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An influence of ligands of metabotropic glutamate receptor subtypes on parkinsonian-like symptoms and the striatopallidal pathway in rats

Review Article

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Summary. Several data indicate that inhibition of glutamatergic transmission may be important to alleviate of parkinsonian symptoms. Therefore, the aim of the present paper is to review recent studies on the search for putative antiparkinsonian-like effects of mGluR ligands and their brain targets. In order to inhibit glutamatergic transmission, the group I mGluRs (mGluR1 and mGluR5) were blocked, and group II (mGluR2/3) or III (mGluR4/7/8) mGluRs were activated.

Systemic or intrastriatal administration of group I mGluR antagonists (mGluR5 – MPEP, MTEP; mGluR1 – AIDA) was found to inhibit parkinsonian-like symptoms (catalepsy, muscle rigidity) in rats. MPEP administered systemically and mGluR1 antagonists (AIDA, CPCCOEt, LY367385) injected intrastriatally reversed also the haloperidol-increased proenkephalin (PENK) mRNA expression in the striatopallidal pathway. Similarly, ACPT-1, a group III mGluR agonist, administered into the striatum, globus pallidus or substantia nigra inhibited the catalepsy. Intrastriatal injection of this compound reduced the striatal PENK expression induced by haloperidol. In contrast, a group II mGluR agonist (2R,4R-APDC) administered intrastriatally reduced neither PENK expression nor the above-mentioned parkinsonian-like symptoms. Moreover, a mixed mGluR8 agonist/AMPA antagonist, (R,S)-3,4-DCPG, administered systemically evoked catalepsy and enhanced both the catalepsy and PENK expression induced by haloperidol.

The results reviewed in this article seem to indicate that group I mGluR antagonists or some agonists of group III may possess antiparkinsonian properties, and point at the striatopallidal pathway as a potential target of therapeutic intervention.

Keywords: Metabotropic glutamate receptors – Antiparkinsonian-like effects – Striatum – Striatopallidal pathway – Proenkephalin mRNA

Introduction

Loss of the striatal dopamine due to degeneration of the nigrostriatal pathway is a primary cause of symptoms of Parkinson's disease (Ehringer and Hornykiewicz, 1960). However, this alteration leads to secondary disturbances affecting neuronal loops connecting the basal ganglia, thalamus and cerebral cortex. The two striatal efferent systems, an ''indirect'' and a ''direct'' pathway, oppositely regulate activity of the main basal ganglia output pathway – the GABAergic nigrothalamic projection. Whereas stimulation of the ''direct'' GABAergic striatonigral pathway directly inhibits nigrothalamic neurons, stimulation of the ''indirect' pathway activates them *via* a complex striato-pallido-subthalamo-nigral connections. The ''indirect'' pathway begins with the medium spiny striatopallidal GABAergic neurons, sending their axons to the external globus pallidus, whose activation inhibits the next link of this neuronal chain – the GABAergic pallidosubthalamic projection, which leads to disinhibition (activation) of the glutamatergic subthalamonigral neurons and activation of the GABAergic nigrothalamic pathway. Dopamine stimulates the medium spiny neurons of the striatonigral pathway *via* D1 receptors and inhibits the striatopallidal route *via* D2 receptors. Therefore, lack of dopamine in the course of Parkinson's disease has been suggested to result in an imbalance between the two above-mentioned ''indirect'' and ''direct'' pathways: activation (disinhibition) of the striatopallidal pathway and inhibition of the striatonigral one, which finally leads to an increase in activity of the GABAergic nigrothalamic pathway (Gerfen et al., 1990; Gerfen, 2000). GABA released from nigrothalamic terminals inhibits, in turn, glutamatergic thalamocortical neurons, which indirectly leads to activation

of the glutamatergic corticostriatal pathway closing the above-mentioned neuronal circuit.

