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Invited review

Shifting towards a model of mGluR5 dysregulation in schizophrenia: Consequences for future schizophrenia treatment

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ABSTRACT

Metabotropic glutamate receptor subtype 5 (mGluR5), encoded by the *GRM5* gene, represents a compelling novel drug target for the treatment of schizophrenia. mGluR5 is a postsynaptic G-protein coupled glutamate receptor strongly linked with several critical cellular processes that are reported to be disrupted in schizophrenia. Accordingly, mGluR5 positive allosteric modulators show encouraging therapeutic potential in preclinical schizophrenia models, particularly for the treatment of cognitive dysfunctions against which currently available therapeutics are largely ineffective. More work is required to support the progression of mGluR5-targeting drugs into the clinic for schizophrenia treatment, although some obstacles may be overcome by comprehensively understanding how mGluR5 itself is involved in the neurobiology of the disorder. Several processes that are necessary for the regulation of mGluR5 activity have been identified, but not examined, in the context of schizophrenia. These processes include protein–protein interactions, dimerisation, subcellular trafficking, the impact of genetic variability or mutations on protein function, as well as epigenetic, post-transcriptional and post-translational processes. It is essential to understand these aspects of mGluR5 to determine whether they are affected in schizophrenia pathology, and to assess the consequences of mGluR5 dysfunction for the future use of mGluR5-based drugs. Here, we summarise the known processes that regulate mGluR5 and those that have already been studied in schizophrenia, and discuss the consequences of this dysregulation for current mGluR5 pharmacological strategies.

This article is part of the Special Issue entitled 'Metabotropic Glutamate Receptors, 5 years on'.

Abbreviations: 7TMD, 7-transmembrane domain; BA, Brodmann Area; BDNF, brain-derived neurotrophic factor; CA, Cornu ammonis; Ca^{2+}, Calcium ions; Calcineurin/PPB2, protein phosphatase 2B; CaM kinase II or CaMKII, calcium/calmodulin-dependent protein kinase II; CaMKs, calcium/calmodulin-dependent protein kinases; cAMP, cyclic adenosine monophosphate; CDK5, cyclin-dependent protein kinase 5; CRD, cysteine rich domain; CREB, cAMP response element-binding protein; CRMPD1, collapsing-response mediator protein 1; DISC1, disrupted in schizophrenia protein 1; DLPFC, dorsolateral prefrontal cortex; ERK, extracellular signal-regulated kinases; GABA, gamma-Aminobutyric acid; GKAP, guanylate kinase-associated protein; GPCR, G-protein coupled receptors; GRKs, GPCR regulatory kinases; ^{ic}mGluR5, intracellular mGluR5; iGluR, ionotropic glutamate receptor; Intrabodies, intracellular antibodies; JNK, c-Jun N-terminal kinases; LTD, long-term depression; LTP, long-term potentiation; MAPKs, mitogen-activated protein kinases; mGluR5, Metabotropic glutamate receptor subtype 5; mTOR, mammalian target of rapamycin; NAM, negative allosteric modulator; NMDAR, *N*-methyl-D-aspartate receptor; Norbin/neurochondrin-1, neurite-outgrowth related rat brain protein; PAM, positive allosteric modulator; Pharmacoperone, pharmacological chaperones; PI3Ks, phosphoinositide 3-kinase (PI3K); PKA, protein kinase A; PKC, protein kinase C; PLC, protein lipase C; Preso1/FRMPD4, FERM and PDZ domain containing protein 4; PSD, post-synaptic density; PSD95, postsynaptic density 95 protein; S-SCAM, membrane-associated guanylate kinase inverted-2; SHANK, SH3 and multiple ankyrin repeat domain; Siah1a, seven in absentia homolog 1a; Tamalin/GRASP, GRIP-associated protein-1; VFTD, Venus-fly-trap domain.

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Contents

1. Introduction

1.1. Schizophrenia and metabotropic glutamate receptor 5

Schizophrenia is a neuropsychiatric disorder characterised by compromised neurotransmission and a loss of normally tight regulation (Deng and Dean, 2013). It has been hypothesised that the chain of neurotransmitter dysregulation might originate with ionotropic glutamate receptor (iGluR) abnormalities (see Hu et al., 2014), considering dysfunction of the main glutamate *N*-methyl-D-aspartate receptor (NMDAR) is strongly associated with psychosis, mood and cognition (Kantrowitz and Javitt, 2010). Since iGluR activity is largely refined by metabotropic glutamate receptors (mGluRs), mGluRs have gained attention as factors that contribute to the pathology of schizophrenia, as well as novel therapeutic targets to restore glutamatergic dysfunction (Moghaddam and Javitt, 2011; Newell et al., 2014; Rubio et al., 2013).

Converging evidence from genetic and animal studies over the last two decades indicates that mGluR5 critically modulates the activity of the glutamatergic NMDAR (Alagarsamy et al., 2005, 2002). In rodents, pharmacological blockade of mGluR5 with selective negative allosteric modulators, MPEP (2-methyl-6-(phenylethynyl)-pyridine) or MTEP (3- [(2-methyl-1,3-thiazol-4-yl) ethynyl]-pyridine) induces a wide range of schizophrenia-like behaviours, including deficits in social interactions, working memory, instrumental learning and potentiation of locomotive and sensorimotor deficits induced by NMDAR antagonists (Campbell et al., 2004; Henry et al., 2002; Pietraszek et al., 2005; Vales et al., 2010; Vollenweider et al., 1998; Zou et al., 2007). Further, *grm5* knockout mice display behaviours relevant to the pathophysiology of schizophrenia, including disruptions to prepulse inhibition, short-term spatial memory and severe locomotor deficits in response to NMDAR antagonism (Brody et al., 2003; Burrows et al., 2015; Chiamulera et al., 2001; Gray et al., 2009; Lu et al., 1997). Conditional cortical knockout of mGluR5 specifically modulates locomotor reactivity in response to a novel environment, but does not affect sensorimotor gating, anxiety, motor coordination, and social interactions, which are likely attributable to subcortical and/or other brain structure mGluR5 activity (Jew et al., 2013).

mGluR5 is also critically involved in long-term potentiation (LTP) and long-term depression (LTD), both mechanisms involved in learning and memory processes and disrupted in schizophrenia (Barch and Ceaser, 2012; Mukherjee and Manahan-Vaughan, 2013). For example, *grm5* knockout mice have reduced performance in NMDAR-mediated memory tasks due to deficits in hippocampal NMDAR-induced LTP; these deficits can be rescued by stimulation of PKC (Jia et al., 1998). Furthermore, LTP induced by theta-burst stimulation in hippocampal slices are impaired by treatment with MPEP (Francesconi et al., 2004; Shalin et al., 2006), and accordingly antagonism of mGluR5 in rats impacts on spatial learning performance and synaptic plasticity, specifically via inhibition of LTP in CA1 and the dentate gyrus (Manahan-Vaughan and Braunewell, 2005). The Group I mGluR agonist DHPG is also able to induce LTD, which is blocked only by an mGluR5 antagonist, and is not present in mGluR5 knockout mice (Faas et al., 2002; Gasparini et al., 1999; Huber et al., 2001). A recent study also reported that the cellular location of mGluR5 may impact on the exact role it plays in synaptic plasticity, with cell-surface expressed mGluR5 regulating both LTP and LTD, whilst intracellularly expressed mGluR5 modulate LTD only (Purgert et al., 2014). These studies collectively