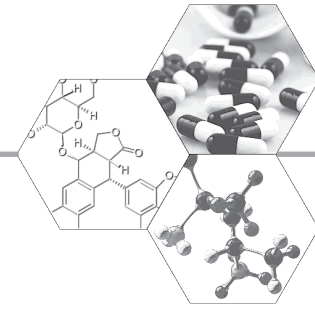

Metabotropic glutamate receptor 5 in schizophrenia: emerging evidence for the development of antipsychotic drugs

"*With recent studies implicating the mGluR5 gene,* GRM5*, in schizophrenia, coupled with the schizophrenia-like behavioral phenotype in mGluR5 knockout mice, a role of mGluR5 in the development of schizophrenia is feasible.*"

Keywords: GRM5 ■ mGlu ■ mGluR5 ■ NMDA receptor ■ novel therapeutic ■ positive allosteric modulator ■ schizophrenia

Metabotropic glutamate receptor 5 (mGluR5) is an exciting novel drug target for the treatment of several psychiatric disorders, including schizophrenia. mGluR5 is a seven transmembrane spanning, G protein-coupled receptor that modulates glutamatergic signaling, especially in association with the NMDA receptor (NMDAR). The NMDAR is well documented to play a critical role in schizophrenia pathophysiology, especially the associated cognitive dysfunctions [1,2]. Therapeutics that target the NMDAR directly are problematic because the NMDAR is an ionotropic receptor; its activation allows calcium entry into the neuron, which at high levels activates an excitotoxic cascade, ultimately leading to neuronal death. Researchers have been trying to overcome this and target the NMDAR via a 'back door' approach for many years. The NMDAR shares a structural connection with mGluR5, via one or a combination of various scaffolding proteins (e.g., Homer, Shank, GKAP and PSD-95); through this link, mGluR5 activation enhances NMDAR activity, thereby forming the basis of mGluR5 as a novel drug target for the treatment of schizophrenia.

So, what role does mGluR5 itself play in schizophrenia? This is an important question to address, not only to enable us to understand the role of the glutamatergic system in the pathophysiology of schizophrenia, but also because the status of mGluR5 in schizophrenia has implications for the effectiveness of mGluR5-based therapeutics in these patients. At the surface there appears to be no alteration in mGluR5 protein or mRNA levels in the brain of schizophrenia subjects [3,4]. However, this still leaves many unanswered questions. Is mGluR5 altered in specific cellular compartments or neuronal populations? Is mGluR5 trafficking or function altered? Is mGluR5 coupling with the NMDAR or its specific subunits altered? There is evidence to suggest that mGluR5 function and/or coupling with the NMDAR could indeed be altered in schizophrenia. Studies have shown that Homer1, a key molecule that coordinates signaling between mGluR5 and NMDAR, has reduced protein expression in the hippocampus and prefrontal cortex in schizophrenia [5], suggesting a possible disruption to the association between mGluR5 and the NMDAR. Additionally, mGluR5 knockout mice, Homer1 knockout mice and rats treated with mGluR5 antagonists all present with a schizophrenia-like behavioral phenotype [4]. This suggests that mGluR5 could play a role in schizophrenia pathophysiology, however admittedly these behaviors could arise due to associated alterations in the NMDAR. Furthermore, mGluR5 plays a significant role in long-term potentiation and long-term depression [6] – molecular processes that are critical in cognition, and which are disrupted in schizophrenia. Finally, emerging evidence suggests that mGluR5 activation modulates microglia function [7], and therefore may be associated with microglia-induced changes in the schizophrenia brain. Clearly, there is ample indirect evidence suggesting mGluR5 could be altered in schizophrenia, which warrants further research in this direction.

mGluR5 plays a key role in brain development, including the regulation of stem cell proliferation and migration [8]. In addition, Matta *et al.* recently found evidence that mGluR5 stimulates the normal developmental NMDAR NR2 subunit switch within the hippocampus, in which the ratio of NR2A-containing NMDARs compared with NR2B-containing NMDARs increases [9]. This is noteworthy as NR2A and NR2B subunits have differing kinetics, synaptic localizations and activate different

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cellular pathways [10]. Of particular importance, NR2A-containing receptors play a critical role in the development and maturation of GABAergic circuits, particularly parvalbumin-containing interneurons, which are deficient in schizophrenia [11]. This NR2B/NR2A subunit 'switch' is hypothesized to be disturbed during development in the schizophrenia brain resulting in altered NMDAR stoichiometry as well as GABAergic deficits. Therefore, it is plausible to suggest that while post-mortem studies indicate that mGluR5 levels may not be altered in the adult schizophrenia brain, alterations in mGluR5 during early brain development could indeed contribute to the dysfunctions in NMDAR and GABAergic circuitry observed in schizophrenia. With recent studies implicating the mGluR5 gene, *GRM5,* in schizophrenia [12], coupled with the schizophrenia-like behavioral phenotype in mGluR5 knockout mice [13], a role of mGluR5 in the development of schizophrenia is feasible.