Enkephalin is co-localized with GABA mainly within the striatopallidal neurons whereas substance P and dynorphin are present within the striatonigral cells (Gerfen et al., 1990; Gerfen, 2000). Gene expression of these neuropeptides seems to parallel, at least to some extent, changes in activity of the above pathways. Several animal studies have shown that a lesion of dopaminergic nigrostriatal pathway induces an activation of the striatopallidal pathway and an increase in proenkephalin (PENK) mRNA level, as well as an inhibition of the striatonigral pathway and a decrease in preprotachykinin and prodynorphin gene expression (Gerfen et al., 1990; Gerfen, 2000). Similar results regarding the striatopallidal pathway have been observed after the blockade of the striatal dopamine D2 receptors by haloperidol (a typical neuroleptic producing parkinsonism in humans) (Drew et al., 1990; Chapman and See, 1996; Grimm and See, 2000; Angulo, 1992; Sakai et al., 2001).

Several data have suggested that the striatopallidal neurons may be a potential target for therapeutic antiparkinsonian intervention. First, stimulation of dopamine D2 receptors by their agonists and the blockade of muscarinic receptors, the two well-known antiparkinsonian strategies in clinical practice, inhibit the activity of this pathway and decrease the striatal PENK expression (Gerfen et al., 1990; Wang and McGinty, 1996, 1997; Gerfen, 2000). Secondly, the blockade of adenosine A_{2A} receptors which are localized exclusively on these neurons influences this pathway in a similar way and produces antiparkinsonian effects in animals and humans (Pinna et al., 2005).

The role of glutamate in regulation of the striatopallidal pathway

Glutamate, the main stimulatory neurotransmitter in the brain, contributes also to stimulation of the striatopallidal pathway. Striatopallidal neurons are excited *via* activation of ionotropic NMDA and AMPA/kainate receptors by glutamate released from the cortico/thalamo-striatal pathways (Kita, 1996; Pisani et al., 2001b). Stimulation of these receptors increases PENK mRNA expression in the striatum, which is antagonized by their respective antagonists (Beckstead, 1995). Moreover, antagonists of NMDA receptors decreased normal and neuroleptic-enhanced expression of the neuropeptide in this structure (Sommers and Beckstead, 1992; Jolkkonen et al., 1995; Noailles et al., 1996; Leveque et al., 2000). Since systemic or intrastriatal administration of NMDA receptor antagonists has been found to inhibit parkinsonian symptoms in humans and their equivalents in animals (for review see Ossowska, 1994; Kretschmer and Schmidt, 1996; Ossowska and Konieczny, 1996; Kaur and Starr, 1997; Lorenc-Koci et al., 1998), an inhibition of a stimulatory influence of glutamate on the striatopallidal pathway may be important for antiparkinsonian effects.

A potential role of metabotropic glutamate receptors (mGluRs) in regulation of the striatopallidal pathway

Besides ionotropic receptors, glutamate acts also on the G-protein-coupled metabotropic receptors (mGluRs). The mGluRs have been classified into 3 groups: group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7, mGluR8) (for review see Ossowska, 2005). Receptors belonging to group I are excitatory, localized mainly postsynaptically at the edge of both axo-spinous and axodendritic synaptic junctions (Hanson and Smith, 1999; Hubert et al., 2001). Receptors belonging to groups II and III are mostly presynaptic. Group II mGluRs are localized in the preterminal axonal region, and on extrasynaptic membrane of axon terminals, while group III mGluRs are abundant in the active zone of the presynaptic membrane (Shigemoto et al., 1997). Activation of either group II or III receptors inhibits glutamate release from presynaptic terminals (Battaglia et al., 1997; East et al., 1995). Since group I and II mGluRs are localized perisynaptically, these receptors can be activated only when the glutamatergic synapse is overactivated and the level of the released glutamate is high enough to reach distant receptors. Therefore, such a modulatory function of the above receptors may be of special importance in diseases (e.g. Parkinson's disease), in which glutamatergic transmission seems to be abnormally increased.

