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Group II metabotropic glutamate receptors and schizophrenia

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Abstract

Schizophrenia is one of the most common mental illnesses, with hereditary and environmental factors important for its etiology. All antipsychotics have in common a high affinity for monoaminergic receptors. Whereas hallucinations and delusions usually respond to typical (haloperidol-like) and atypical (clozapine-like) monoaminergic antipsychotics, their efficacy in improving negative symptoms and cognitive deficits remains inadequate. In addition, devastating side effects are a common characteristic of monoaminergic antipsychotics. Recent biochemical, preclinical and clinical findings support group II metabotropic glutamate receptors (mGluR2 and mGluR3) as a new approach to treat schizophrenia. This paper reviews the status of general knowledge of mGluR2 and mGluR3 in the psychopharmacology, genetics and neuropathology of schizophrenia

Keywords

Schizophrenia; Antipsychotics; G protein-coupled receptors (GPCR); Serotonin receptors; 5-HT_{2A}; Metabotropic glutamate receptors; mGluR2; mGluR3

Introduction

Schizophrenia is a chronic mental disorder that affects approximately 1% of the population worldwide with similar prevalence throughout diverse cultures and geographic areas [1–5]. The symptoms of schizophrenia include “positive” symptoms (e.g., hallucinations, delusions, paranoia), negative symptoms (e.g., social withdrawal, apathy, abnormal emotional responses), and cognitive deficiencies such as impaired memory, attention deficit, and reduced executive functioning. Serendipity played a role in the discovery of both the first (typical, haloperidol-like) and second (atypical, clozapine-like) generation of antipsychotics. The first antipsychotic chlorpromazine was discovered in 1952 as an antihistaminic that decreased psychosis [6]. Haloperidol was first developed as a pain reliever [7], and clozapine was originally a “tricyclic antidepressant with neuroleptic properties” [8,9]. To date, both the mechanism of action of antipsychotics and the pathogenesis of the disease remain largely unknown.

Since schizophrenia is incurable, treatment with antipsychotics typically continues for life. Typical antipsychotics do not resolve negative symptoms, may fail to improve positive symptoms, and worsen cognitive symptoms in some patients [10,11]. Atypical antipsychotics

have a reduced risk of extrapyramidal symptoms, and have become the first-line treatment for schizophrenia [12,13]. However, whereas positive symptoms usually respond to antipsychotic medication, success in treating schizophrenia remains limited by low efficacy of the neuroleptics in the treatment of negative symptoms and cognitive deficits [14,15]. Clozapine was discovered more than 50 years ago and approved by the FDA in 1989, yet it remains the only antipsychotic medication with established efficacy in treatment-resistant schizophrenia patients. Clozapine could also be beneficial for less severely ill patients who show only partial response to other antipsychotic drugs. Despite its efficacy, clozapine has substantial undesirable effects on metabolic parameters causing weight gain, glucose abnormalities, hypertriglyceridemia, and hypertension. Reports have also shown that 1–2% of patients who take clozapine will develop agranulocytosis, a sometimes fatal side effect that severely limits the use of the most efficacious antischizophrenia drug [16–19]. All the antipsychotic medications currently prescribed have in common a high affinity for monoaminergic receptors. Notably, recent preclinical and clinical findings suggest metabotropic glutamate receptors 2 and/or 3 as a new target to treat schizophrenia [20–24]. Treatment of schizophrenic patients with the mGluR2/3 agonist LY2140023 led to an improvement of both positive and negative symptoms without significant side effects compared to placebo [25]. Studies with twin, family and adoption suggest that schizophrenia results from a combination of predisposing genes and hazardous environmental factors [26,27]. Here, we review the potential implications of mGluR2 and mGluR3 in the pharmacological, genetic and epigenetic aspects of the disorder.