> "*There is ample indirect evidence suggesting mGluR5 could be altered in schizophrenia.*"

mGluR5 positive allosteric modulators (PAMs) are a potential new class of therapeutics for the treatment of schizophrenia. These drugs uniquely target the allosteric site of the receptor, rather than the orthosteric site where glutamate binds, which allows the generation of drugs that are highly specific to mGluR5, that also presumably lack the receptor desensitizing consequences of typical agonists (although see [14]). The preclinical studies to date on the therapeutic effectiveness of mGluR5 PAMs are convincing, with most studies showing they are able to attenuate NMDAR antagonist-induced cognitive deficits, as well as NMDAR antagonist- and amphetamine-induced psychotomimetic effects, indicating their potential to alleviate the positive, negative and importantly the cognitive symptoms in schizophrenia patients [4]. This is in contrast to current antipsychotics, which although widely efficacious for positive symptoms, display minimal benefits for negative and cognitive symptoms, which are arguably the most debilitating for patients.

While the preclinical evidence is promising, mGluR5 PAMs have not yet reached clinical trial. A major issue with mGluR5 PAMs has been their lack of solubility and oral bioavailability. However, recent analogs, VU0360172, LN2463359 and LN2814617, show potential, with increased solubility and oral bioavailability, demonstrating up to 99% hippocampal receptor occupancy following oral administration [15,16]. Although these new soluble PAMs show encouraging behavioral effects, their inconsistency in reversing NMDAR antagonist- and amphetamine-induced hyperlocomotion [15–17], suggests they may not be as effective against positive schizophrenia symptoms. In this regard we need to seriously consider the interaction between mGluR5 and the dopaminergic system. Nearly all antipsychotics to date have required some mechanism of action on the dopaminergic system to have reasonable therapeutic effects. It is likely that PAMs specific for mGluR5 still have some indirect impact on the dopaminergic system, due the reported associations between mGluR5 and dopamine. For example, the mGluR5 PAM CDPPB has been shown to reduce amphetamine-induced hyperlocomotion and prepulse inhibition deficits, presumably mediated through the dopaminergic system [18]. Furthermore, the dopamine D2 receptor and mGluR5 reportedly form heterodimers in the striatum, particularly at the corticostriatal glutamate synapse, suggesting a possible avenue for indirect effects of mGluR5 PAMs on striatal dopaminergic signaling [19]. However, considering the newer mGluR5 analogs may have less effect on striatal dopamine-mediated behaviors, it may be that they are targeting a different mGluR5 subclass or different mGluR5-mediated signaling pathways [20], distinct from those that interact with the dopaminergic system. This avenue needs to be further explored to determine whether these novel mGluR5 PAMs are likely to be stand-alone therapeutics or rather co-therapies with traditional antipsychotics.

An important issue that remains to be addressed with mGluR5 PAMs is their therapeutic effects in the presence of comorbid symptoms. mGluR5 negative allosteric modulators (NAMs) are currently in preclinical and clinical trials for the treatment of major depression and anxiety. These same NAMs however can induce schizophrenia-like behaviors in rodent models [4]. In a similar manner, mGluR5 PAMs, although a promising treatment for schizophrenia, may worsen symptoms in depressed or anxious subjects, thereby having implications for schizophrenia patients with depressive symptoms or comorbid depression. This is therefore a serious issue with clinical consequences that remains to be resolved.

Research led by the Conn group on functional selectivity has begun to address this. As mGluR5 couples to multiple signaling pathways, mGluR5 PAMs may be able to preferentially impact specific signaling pathways to achieve the desired therapeutic response, while having no effect on other mGluR5-mediated signaling pathways [20]. For example, while high doses of traditional mGluR5 NAMs (e.g., the promising anxiolytic MTEP) enhance the psychotomimetic effects of PCP, newer analogs developed by the Conn group (e.g., VU0285683) do not have this property [16]. This indicates that these limitations can be overcome by specialist drug design. While no studies to date have investigated whether mGluR5 PAMs have anxiogenic or depressive-like properties, this should be pursued in the future.

> *"Although there are critical research questions that remain to be answered, studies so far suggest mGluR5 will be an efficacious therapeutic target."*

Agonists and allosteric modulators for other mGluRs have also been of interest for schizophrenia treatment. Most prominently, the move forward for mGluR2/3 agonists from promising preclinical studies to unsuccessful clinical trials was disheartening for the schizophrenia research community, although these trials did reveal that specific single-nucleotide polymorphisms within relevant genetic markers (*GRM2, GRM3, HTR2A, DRD2, DRD3, NRG1, COMT* and *PKHD1*) were significantly associated with treatment–response in these trials [21]. Considering the heterogeneity of schizophrenia from symptom profiles, to genetic variations and antipsychotic effectiveness, it is not surprising to see differential treatment responses. In reality it is likely that this is exactly where schizophrenia treatment is headed: towards a much more individualized approach. Future examination of the effects of mGluR5 PAMs in genetic mutant animal models such as *Nrg1*, *DISC1* or *reelin* mutant mice, will help shed light on the interactions of known candidate genes with these novel therapeutics. Furthermore, studies in the exciting avenue of human induced pluripotent stem cells will advance the field of pharmacogenomics, allowing us to predict the efficacies of these novel therapeutics in the presence of common genetic variations present in human patients.

In summary, there is still much to be uncovered regarding the role of mGluR5 in schizophrenia pathophysiology and subsequently the potential of mGluR5 PAMs as a therapeutic tool to combat schizophrenia. Although there are critical research questions that remain to be answered, studies so far suggest mGluR5 will be an efficacious therapeutic target. As better avenues of antipsychotic drug intervention are desperately required, mGluR5 provides hope that there may be a more effective treatment on the horizon.

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