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The role of group I metabotropic glutamate receptors in schizophrenia

Review Article

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Summary. It has been proposed that glutamatergic transmission, in particular NMDA receptor function, might be altered in schizophrenia. This hypothesis is mainly based on the observation that uncompetitive NMDA receptor antagonists, e.g. phencyclidine, evoke psychotic symptoms in healthy subjects, whereas agonists interacting at the glycine site of the NMDA receptor complex, e.g. glycine or D-serine, administered jointly with typical neuroleptics, can alleviate schizophrenic symptoms. The function of NMDA receptors may be modulated by group I mGluRs (mGluR1 and mGluR5), which have also been shown to be altered in schizophrenia. In rodents, mGluR5 antagonists, but not mGluR1 ones, potentiate the locomotor activity and the deficit of prepulse inhibition (PPI) induced by uncompetitive NMDA receptor antagonists. These antagonists (of either type) administered alone are not active in the above tests. Hence, antagonists of mGluR1 and mGluR5 may evoke different effects on the NMDA receptor antagonists-induced behavior and, possibly, on schizophrenic symptoms.

Keywords: NMDA receptors – mGluR1 – mGluR5 – Prepulse inhibition – Locomotor activity – Schizophrenia

Introduction

Schizophrenia is a chronic mental disorder which affects nearly 1% of the world population. Disturbances in dopaminergic and glutamatergic transmission have been implicated in the pathological mechanism of this disease (Ellison, 1994; Meador-Woodruff and Healy, 2000; Seeman, 1992). Glutamate regulates neuronal activity via two types of receptors: inonotropic and metabotropic glutamate receptors (mGluR). There are three types of ionotropic glutamate receptor: N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) and kainate, whereas there are eight known subtypes of mGluRs, which are categorized into three groups (Parsons et al., 1998; Schoepp et al., 1999). Group I mGluRs (mGluR1 and mGluR5) are coupled to inositol phosphate hydrolysis, whereas group II (mGluR2/3) and group III (mGluR4/6/7/8) are negatively linked to adenylate cyclase (Parsons et al., 1998; Schoepp et al., 1999).

The involvement of glutamatergic transmission in schizophrenia is supported by the observation that phencyclidine (PCP) and ketamine, both uncompetitive NMDA receptor antagonists, induce schizophrenic symptoms in healthy subjects and exacerbate existing psychoses in schizophrenic patients (Krystal et al., 1994; Luby et al., 1959). PCP and ketamine have been shown to trigger both positive and negative symptoms as well as to induce cognitive impairments (Krystal et al., 1994; Luby et al., 1959; Malhotra et al., 1997). Atypical neuroleptics such as clozapine alleviate psychotic symptoms evoked by ketamine (Malhotra et al., 1997), whereas combined administration of typical neuroleptics with NMDA receptor glycine site agonists, such as glycine or D-serine, improves schizophrenic symptoms (Javitt et al., 1994; Tsai et al., 1998). Additionally, alterations in expression of NMDA receptors have been found in cerebral cortex, hippocampus and thalamus of schizophrenic patients (Meador-Woodruff and Healy, 2000). Based on these observations, it has been proposed that glutamatergic transmission, and in particular NMDA receptor function, may be disrupted in schizophrenia.

Interestingly, the function of NMDA receptors can be modulated by group I mGluRs and it has been proposed that these receptors, and in particular mGluR5 may also contribute to schizophrenia. For instance, genetic linkage

studies suggest the involvement of mGluR5 in this disease (Devon et al., 2001) and increased mGluR5 mRNA levels and mGluR1 protein expression have been found in prefrontal cortex of schizophrenic patients (Gupta et al., 2005; Ohnuma et al., 1998). Furthermore, RGS4, a regulator of G-protein signalling which inhibits signal transduction by the mGluR1 and mGluR5, has recently been implicated in this disease (Chowdari et al., 2002; Saugstad et al., 1998; Williams et al., 2004). Thus, it has been proposed that group I mGluRs might play a role in pathophysiology of schizophrenia.