Group I mGluRs (mGluR1 and mGluR5) may contribute to stimulation of the striatopallidal pathway. First, the density of mGluR5 in the striatum is one of the highest in the brain (Testa, 1994; Messenger et al., 2002). The level of mGluR1 is much lower (Testa, 1994; Messenger et al., 2002). Secondly, both these receptor subtypes are localized postsynaptically on striatal neurons: medium spiny GABAergic striatopallidal and striatonigral neurons, cholinergic interneurons and others (Messenger et al., 2002; Testa et al., 1994, 1995; Kerner et al., 1997; Tallaksen-Greene et al., 1998). Electrophysiological studies have shown that stimulation of mGluR5 but not mGluR1 potentiates the NMDA-induced membrane depolarization and inward current in striatal efferent neurons, whereas this effect disappeared in knock-out mice lacking the former

receptor (Pisani et al., 2001b). Moreover, stimulation of mGluR5 leads to an increase in the striatal proenkephalin mRNA level (Parelkar and Wang, 2003). The striatopallidal pathway is also stimulated by acetylcholine released from the striatal cholinergic interneurons (Wang and McGinty, 1996) which are activated by both mGluR1 and mGluR5 (Bell et al., 2002; Pisani et al., 2001a, 2003; Marti et al., 2001).

As mentioned above, group II and III mGluRs are predominantly presynaptic receptors which inhibit glutamate-induced neuronal excitation. In the striatum, these receptors are localized mainly presynaptically at the corticostriatal terminals (Petralia et al., 1996; Bradley et al., 1999b). They have been found to inhibit glutamate release in the striatum (East et al., 1995; Battaglia et al., 1997) and to diminish excitatory postsynaptic currents/potentials induced by stimulation of afferents of this structure and recorded in the medium spiny neurons (Lovinger and McCool, 1995; Pisani et al., 1997; Picconi et al., 2002). The stimulation of group II but not III mGluRs reduces additionally excitability of cholinergic interneurons (Lovinger et al., 1995; Pisani et al., 2003) and acetylcholine release (Pisani et al., 2002). These data may suggest an indirect inhibitory influence of these receptors on the activity of the striatopallidal pathway, *via* a decrease in glutamate release from the corticostriatal and/or thalamostriatal terminals. Moreover, agonists of group III mGluRs diminish GABAergic inhibitory transmission in the external globus pallidus acting at the level of striatopallidal terminals (Marino et al., 2003; Valenti et al., 2003). The contribution of individual receptor subtypes of group II and III to final effects produced by their agonists is difficult to establish, because of poor selectivity of these compounds. However, several data seem to indicate that mGluR4 is the main receptor responsible for inhibition of GABAergic transmission in the globus pallidus (Bradley et al., 1999b, c; Marino et al., 2003; Valenti et al., 2003). In contrast, mGluR7 is the most abundant group III receptor on corticostriatal terminals (Bradely et al., 1999b; Messenger et al., 2002) and, therefore, it is the most probable modulator of glutamate release in this structure.

Influence of metabotropic receptor ligands on the catalepsy, muscle rigidity and proenkephalin mRNA expression in rats

The aim of the present work is to review our attempts to elucidate whether the striatopallidal pathway may be involved in antiparkinsonian effects of mGluR ligands. To this end, we examined an influence of mGluR1 and mGluR5 antagonists, as well as group II and III mGluR agonists on parkinsonian-like symptoms and PENK mRNA expression in the striatum of animals. For our studies we used: (1) mGluR1 antagonists – RS-1-aminoindan-1,5-dicarboxylic acid (AIDA), 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate (CPCCOEt) and (S)-(+)-α-amino-4-carboxy-2-m ethylbenzeneacetic acid (LY 367385), (2) mGluR5 antagonists – 2-methyl-6-(phenylethynyl)pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP), (3) a group II mGluR agonist – (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), (4) group III mGluR agonists – (R,S)-3,4-dicarboxyphenylglycine [(R,S)-3,4-DCPG] and (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-1).

Experimental models

Parkinsonian-like symptoms were induced by haloperidol administration. As it has already been described (Lorenc-Koci et al., 1996), haloperidol induces muscle rigidity, measured as an increased muscle resistance of rats' hind leg, developed in response to its passive flexion and extension in the ankle joint. The haloperidol-induced muscle rigidity is related to an increase in the EMG activity of antagonistic muscles of that joint: the gastrocnemius and tibialis anterior muscles, measured before, during and after each movement (flexion and extension) (Lorenc-Koci et al., 1996). Haloperidol is also well known to induce catalepsy in rodents which is characterized by an inability of an animal to change an uncomfortable position, imposed by an experimenter.