Group II metabotropic glutamate receptors

L-Glutamate is the major excitatory neurotransmitter in the mammalian CNS, acting through both ligand-gated ion channels and G protein-coupled receptors (GPCRs). The ionotropic glutamate receptors are multimeric assemblies of four or five subunits, and are subdivided into three groups (AMPA, NMDA, and kainate receptors) [28]. GPCRs represent the largest family of signal transduction membrane proteins, and a major target for therapeutic drugs. All known GPCRs have a common structural template composed by seven membrane-spanning alpha helices joined by hydrophilic loops [29,30]. The three major families of GPCRs include the rhodopsin-like receptors (family A), the glucagon-related receptors (family B), and metabotropic glutamate-related receptors (family C). Family C is characterized by a large amino terminus extracellular domain that consists of two lobes separated by a large cleft that contains the agonist binding site [31,32]. This family includes the metabotropic glutamate receptors (mGluRs), the γ -aminobutyric acid (GABA_B) receptor, and the calcium sensing receptors. Metabotropic glutamate receptors have been subdivided into three groups, based on sequence similarity, pharmacology, and G protein coupling. The group I mGluRs is represented by mGluR1 and mGluR5, both coupled to G_{q/11} proteins and activation of phospholipase C. The group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8) receptors are coupled to G_{i/o} proteins and typically inhibit adenylyl cyclase activity. With the exception of the mGluR6 isoform, which is expressed restrictedly at the postsynaptic site of retinal ON-bipolar cells, metabotropic glutamate receptors are widely distributed in the brain.

Although much biochemical and biophysical data are consistent with the ability of GPCRs to bind and activate G proteins in a monomeric form [33–38], many recent studies support the hypothesis that G protein coupling in cell membranes involves the formation of GPCR homo- and heterodimers or higher order oligomers [39–41]. In particular, much evidence indicates that family C receptors exist and function as dimers [31]. Thus, the co-assembly of two non-functional GPCRs, GB1 and GB2, is required for the expression of functional GABA_B receptors, and the heterodimer GABA_B receptor has been demonstrated to activate through a mechanism of trans-activation [42–44]. The functional significance of family C receptor dimerization is further supported by the demonstration that a closed state of both binding domains in the homodimeric mGluR5 is required for full activity [45], and that mGluR1 [46]

and mGluR5 [47] are expressed in the cell membrane as a dimer, not as a higher order oligomer. The crystal structure of the amino terminus ligand-binding domain of the mGluR1 receptor presents a disulphide bridge connecting the two protomers [48,49]. Similarly, disulphide bonding within the amino terminus domains of mGluR5 and the calcium-sensing receptor has been reported to be important for covalent dimerization [50]. In addition, the expression of heterocomplexes between rhodopsin-like and metabotropic glutamate receptors have been reported for mGluR5, dopamine D₂, and adenosine A_{2A} [51,52], and for mGluR2 and serotonin 5-HT_{2A} receptors [53], thus further complicating the interpretation of signaling through metabotropic glutamate receptors.

Group II metabotropic glutamate receptors as a new antipsychotic target

The lack of clear pathological lesions in schizophrenia represents one of the main limitations for research on this disease using rodent models. Psychotomimetic drugs such as phenylclidine (PCP) and lysergic acid diethylamide (LSD) induce schizophrenia-like psychosis in humans and represent in mouse a pharmacological tool that has led to a better understanding of the neurochemical basis underlying schizophrenia and psychosis [54–57]. A single dose of PCP has been shown to intensify the symptoms in patients with schizophrenia, to produce hallucinations, and to reduce cognitive ability. In addition, acute PCP administration in rodents has been shown to elicit deficits in pre-pulse inhibition (PPI) of the startle response, a measure of sensorimotor gating deficits, to increase locomotor activity, to decrease social recognition, and to produce cognitive deficits of particular relevance to schizophrenia [58]. Studies with healthy volunteers showed similarities between the early stages of schizophrenia and the psychological effects induced by the LSD-like hallucinogen psilocybin [59]. The cellular and behavioral responses induced by hallucinogens are abolished in serotonin 5-HT_{2A} knock-out mice [60,61]. The complexity of schizophrenia makes it unfeasible to mimic the entire syndrome in mouse models. However, all these findings suggest that PCP-like and LSD-like drugs may be used as tools to model specific signs or symptoms associated with schizophrenia.

The demonstration in rodents that mGluR2/3 activation attenuates the effects of PCP on locomotion and working memory [62], and that suppresses the head-twitch response induced by the hallucinogenic 5-HT_{2A} receptor agonist DOI [63], led to a tremendous amount of research showing functional and behavioral interactions between 5-HT_{2A}, mGluR2/3, and NMDA receptors (see [57] for review). Studies in healthy human subjects reported that the behavioral effects of ketamine are disrupted by the mGluR2/3 agonist LY354740 [64]. Recent clinical trials support the significance of mGluR2/3 agonists as a new class of antipsychotics [25]. Thus, treated patients with LY2140023 showed significant improvements in both positive and negative symptoms of schizophrenia. Importantly, patients taking the LY2140023 did not show Parkinsonian side effects. Moreover, in contrast to atypical antipsychotics such as clozapine and olanzapine, the mGluR2/3 agonist did not result in undesirable effects on metabolic parameters. A long-standing question was whether mGluR2, mGluR3 or both are responsible for the antipsychotic effects of the mGluR2/3 agonists. Recent preclinical results in mouse models together with studies of allelic variation in humans suggest different roles for mGluR2 and mGluR3 in the mechanism of action of glutamate antipsychotics and the genetic link to schizophrenia.