The role of mGluR5 in animal model relevant for schizophrenia

MGluR5 are widely distributed in the central nervous system. They are enriched in the striatum, nucleus accumbens, olfactory tubercle, hippocampus and cerebral cortex (Kerner et al., 1997; Spooren et al., 2003). In several brain regions the distribution of mGluR5 and NMDA receptors overlaps (Laurie and Seeburg, 1994; Spooren et al., 2003), and it has been reported that mGluR5 and NMDA receptors can be physically connected via chains of anchoring proteins, including the PSD95, shank and Homer proteins (Tu et al., 1999). Moreover, stimulation of mGluR5 enhances NMDA receptor function in brain regions implicated in schizophrenia, including the cerebral cortex, hippocampus and striatum (Attucci et al., 2001; Benquet et al., 2002; Doherty et al., 1997; Mannaioni et al., 2001; Pisani et al., 2001). Interestingly, NMDA receptors may also reciprocally regulate function of mGluR5. It has been shown that NMDA at low concentrations potentiates the function of mGluR5, whereas at high concentrations, NMDA inhibits the response to mGluR5 activation (Alagarsamy et al., 1999, 2002). Changes in activity of one receptor could therefore potentially affect the function of the other. Thus, the effects of mGluR5 ligands (antagonists) either alone or in combination with uncompetitive NMDA receptor antagonists have been tested in animal models relevant for schizophrenia.

Since uncompetitive NMDA receptor antagonists induce psychotic symptoms in humans, PCP, (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate ((+)MK-801) and ketamine have been used to model schizophrenia symptoms in animals. For example, uncompetitive NMDA receptor antagonists increase locomotor activity and induce stereotypy in animals (Danysz et al., 1994; Homayoun et al., 2004; Sams-Dodd, 1996). It has been proposed that such behaviors may correspond to the positive symptoms of schizophrenia (Chartoff et al., 2005; Sams-Dodd, 1996; Takahata and Moghaddam, 2003). Previously, it has been found that locomotor activity was unaltered in mGluR5 knockout mice (Chiamulera et al., 2001; Lu et al., 1997). In agreement with this, mGluR5 antagonists do not enhance locomotor activity or induce stereotypy in rats (Henry et al., 2002; Homayoun et al., 2004; Kinney et al., 2003). However, mGluR5 antagonists may act in a cooperative manner with uncompetitive NMDA receptor antagonists to produce such behavioral impairment. The mGluR5 antagonist (2-methyl-6-(phenylethynyl)pyridine) MPEP has been found to potentiate locomotor activity and stereotypy evoked by PCP or MK-801 in rats and mice (Henry et al., 2002; Homayoun and Moghaddam, 2005; Homayoun et al., 2004; Kinney et al., 2003; Pietraszek et al., 2004) and our most recent study supports those findings by showing that the more potent and selective antagonist of mGluR5, MTEP also enhanced MK-801-induced locomotor activity in rats (Pietraszek et al., 2005).

Uncompetitive NMDA receptor antagonists also induce sensorimotor gating deficits as reflected by reduced prepulse inhibition (PPI) (Henry et al., 2002; Kinney et al., 2003). In the PPI model, the presentation of a subthreshold stimulus (prepulse) shortly before an intense startling-eliciting stimulus (pulse) results in attenuation of the startle response. The main advantage of this model is that PPI can also be measured in humans and deficit of PPI has been reported in schizophrenic patients (Braff et al., 2001). Impaired PPI has also been found in mGluR5 knockout mice (Brody et al., 2004a, b; Kinney et al., 2003). Moreover, it has recently been suggested that a deficit in mGluR5-PLC signaling may be associated with decreased PPI in C57BL/6J mice (Grottick et al., 2005). All the above studies suggest that mGluR5 are involved in regulation of PPI and their hypofunction may contribute to the deficit of PPI observed in schizophrenic patients. However, this notion is not supported by other findings. Acute treatment with clozapine did not improve disruption of PPI in mGluR5 knockout mice, although this neuroleptic has been shown to reverse the PPI deficit induced by uncompetitive NMDA receptor antagonists (Brody et al., 2004a). Furthermore, the uncompetitive mGluR5 antagonist MPEP did not impair PPI in mice and rats (Brody and Geyer, 2004; Henry et al., 2002; Kinney et al., 2003). Likewise, our study revealed that neither acute (Pietraszek et al., 2005) nor subchronic (5 days) treatment with MTEP (5 mg/kg) affected PPI in rats (unpublished), which suggests that the PPI deficit observed in mGluR5 knockout mice might be linked to developmental processes. However, it is important to note that acute treatment with

mGluR5 antagonists did significantly potentiate both PCP- and MK-801-induced PPI disruption (Henry et al., 2002; Kinney et al., 2003; Pietraszek et al., 2005). Overall, those studies suggest that changes in mGluR5 function are neither sufficient nor crucial for induction of psychotic symptoms, but may cooperate with NMDA receptors in producing such effects.