The muscle rigidity induced by haloperidol seems to be a good model of parkinsonian muscle rigidity since it shows some similarities to muscle rigidity in parkinsonian patients (Lee, 1989; Lorenc-Koci et al., 1996) and is antagonized by antiparkinsonian drugs (Lorenc-Koci and Wolfarth, 1999; Wardas et al., 2001). This phenomenon has been suggested to be mostly dependent on the enhanced, electromyographically recorded, activity of polysynaptic spino-supraspinal reflexes involving motor areas of the cerebral cortex (Lorenc-Koci et al., 1996). In contrast, the catalepsy induced by haloperidol, which is a model of parkinsonian akinesia, seems to be a much more complex phenomenon. Cataleptic animals not only exhibit exaggerated reflex reactions necessary to maintain postural stability but they are unable to actively challenge stable static equilibrium and to initiate phasic locomotor movements (De Ryck et al., 1980). This may suggest that, similarly to the parkinsonian akinesia (Brown and Jahanshahi, 1996), deficits of motivation,

cognition and/or somatosensory orientation contribute to this phenomenon.

Haloperidol administered acutely or subchronically at higher doses increases the proenkephalin expression in the striatum (Ossowska et al., 2003, 2004; Wardas et al., 2003) which seems to reflect the striatopallidal pathway activation (Drew et al., 1990; Chapman and See, 1996; Grimm and See, 2000).

Antagonists of mGluR5

Two non-competitive mGluR5 antagonists, MPEP and MTEP, which bind to this receptor at nanomolar concentrations and penetrate well the blood–brain barrier (Consford et al., 2003b) were used for our studies.

First we found that MPEP administered ip at doses of 5–10 mg/kg decreased both the muscle tone and EMG reflex activity of the gastrocnemius and tibialis anterior muscles increased by haloperidol (1 mg/kg) (Ossowska et al., 2001). MPEP (5 mg/kg) injected alone did not produce myorelaxation (Ossowska et al., 2001). MPEP (5 and 10 mg/kg) significantly decreased also the catalepsy induced by this neuroleptic (Ossowska et al., 2001).

MPEP (10 mg/kg ip) administered 6 times at 1.5 h intervals inhibited the haloperidol-increased PENK mRNA expression in the ventral region of the rostral striatum and in both the dorsal and ventral parts of the central striatum. Repeated treatments with MPEP alone did not influence the PENK mRNA expression in any region of that structure (Wardas et al., 2003).

The above results suggest that the mGluR5 blockade may normalize function of the striatopallidal pathway and that this process may be important for antiparkinsonian effects. They are in an agreement with other studies which have shown that MPEP counteracts PENK expression enhanced by another dopamine D2 receptor antagonist, eticlopride (Parelkar and Wang, 2003). Furthermore, some antiparkinsonian-like effects of this compound have also been reported by others. Spooren et al. (2000) described ipsilateral rotations after administration of this compound in rats unilaterally lesioned with 6-OHDA. Breysse and co-workers (2002, 2003) and Turle-Lorenzo and co-workers (2005) found that chronic but not acute treatment with this compound given alone or in a combination with NMDA receptor antagonist, reversed akinetic deficits induced by a bilateral lesion of dopaminergic neurons. However, the latter group of authors did not find any effect of MPEP on the haloperidol-induced catalepsy (Breysse et al., 2002).

The striatopallidal pathway does not seem to be the only target for therapeutic action of MPEP. According to Breysse et al. (2003) chronic MPEP administration reverses metabolic activation of the subthalamic nucleus and substantia nigra pars reticulata induced by a partial lesion of the dopaminergic pathway. Although the above effect of MPEP may be secondary to its influence on the striatopallidal pathway, a direct effect of this compound on these structures cannot be excluded since mGluR5 has been found to contribute to their neuronal excitation (Awad et al., 2000; Marino et al., 2002).