Antipsychotic-like effects in mouse are mGluR2, and not mGluR3, dependent

The absence of selective orthosteric ligands has precluded detailed studies on the physiological and behavioral significance of mGluR2 and mGluR3 for the mechanism of action of glutamate antipsychotics. Experiments with mGluR2 knock-out mice suggested that mGluR2 mediated the inhibition of the PCP-induced locomotor activity by the mGluR2/3 agonist LY314582 [65]. Concurrent studies with LY404039 [66] and LY379268 [67] provided evidence that the

effects of the mGluR2/3 agonists blocking the locomotor activity induced by PCP and amphetamine are abolished in mGluR2 knock-out mice, and are unaffected in mGluR3 knock-out mice. These data suggest that mGluR2, and not mGluR3, is the receptor responsible for the antipsychotic-like effects of the mGluR2/3 agonists in murine models.

The great majority of GPCR ligands used in the clinic and in basic research are orthosteric ligands (i.e., agonists, antagonists, and inverse agonists) that compete with endogenous ligands for the same binding site. Allosteric ligands modulate receptor function by binding not to the orthosteric site but to different regions in the receptor, the allosteric sites [68]. Interestingly, positive allosteric modulators of mGluR2 have behavioral effects similar to mGluR2/3 orthosteric agonists. The mGluR2 positive allosteric modulator LY487379 reduced the PCP- and amphetamine-induced locomotion activity in a comparable manner to the allosteric mGluR2/3 agonist LY379268 [69]. In the same context, the mGluR2 positive allosteric modulator biphenyl-indanone A (BINA) blocks the head-twitch behavioral response induced by the hallucinogenic 5-HT_{2A} agonist DOB [70]. Since allosteric modulators are unable to induce a functional response in the absence of orthosteric agonists, the effects of LY487379 and BINA on the behavioral effects of psychotomimetic drugs suggest that the allosteric modulators potentiate the mGluR2-dependent responses induced by the endogenous agonist glutamate.

The mGluR2 is likely to be responsible for the effects of antipsychotic mGluR2/3 agonists, and all the clozapine-like atypical antipsychotics have a high affinity for the 5-HT_{2A} receptor. The functional and behavioral interaction between 5-HT_{2A} and mGluR2 receptors is well established (Fig. 1), and activation of mGluR2 inhibits the cellular, electrophysiological, and behavioral responses induced by PCP-like and LSD-like psychotomimetic drugs (see [57] for review). Recent findings showed that 5-HT_{2A} and mGluR2 co-localize in cortical pyramidal neurons and form a receptor heterocomplex [53,57]. Interestingly, chronic treatment with the hallucinogenic 5-HT_{2A} agonist DOB alters the behavioral responses to the mGluR2/3 agonist LY379268 [71]. In addition, the locomotor activity induced by the mGluR2/3 antagonist LY341495 is reversed by antipsychotic drugs [72], and decreased in 5-HT_{2A} knock out mice [53,57]. These and other data [57], together with the expression of 5-HT_{2A} and mGluR2 as a receptor heterocomplex in mouse and human brain [53,57], suggest that the 5-HT_{2A}-mGluR2 heterocomplex might represent a new target for antipsychotic therapies (Fig. 1). On the other hand, the blockage of the PCP-induced hyperlocomotion elicited by high doses of clozapine, risperidone, and olanzapine is not affected in mGluR2/3 double-knock out mice [25,66]. Although the risks of extrapyramidal symptoms are much less with atypical antipsychotics when compared to haloperidol, it has been reported that high doses of clozapine and other atypical antipsychotics produce motor suppression and catalepsy in rodents [73]. Since all atypical antipsychotics have a high affinity for the 5-HT_{2A} and a modest affinity for the dopamine D₂ receptor, further investigations with lower and therapeutically relevant doses of clozapine-like drugs are necessary to determine whether the 5-HT_{2A}-mGluR2 complex is fully or in part responsible for the effects of atypical antipsychotics, as well as for the effects of glutamate antipsychotics.

