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Metabotropic glutamate receptors

Editorial

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It has been estimated that ca. 50% of neurons in the brain may utilize glutamate as a neurotransmitter (McGeer et al., 1987). Glutamate, the major excitatory amino acid in the central nervous system (CNS) acts by stimulating ionotropic (iGlu) and metabotropic (mGlu) receptors (Monaghan et al., 1989) and seems to play a major role in both physiology and pathophysiology (see Kretschmer et al., 2002). Some data show that changes in ionotropic glutamate neurotransmission may be involved in a variety of neuropsychiatric disorders (Wroblewski and Danysz, 1989).

Converging lines of evidence indicate a crucial involvement of glutamate receptors in the mechanism of action of antidepressant (for review see Pałucha and Pilc, 2005), antipsychotic (Moghaddam and Adams, 1998; Moghaddam, 2004) and antiparkinsonian drugs (for review see Ossowska, 1994). The great hope that ionotropic glutamate receptor (iGlu) antagonists, mainly NMDA receptor antagonists, could be used for a variety of CNS disorders was hampered by the fact that these compounds produce pronounced adverse reactions, such as psychotomimetic effects, memory impairment and ataxia in preclinical studies (Danysz et al., 1996). One of the possible solutions to the problem of adverse effects produced by iGlu receptor antagonists is to modulate the function of the glutamatergic system by using substances acting as ligands of metabotropic glutamate (mGlu) receptors.

Metabotropic glutamate receptors are members of a novel class of the C family of G protein-coupled receptors (GPCRs), involved in the modulation of CNS excitability (for review see Ossowska, 2005; Kretschmer et al., 2002). In 2005, over 800 papers were published on mGlu receptors, and this is one of the most rapidly developing topics of neuroscience. Eight different subtypes of mGlu receptors have been cloned so far ($mGlu_{1-8}$). On the basis of their sequence homology, effector coupling and pharmacology, mGlu receptors have been subdivided into three groups: group I mGlu receptors ($mGlu_1$ and $mGlu_5$), positively coupled to phospholipase C, group II mGlu receptors ($mGlu_2$ and $mGlu_3$) and group III mGlu receptors ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$), negatively coupled to adenylate cyclase (Conn and Pin, 1997; Pin and Bockaert, 1995; for review see Ossowska, 2005).

Group II and III mGlu receptors have mainly presynaptic localization (Schoepp, 2001) and may serve as autoreceptors in some brain structures (Cartmell and Schoepp, 2000; Ugolini and Bordi, 1995). It has been shown that the activation of presynaptic mGlu receptors located on glutamatergic nerve terminals causes a decrease in glutamate release, thereby inhibiting glutamatergic excitatory transmission (for review see Cartmell and Schoepp, 2000; Glaum and Miller, 1994). Hence, agents stimulating presynaptic autoreceptors (including group II and III mGlu receptors) can act as functional antagonists of the glutamatergic system (Lovinger and McCool, 1995; Manzoni et al., 1995). Stimulation of presynaptic group II and III mGlu receptors leads also to the inhibition of cAMP accumulation in the brain (Schoepp et al., 1992).

The papers included in the present chapter deal with a potential role of mGlu receptors in the action of antidepressant (Kłak et al., 2007), antiparkinsonian (Bonsi et al., 2007; Ossowska et al., 2007), and antipsychotic drugs (Pietraszek et al., 2007). The first of these papers (Kłak et al., 2007) shows that allosteric modulation of $mGlu_4$ by intraventricular injection of PHCCC may be important for antidepressant-like effects of drugs studied in the forced swimming test in rats. That paper is a continuation of previous studies of the same group of researchers who have earlier found that antagonists of group I mGlu receptors and agonists of group II or III mGlu receptors, may produce antidepressant-like effect in animal tests and models (Kłodzińska et al., 1999; Pilc et al., 2002; Tatarczyńska et al., 2002) via subtle inhibition of glutamatergic neurotransmission (Schoepp, 2001).

The main argument for a role of glutamate in schizophrenia comes from the well-known observation that phencyclidine or ketamine which are NMDA receptor antagonists induce psychoses in humans (Krystal et al., 1994; Luby et al., 1959). As a secondary effect, these drugs have been found to increase glutamate release in the prefrontal cortex (Moghaddam and Adams, 1998). Stimulation of group II mGlu receptors has already been proposed to exert anti-psychotic effects by a reversal of glutamate release and inhibition of excitatory postsynaptic currents (EPSCs) in the prefrontal cortex, induced by stimulation of 5HT2A receptors or by phencyclidine and ketamine (Gewirtz and Marek, 2000; Kłodzińska et al., 2002; Marek et al., 2000; Lorrain et al., 2003; Moghaddam and Adams, 1998). The study of Pietraszek et al. (2007) reviewed the most recent data showing that antagonists of $mGlu_5$ but not those of $mGlu_1$ may enhance behavioural disturbances like hyperactivity, deficits of sensorimotor gating or working memory elicited by NMDA receptor antagonists in rodents, which are accepted as predictive models of human psychotic symptoms. This paper discusses a potential role of mGlu receptors belonging to group I in schizophrenia and postulates the therapeutic significance of positive allosteric $mGlu_5$ modulators for the treatment of psychoses.

The two following studies review data on a potential role of mGlu receptors in Parkinson's disease, searching for targets for the therapeutic action of mGlu ligands. Two main targets are considered: the striatal cholinergic interneurons (Bonsi et al., 2007) and the GABAergic striatopallidal pathway (Ossowska et al., 2007).

It is well known that degeneration of dopaminergic nigrostriatal pathway in Parkinson's disease disturbs the balance between dopaminergic and cholinergic systems. As a result of the degeneration of the dopaminergic neurons, the striatal cholinergic interneurons have been proposed to be activated, acquiring a synchronous firing activity (Raz et al., 2001). The mGlu receptors seem to contribute to this effect. On the basis of electrophysiological studies, Bonsi et al. (2007) proposes that the interaction between $mGlu_1$ and $mGlu_5$ receptors, shaping the excitability of cholinergic interneurons, represents a novel target for a therapeutic strategy of Parkinson's disease.

The striatopallidal GABAergic pathway seems to be another target for pharmacological treatments. Several experimental studies have suggested that this pathway is overactivated in Parkinson's disease, and its activity is normalized by antiparkinsonian drugs (Gerfen et al., 1990; Wang and McGinty, 1996; Gerfen, 2000; Pinna et al., 2005). The mGlu receptors belonging to group I ($mGlu_5$ and to a smaller degree $mGlu_1$) are localized on cell bodies of these neurons in the striatum, and $mGlu_4$ on their terminals in the globus pallidus (Kerner et al., 1997; Bradley et al., 1999). The paper by Ossowska et al. (2007) reviews several studies showing that antagonists of $mGlu_5$ and $mGlu_1$ or some agonists of group III, may exert antiparkinsonian-like effects in animal models via normalization of activity of the striatopallidal pathway.

In conclusion, the papers of the present chapter provide new, exiting data about perspectives of therapeutic use of mGlu receptor ligands in different CNS disorders.

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