Recent studies have shown that MPEP is not an absolutely selective compound and at higher concentrations, it blocks NMDA receptors [20–200 μM (O'Leary et al., 2000)], allosterically modulates mGluR4 receptors [50–100 μM (Mathiesen et al., 2003)], inhibits norepinephrine transporter [$Ki = 234$ nM (Heidbreder et al., 2003)] and MAO_A [$IC_{50} = 8$ μM (Cosford et al., 2003b)]. Moreover, MPEP administered systemically at a dose of 3 mg/kg has been reported to reach submicromolar concentration in the brain [0.83 μM (Cosford et al., 2003b)]. The latter finding suggests that the doses of this compound which produced antiparkinsonian-like effects seemed to be sufficient to influence at least norepinephrine transporter in the brain.

Therefore, the question emerged whether the blockade of mGluR5 is actually responsible for antiparkinsonian effects of this compound or other mechanisms may also contribute to them. The latter possibility seems feasible since several previous experimental studies have indicated that inhibition of glutamatergic transmission by the blockade of postsynaptic NMDA receptors (for review see Ossowska, 1994) or stimulation of presynatic group III mGluRs (MacInnes et al., 2003) decreases parkinsonian symptoms in humans and/or in animal models. Similar effects may also result from inhibition of norepinephrine transporter or MAO_A which enhances noradrenergic transmission, and in this way may decrease parkinsonian symptoms (Carlsson et al., 1991).

To solve the above-mentioned problem, we administered another non-competitive antagonist of mGluR5, MTEP. This compound seems to be superior to MPEP in respect of specificity and bioavailability (Cosford et al., 2003a, b). MTEP does not influence mGluR2, mGluR7, NMDA, AMPA or kainate receptors, and inhibits MAO_A at a concentration 3 times higher than MPEP (Cosford et al., 2003b).

MTEP administered in rats inhibited both the haloperidol-induced muscle rigidity (increased muscle tone and EMG reflex activity) and catalepsy which substantiated significance of mGluR5 to antiparkinsonian-like action (Ossowska et al., 2005). However, some differences

between properties of this compound and those of MPEP were discovered which may suggest the presence of some additional mechanisms involved in the effects of the latter compound. First, an influence of MTEP on the haloperidol-induced muscle rigidity showed U-shaped dose-dependence. This compound administered at lower doses (0.5–3 mg/kg ip) decreased the haloperidol-induced muscle rigidity, however, the dose of 1 mg/kg was the most efficacious and its effect lasted the longest. The doses of 0.5 and 3 mg/kg were less effective and their action was shorter, whereas the dose of 5 mg/kg was completely ineffective. MTEP doses ranging between 0.5–3 mg/kg ip reversed the haloperidol-increased EMG activity in both muscles during both movements (Ossowska et al., 2005).

In contrast, the doses of MTEP which inhibited the catalepsy induced by haloperidol were ca. 5 times higher (3–5 mg/kg ip) than those necessary to alleviate muscle rigidity (Ossowska et al., 2005). The difference between anticataleptic and anti-rigor doses of MTEP differentiates this compound from MPEP, which was equally potent in inhibiting both symptoms.

The reason of various susceptibility of the haloperidol-induced catalepsy and muscle rigidity to MTEP is unknown. It may be speculated that inhibition of such a complex phenomenon like catalepsy requires the blockade of larger number of mGluR5 receptors at different levels of motor and non-motor neuronal circuits. In fact, the doses of MTEP which induce anti-rigor effects have been reported to occupy 50% of mGluR5 in the rat brain [$ED_{50} = 1.1$ mg/kg ip (Anderson et al., 2003)] while the strongest anticataleptic dose used (5 mg/kg ip) produces their full occupancy (Anderson et al., 2003). Moreover, a U-shaped dose-dependence and a loss of ability of higher doses of MTEP to reverse muscle rigidity may be due to occupation of receptors which play an opposite role in regulation of the muscle tone. Although such antagonistic mechanisms may operate at different levels of the central nervous system, the striatum may be one of the structures involved. In fact, our previous studies have shown that the blockade of NMDA receptors localized in the rostral part of this structure inhibits the muscle rigidity induced by haloperidol, while inhibition of these receptors in its intermediate-caudal region induces muscle rigidity (Ossowska and Konieczny, 1996). Since NMDA receptors in the striatum are known to be positively modulated by mGluR5 (Pisani et al., 2001b), a similar regional role of both types of receptors in the regulation of the muscle tone may be supposed.

