways diverge: PKC continues to signal downstream in which (*l*) cAMP response element-binding (CREB) and (*m*) brain-derived neurotrophic factor (BDNF) are activated. Additionally, PKC stimulates the phosphorylation of (*n*) proline-rich tyrosine kinase/cell adhesion kinase ß (Pyk2/CAKß) and subsequently the (*o*) Src protein. In turn, Src directly potentiates the NMDAR (*p*). Negative feedback within this system also occurs by (*e*) calcium influx through the NMDAR, which activates (*q*) calcium dependant protein phosphatase 2B/calcineurin (PP2B/CaN), which dephosphorylates mGluR5.