GRM2 and GRM3 genes in schizophrenia

Twin studies show the existence of a genetic predisposition to schizophrenia, with estimates of heritability of risk at 73–90% [74–76]. While other factors besides genetics are definitely involved, investigation of the genetic alterations responsible for schizophrenia represents a useful approach to better understand the cause of the disease [27]. Metabotropic glutamate receptor 2 gene (GRM2) has been mapped to chromosome 3p21.1–p21.2 [77], and linkage studies of schizophrenia show no positive results regarding this region [78–83]. The polymorphisms identified in the coding exons of GRM2 revealed ten missense mutations and

one silent mutation [84]. However, these polymorphisms did not show statistically significant differences in schizophrenics and controls [84]. Further investigation with different cohorts might be necessary to better understand the potential role of the polymorphisms of the human GRM2 in receptor function, and to extend our knowledge of a potential association between SNPs in GRM2 and schizophrenia. In contrast to GRM3 (see below), no alternative splicing of GRM2 is expressed in human brain [85–87].

Metabotropic glutamate receptor 3 gene (GRM3) has been mapped to chromosome 7q21.1–q21.2 [88], and several linkage studies reported one of the schizophrenia susceptibility loci as located in the proximity of the GRM3 region [78–80,82,83]. A unique case was reported with familial 7q21 reciprocal translocation and childhood-onset schizophrenia (COS) [89]. Polymorphisms in GRM3 have been associated with negative symptom improvement with clozapine [90]. Combined genomic and neurobiological approaches showed that GRM3 genotype affects cognition as well as prefrontal and hippocampal physiological responses [91], which was hypothesized as an increased risk for schizophrenia. The SNP proposed as associated with schizophrenia (rs6465084) showed lower levels of prefrontal *N*-acetyl-aspartate (NAA), which is a reservoir for glutamate [91,92]. Catechol-*o*-methyltransferase (COMT) degrades catecholamines such as dopamine, serotonin adrenaline, and noradrenaline. Epistasis between COMT genotypes or haplotypes and SNPs in GRM3 has been explored showing association with working memory [93,94]. Concurrently, these data suggest an association of SNPs in GRM3 and schizophrenia, yet the potential link between genetic variations in GRM3 and schizophrenia remains debatable. First, genome-wide scans have implicated several regions of the genome; however, meta-analysis showed that the GRM3 locus did not reach statistical significance as implicated in schizophrenia [27]. Second, while five studies found association between individual SNPs and/or haplotypes in GRM3 and schizophrenia [91,93,95–97], eight studies including one meta-analysis did not [83,98–104]. Among the five positive studies, the research findings showing associations have not been consistent for the specific SNP patterns. It is therefore not established that GRM3 variants play a major role in predisposing to schizophrenia. Furthermore, since all SNPs within GRM3 are either noncoding or synonymous, the mechanisms underlying the genetic associations between polymorphisms in GRM3 and schizophrenia remain controversial. Recent evidences indicate that silent SNPs may result in different three-dimensional folding patterns of the transcribed mRNA that can affect mRNA degradation and in vivo protein folding and, consequently, protein function [105–107]. However, most of the studies suggest that the level of expression of *mGluR3* mRNA is unaffected in schizophrenia brain (see below). Alternative pre-mRNA splicing also represents an important mechanism involved in the generation of transcript and protein diversity [86]. Alternative splicing of GRM3 studies in human brain reported four splice variants: full-length GRM3 (2.8 kb), GRM3 with exon 2 deleted (GRM3Δ2, 2.2 kb), GRM3 with exon 4 deleted (GRM3Δ4, 1.8 kb), and GRM3 with exons 2 and 3 deleted (GRM3Δ2Δ3, 1.4 kb) [87]. The most abundant variant GRM3Δ4 corresponds with a truncated protein with a conserved extracellular ligand binding domain, absence of seven-transmembrane domains, and a 96-amino acid C-terminus. A SNP in GRM3 was found to correlate with the expression of the GRM3Δ4 splice variant [108], but it is not the GRM3 variant rs6465084 that has been reported to affect cognition (see above and [91]). In conclusion, while the current data concerning GRM3 do not allow rejection of the null hypothesis, to date there is no clear association between any SNP, genotype, or haplotype with schizophrenia.