Antagonists of mGluR1

Three mGluR1 antagonists: AIDA, CPCCOEt and LY 367385 were administered bilaterally into the rostral region of the striatum in rats (Ossowska et al., 2002, 2003; Wardas et al., 2003).

AIDA injected at a dose of 15 μg/0.5 μl significantly inhibited the muscle rigidity induced by haloperidol, and given alone produced myorelaxation (Ossowska et al., 2002). AIDA at doses of 7.5–15 μg/0.5 μl inhibited also the haloperidol-induced catalepsy (Ossowska et al., 2003).

AIDA (15 μg/0.5 μl), LY 367385 (5 μg/0.5 μl) or CPCCOEt (2.5 μg/0.5 μl) injected bilaterally 3 times into the rostral striatum counteracted the haloperidol-increased striatal PENK expression. Effects of LY 367385 and CPCCOEt were stronger than that of AIDA and encompassed the whole rostral and central striatal regions. None of these compounds given alone influenced PENK mRNA expression (Ossowska et al., 2003; Wardas et al., 2003).

The above results may suggest that not only mGluR5 but also striatal mGluR1 may be involved in antiparkinsonian effects and modulation of the striatopallidal pathway. However, some contribution of the mGluR5 blockade to the effects of the above antagonists cannot be excluded.

AIDA is a low potency mGluR1 antagonist which at micromolar concentrations selectively blocks these receptors; however, at concentrations higher than 1 mM, it also weakly blocks the cloned mGluR5 (Moroni et al., 1997). Similarly, LY 367385 and CPCCOEt at concentrations lower than 100 μM are potent and highly selective mGluR1 antagonists (Annoura et al., 1996; Clark et al., 1997; Litschig et al., 1999), but at higher ones [LY 367385 > 100 μM (Clark et al., 1997), CPCCOEt ~100 μM (Annoura et al., 1996), or ~1 mM (Casabona et al., 1997)], they may also block mGluR5. In our study, all compounds were injected at millimolar concentrations (AIDA – 68 mM = 7.5 μg/0.5 μl, 135 mM = 15 μg/0.5 μl, CPCCOEt – 20 mM = 2.5 μg/0.5 μl, LY 367385 40 mM = 5 μg/0.5 μl) (Ossowska et al., 2002, 2003; Wardas et al., 2003). Although the exact concentrations of these compounds in the striatal tissue surrounding the cannula tip were not estimated, earlier studies using labeled dopamine suggest that they could be much lower, amounting to 1–10% of their initial values at the most (Wofson and Brown, 1983). As a final result, the concentrations of all these mGluR1 antagonists could have been at the border of their selectivity towards mGluR1 receptors. Therefore, a contribution of the mGluR5 blockade to the above-mentioned antiparkinsonian-like effects of AIDA and to the inhibitory influence of all mGluR1 antagonists on PENK

expression cannot be excluded. However, AIDA-induced myorelaxation (Ossowska et al., 2002) was the most probably related to the mGluR1 blockade since such an effect was not observed after mGluR5 antagonists (Ossowska et al., 2001, 2005). Further studies are necessary to clearly differentiate between the contribution of mGluR1 and mGluR5 to antiparkinsonian action.

Agonists of group II mGluRs

2R,4R-APDC (7.5–15 μg/0.5 μl) injected into the rostral region of the striatum influenced neither the catalepsy nor muscle rigidity induced by haloperidol (Ossowska et al., 2002). This compound (3 × 15 μg/0.5 μl) did not affect the haloperidol-increased PENK mRNA expression and normal level of this neuropeptide, either (Wardas et al., 2003).

Earlier studies showed that other group II mGluR agonists might possess antiparkinsonian properties. LY 354740, a systemically active agonist of these receptors, and DCG-IV administered intraventricularly reduced the haloperidol-induced muscle rigidity and catalepsy (Konieczny et al., 1998; Bradley et al., 2000), or the reserpine-induced akinesia (Dawson et al., 2000). However, intrastriatal injections of another group II agonist, L-CCG-I did not reverse the haloperidol-induced deficits (Kronthaler and Schmidt, 2000). The lack of any influence of 2R,4R-APDC or L-CCG-I administered intrastriatally on parkinsonian-like symptoms and PENK expression in rats suggests that the striatum is not the target for potential antiparkinsonian action of group II agonists.