A recent study showed that in awake rats, MK-801 increased prefrontal cortex (PFC) firing activity and this effect was enhanced by MPEP (Homayoun and Moghaddam, 2005). Since disturbed PFC function has been correlated with stereotypy in animals, this may be the mechanism by which mGluR5 and NMDA receptor antagonists interact to produce motor impairment (Homayoun and Moghaddam, 2005). Along with the hippocampus and amygdala, the PFC has been suggested to play an important role in the PPI-disruptive effects of NMDA receptor antagonists (Bakshi and Geyer, 1998; Schwabe and Koch, 2004). Moreover, the PFC is a key brain region involved in regulation of working memory (Castner et al., 2004; Moghaddam et al., 1997), a deficit of which has been observed in schizophrenic patients (Spindler et al., 1997) as well as in humans and animals treated with uncompetitive NMDA receptor antagonists (Homayoun et al., 2004; Krystal et al., 2005; Moghaddam et al., 1997). Recently, MPEP has also been found to impair working memory (as assessed by spontaneous alternation tasks) and potentiated such deficits produced by MK-801 (Homayoun et al., 2004).

Other studies revealed that in mGluR5 knockout mice, NMDA-dependent long-term potentiation (LTP) is reduced in the CA1 and dentate gyrus of the hippocampus (Jia et al., 1998; Lu et al., 1997). Moreover, such mice show deficits in the Morris water maze task (Lu et al., 1997). Intracerebroventricular MPEP administration has also been shown to impair LTP in the CA1 and dentate gyrus of the hippocampus, as well as to induce deficits in working and reference memory performance (Manahan-Vaughan and Braunewell, 2005; Naie and Manahan-Vaughan, 2004). However, other studies did not show a disruptive effect of MPEP on cognitive function (Ballard et al., 2005; Campbell et al., 2004; Petersen et al., 2002), but it has been demonstrated that this compound enhances learning and memory impairment evoked by PCP or MK-801 (Campbell et al., 2004; Homayoun et al., 2004).

Based upon the results discussed above, it has been proposed that enhancement of mGluR5 function might produce antipsychotic effects. Indeed, recent studies have found that the mGluR5 positive modulator 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) reverses locomotor activity and deficit of PPI evoked by amphetamine in rodents (Kinney et al., 2005; Lindsley et al., 2004). However, it is noteworthy that the mGluR5 antagonist MPEP has also been found to diminish amphetamine-induced locomotor activity in mice and rats (McGeehan et al., 2004; Pietraszek et al., 2004). Likewise, in unilateral 6-OHDA-lesioned animals, both MPEP and MTEP inhibit rotational response evoked by direct and indirect DA agonists, which suggests antidopaminergic properties of mGluR5 antagonists (Dekundy et al., 2004; Spooren et al., 2000). Further testing of the effects of mGluR5 positive modulators on locomotor activity and deficit of PPI evoked by NMDA receptor antagonists is thus warranted to substantiate the antipsychotic effects of such compounds.

The role of mGluR1 in animal models relevant for schizophrenia

Studies on the role of mGluR1 in schizophrenia are very limited. As mentioned above, post-mortem studies revealed increased expression of mGluR1 in PFC of schizophrenic patients (Gupta et al., 2005). Moreover, mGluR1 knockout mice displayed sensorimotor gating deficits (Brody et al., 2003). However, the mGluR1 antagonists (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM) or (3aS,6aS)-6a-naphtalen-2-ylmethyl-5-methyliden-hexahydro-cyclopenta[c]furan-1-on (BAY 36-7620) did not affect PPI in rats, which suggest that the deficit observed in mGluR1 knockout mice might be due to compensatory changes that occur during development (Pietraszek et al., 2005; Varty et al., 2005). Other observations revealed that mGluR1 antagonists had also no effect or even decreased locomotor activity in animals (Pietraszek et al., 2005; Steckler et al., 2005; Varty et al., 2005).