Level of expression of mGluR2 and mGluR3 in schizophrenia

The majority of the findings in post-mortem human brain suggest that the level of expression of *mGluR3* mRNA is unaffected in schizophrenia [53,91,109–112]. Our current understanding of how the genome regulates gene expression and function is limited. However, the unaffected level of expression of *mGluR3* mRNA is supported by the hypothesis that variation in GRM3

is not associated with schizophrenia (see above). Fewer studies have investigated the level of expression of *mGluR2* mRNA in post-mortem human brain of schizophrenic subjects. Semi-quantitative approaches such as in situ hybridization have reported unaffected *mGluR2* mRNA expression in thalamus [110], and higher *mGluR2* mRNA expression in the prefrontal cortex white matter [111]. However, quantitative real-time PCR assays shown lower level of expression of *mGluR2* mRNA in prefrontal cortex [53] and cerebellum [112] in schizophrenics. Further investigation in larger samples is required to determine the level of expression of *mGluR2* mRNA in schizophrenia brain, as well as to test whether chronic antipsychotics have a significant effect on *mGluR2* mRNA expression.

Discrepant results have been published regarding the level of expression of mGluR2/3 protein in prefrontal cortex, with unaffected [113] and higher [114] mGluR2/3 immunoreactivity in antipsychotic-treated schizophrenic subjects. It has been reported that the density of mGluR2/3 binding sites is lower in cortex from young untreated schizophrenic subjects [53], and recent findings by semi-quantitative western blot assay suggest a reduction in mGluR3 protein in prefrontal cortex in schizophrenic subjects, with mGluR2 protein levels unchanged [115]. Much evidence indicates that metabotropic glutamate receptors exist and function as heterodimers, and the amino terminus ligand-binding domain presents a disulphide bridge connecting the two protomers (see above). Thus, it is reasonable to speculate that metabotropic glutamate receptors are expressed as dimers in the cell membrane under physiological conditions. However, the level of expression of mGluR3 as dimer has been reported to be significantly lower in prefrontal cortex of schizophrenic subjects, whereas total mGluR3 protein was not altered significantly [116]. The unaffected level of expression of *mGluR3* mRNA in schizophrenia brain, as well as the mGluR2-dependent mechanism of action of glutamate antipsychotics in mouse models (see above), makes necessary further investigation of the level of expression and function of mGluR2 and mGluR3 in postmortem human brain of schizophrenic subjects and controls.

Conclusions and future directions

Multidisciplinary approaches suggest that mGluR2, and not mGluR3, is the target of metabotropic glutamate antipsychotics in mouse models. Further investigation is necessary to better understand the molecular and cellular mechanisms by which mGluR2 activation elicits antipsychotic effects. Whereas the etiology of schizophrenia clearly involves genetic factors, inheritance alone is not sufficient for clinical manifestation of schizophrenia, and considerations of the etiology of schizophrenia also include the role of environmental factors. Several approaches have reported that factors such as obstetric complications [117,118], maternal infection [119,120], and prenatal malnutrition [121] influence schizophrenia risk. Interestingly, recent findings suggest that GRM3 gene interacts with obstetric complications to affect the risk of schizophrenia [122]. However, the genetic data available so far are fragmented to fully validate the associations between the polymorphic GRM3 gene and schizophrenia. A better understanding of the genetic and epigenetic mechanisms that regulate the level of expression and function of mGluR2 and mGluR3 in schizophrenia brain will not only continue a fascinating new chapter in neurobiology and molecular psychiatry, but might also ultimately lead to the identification of entirely new classes of antipsychotic drugs.

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Fig. 1.

This schematic presents a model for the neurotransmitter receptors and cellular subtypes implicated in the mechanism of action of metabotropic glutamate antipsychotics. The mGluR2 and the 5-HT_{2A} co-localize and form a receptor heterocomplex in cortical pyramidal neurons. The mGluR2, and not the mGluR3, is responsible for the antipsychotic-like effects induced by mGluR2/3 agonists in mouse models of schizophrenia. All atypical antipsychotics have in common a high affinity for the 5-HT_{2A} receptor, and a lower affinity for dopaminergic receptors. Further investigation is needed to understand the role of the 5-HT_{2A}-mGluR2 complex in the mechanism of action of atypical and glutamate antipsychotics, in addition to the cellular signaling pathways and neuronal circuits responsible for the antipsychotic effects. For the purpose of clarity, not all the neurotransmitter receptors implicated in schizophrenia are shown