These results are surprising since inhibitory action of group II mGluRs on the striatal glutamatergic transmission has been well documented (Battaglia et al., 1997; East et al., 1995). However, since this group of receptors is localized perisynaptically, they are activated only when the terminal is overstimulated and synaptic level of glutamate is excessively elevated. It is possible that haloperidol administered acutely or subchronically does not increase the extracellular level of glutamate to the level high enough to reach distant receptors (Daly and Moghaddam, 1993). Furthermore, antiparkinsonian-like effects of group II mGluR agonists administered either systemically or intraventricularly (Konieczny et al., 1998; Bradley et al., 2000; Dawson et al., 2000) may be related rather to their ability to activate receptors localized at the subthalamonigral terminals which reduces the glutamate-induced overstimulation of the nigral neurons (Bradley et al., 2000). This view is further supported by the finding that DCG-IV administered directly into the substantia nigra pars reticulata decreases the reserpine-induced akinesia (Dawson et al., 2000).

Agonists of group III mGluRs

We administered two group III mGluR agonists: (R,S)-3,4-dicarboxyphenylglycine [(R,S)-3,4-DCPG] (Ossowska et al., 2004) and ACPT-1 (unpublished). (R,S)-3,4-DCPG is a mixed mGluR8 agonist and AMPA receptor antagonist. AMPA antagonistic activity of this agent is attributed to its R isomer (Thomas et al., 1997) while S isomer is responsible for mGluR8 agonistic properties (Thomas et al., 2001). Previous studies have shown that (R,S)-3,4-DCPG is active in vivo after systemic administration (Moldrich et al., 2001). Therefore, in our study this compound was administered ip in mice. In contrast, since no information has been available about ACPT-1 penetration into the brain, this subtype-nonselective group III mGluR agonist was administered bilaterally into the striatum, globus pallidus or substantia nigra pars reticulata in rats.

(R,S)-3,4-DCPG injected in mice at a dose of 100 mg/kg strongly increased the haloperidol-induced catalepsy, and administered alone induced catalepsy by itself. (R,S)-3,4-DCPG at the above-mentioned dose did not influence striatal PENK mRNA expression in naive mice but significantly enhanced it in the ventral region of the central striatum of mice treated with haloperidol (Ossowska et al., 2004).

The above results seem to suggest that the cataleptogenic effect of (R,S)-3,4-DCPG is related to an increase in PENK mRNA expression in the striatum. However, it is not clear which glutamate receptor, AMPA or mGluR8 contributes to both above-mentioned effects. Although AMPA receptor antagonists have been shown to enhance the catalepsy induced by neuroleptics (Maj et al., 1995), these compounds evoke no catalepsy *per se* (Maj et al., 1995). Moreover, the influence of (R,S)-3,4-DCPG on the striatal PENK mRNA expression cannot be attributed to its antagonistic action on AMPA receptors since stimulation but not the blockade of these receptors increases the expression of this neuropeptide (Beckstead, 1995). Therefore, cataleptogenic effects of (R,S)-3,4-DCPG may be rather related to its mGluR8 agonistic properties.

The density of mGluR8 in the basal ganglia structures is rather low in comparison to other subtypes of group III mGluRs (Messenger et al., 2002). Its localization on specific neuronal populations or terminals in the striatum is unknown, so far. Therefore, it is difficult to explain cataleptogenic affect of (R,S)-3,4-DCPG. However, since, in general, mGluRs belonging to group III have been found

not only on glutamatergic but also on GABAergic terminals (Wittmann et al., 2001; Bradley et al., 1999b), the existence of mGluR8 on terminals of striatal GABAergic interneurons or collaterals of GABAergic medium spiny neurons cannot be excluded. If so, (R,S)-3,4-DCPG may inhibit the GABA release, and in this way activate the striatopallidal pathway (Morl et al., 2002).