In vitro studies have indicated that mGluR1 stimulation, like mGluR5, positively regulates the function of NMDA receptors in some brain regions (Benquet et al., 2002; Heidinger et al., 2002). However, our study revealed that, in contrast to mGluR5, the mGluR1 antagonist EMQMCM had no effect on MK-801-induced locomotor activity and sensorimotor gating deficits (Pietraszek et al., 2005). Also, BAY 36-7620 did not affect disruptions of PPI induced by PCP or MK-801 administration (De Vry et al., 2001). Interestingly, the latter compound has been found to reverse MK-801-induced stereotypy (De Vry et al., 2001). Furthermore, BAY 36-7620 blocked intracranial self-stimulation after MK-801 administration, which suggests anti-abuse properties of mGluR1 antagonists

(De Vry et al., 2001). In contrast, other studies found that blockade of hippocampal mGluRs and NMDA receptors produced working memory impairments in a synergistic way (Ohno and Watanabe, 1996). Moreover, working memory deficits produced by intrahippocampal administration of a group I antagonist with preferential activity at mGluR1, RS-1-aminoindan-1,5-dicarboxylic acid (AIDA), have been reduced by D-cycloserine, a partial agonist at glycine site at NMDA receptor complex (Ohno and Watanabe, 1998). However, the effect of mGluR1 antagonists on working memory was not supported by other observations. Intracerebrovertricular injection of the mGluR1 antagonist, (S)-(+)-alpha-amino-4carboxy-2-methylbenzene-acetic acid (LY367385) has been found to impair LTP in dentate gyrus of freely moving rats, and repeated injection for 10 days leaded to disruption of reference, but not working memory in an 8-arm radial maze task (Naie and Manahan-Vaughan, 2005). The latter findings are in line with the observation that systemic administration of the mGluR1 antagonist EMQMCM (2.5–5 mg/kg) had no effect on working memory tested in an 8-arm radial maze task (Gravius, unpublished).

In general, in contrast to uncompetitive NMDA receptor antagonists, neither mGluR5 nor mGluR1 antagonists alone increase locomotor activity or induce stereotypy in animals. Such compounds have no effect on PPI and only some studies have found their disruptive effects upon learning and memory. However, mGluR5 antagonists have been found to potentiate locomotor activity, stereotypy, and disruption of PPI as well as learning and memory impairments evoked by uncompetitive NMDA receptor antagonists. In contrast, mGluR1 antagonists do not modify or even reverse effects of NMDA receptor antagonists in such tests. mGluR1 and mGluR5 exhibit distinct expression pattern in the brain. For example, mGluR1 are highly expressed in cerebellum and mGluR5 are almost absent in this brain structure, whereas the opposite is true for the CA1 region of the hippocampus (Kerner et al., 1997; Shigemoto et al., 1997; Spooren et al., 2003). Moreover, mGluR1 and mGluR5 exhibit distinct localization e.g. in the striatum and cerebral cortex (Kerner et al., 1997). Like mGluR5, mGluR1 stimulation positively modulates NMDA receptor function in some brain regions e.g. in the CA3 region of the hippocampus (Benquet et al., 2002). However, in the CA1 of the hippocampus and in the striatum, mGluR5, but not mGluR1 potentiate NMDA currents (Doherty et al., 1997; Mannaioni et al., 2001; Pisani et al., 2001). Overall, the studies mentioned above, together with other in vitro and in vivo results suggest that mGluR1 and mGluR5 might play different roles in the central nervous system (Awad et al., 2000; Li and Neugebauer, 2004; Mannaioni et al., 2001; Petersen et al., 2002; Valenti et al., 2002).

Conclusions

Existing data do not indicate a role of mGluR1 in the induction of schizophrenic symptoms. In fact, like mGluR1, mGluR5 antagonists do not produce behavioral and cognitive impairments similar to that evoked by uncompetitive NMDA receptor antagonists, which suggests that hypofunction or blockade of mGluR5 may not produce psychotic symptoms in humans. However, inhibition of mGluR5 receptors potentiates the effects of NMDA receptor antagonists on cognitive and psychotic-like symptoms in animals, suggesting that similar effects could be observed in schizophrenic patients treated with mGluR5 antagonists. A potential role for mGluR5 positive modulators in the treatment of psychotic symptoms is therefore feasible.

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