In contrast to the above-mentioned agent, ACPT-1 administered intrastructurally inhibited the catalepsy induced by haloperidol (unpublished). The strongest effect of this compound was observed after intrapallidal injections, followed by the intrastriatal and intranigral ones. Furthermore, this compound injected 3 times at anticataleptic doses into the striatum reversed the haloperidol-increased striatal PENK mRNA expression, but did not influence prodynorphin mRNA expression in this structure (unpublished). These results are in agreement with some previous reports which have shown that other subtype-nonselective group III mGluR agonists: L-SOP or L-AP-4, or an mGluR4 potentiator – PHCCC, administered into the third ventricle, globus pallidus or substantia nigra pars reticulata inhibit the reserpine-induced akinesia or haloperidol-induced catalepsy in rats (Marino et al., 2003; Valenti et al., 2003; MacInnes et al., 2004).

ACPT-1 at low micromolar concentrations is an agonist of mGluR4, mGluR6 and mGluR8. In contrast, its affinity for mGluR7 is much lower (>1 mM) (Moldrich et al., 2003; F. Acher – personal communication). Since mGluR6 is localized uniquely in retina and is not present in the basal ganglia (for review see Ossowska, 2005), the anticataleptic effect of ACPT-1 could not be attributed to this receptor. The mGluR8 seems also to be excluded because of the above-described opposite effect of (R,S)-3,4-DCPG.

MGluR4 is the most probable receptor involved in the effect of ACPT-1 administered into the globus pallidus. This receptor is the most abundant in this structure and is localized mainly on the striatopallidal GABAergic terminals (Bradley et al., 1999b, c). The density of mGluR7 is much lower in this structure (Bradley et al., 1999b, c) and stimulation of mGluR8 does not influence inhibitory postsynaptic potentials (IPSP) (Valenti et al., 2003). Furthermore, the inhibitory effect of L-AP4 on IPSP in the globus pallidus was enhanced by an allosteric potentiator of mGluR4 (Marino et al., 2003) and disappeared in mGluR4 knock-out mice (Valenti et al., 2003).

In contrast, mGluR7 seems to make the biggest contribution to the anticataleptic effect of ACPT-1 injected into the striatum and substantia nigra. First, much higher doses of ACPT-1 were necessary to reverse the haloperidol-induced catalepsy after intranigral or intrastriatal injections than after intrapallidal administration. Furthermore, mGluR7 is the most abundant receptor in these structures (Bradley et al., 1999b; Kosinski et al., 1999; Messenger et al., 2002) and is localized on both the striatonigral (Kosinski et al., 1999; Bradley et al., 1999b) and subthalamonigral terminals (Bradley et al., 1999a). The inhibitory influence of this subtype of group III mGluRs on glutamate-induced excitation of nigral neurons has already been suggested by Wittmann and co-workers (2001) on the basis of high concentrations of L-AP-4 ($EC50 \sim 150\,\mu M$) necessary to inhibit excitatory postsynaptic potentials (EPSP) in this structure. However, the contribution of mGluR4 to the above-mentioned effects of ACPT-1 after its intrastriatal injections cannot be excluded since previous studies have shown that L-AP-4 inhibited EPSP in this structure at low concentrations ($\sim 0.8\,\mu M$) sufficient to influence this receptor but not mGluR7 (Pisani et al., 1997).

Conclusions

The recent studies seem to suggest that:

(1) inhibition of glutamatergic transmission by the group I mGluR (mGluR1 and mGluR5) blockade or group II or III mGluR activation induces antiparkinsonian-like effects in animal models,
(2) inhibition of activity of the striatopallidal pathway may contribute to antiparkinsonian-like effects of mGluR1 and mGluR5 antagonists or mGluR4/7 agonists,
(3) antiparkinsonian-like effects of systemic injections of some group II mGluR agonists are rather related to extrastriatal targets,
(4) stimulation of mGluR8 may exert proparkinsonian effects.

Summing up, inhibition of glutamatergic transmission at the level of both pre- and postsynaptic metabotropic glutamate receptors which leads to normalization of functioning of the striatopallidal pathway may be of value for inhibition of parkinsonian symptoms.

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