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The role of striatal metabotropic glutamate receptors in Parkinson's disease

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Summary. The primary cause of Parkinson's disease is a loss of dopamine in the corpus striatum. It has been postulated that this effect leads to disinhibition of the striopallidal pathway and secondarily, to a functional shift towards glutamatergic stimulation. The aim of the present study was to find out whether inhibition of glutamatergic transmission at a level of metabotropic glutamate receptors (mGluRs) in the striatum may alleviate parkinsonian-like symptoms in rats.

The non-competitive antagonist of receptor subtype 5 (mGluR5), MPEP (1.0–10 mg/kg ip), or the agonist of group II mGluRs, LY354,740 (5–10 mg/kg ip), reduced haloperidol-induced muscle rigidity and catalepsy. Intrastriatal injections of the mGluR1 antagonist, (RS) AIDA (7.5–15 μg/0.5 μl), but not of the agonist of group II mGluRs, 2R,4R-APDC (7.5–15 μg/0.5 μl), inhibited the muscle rigidity induced by haloperidol.

In order to search for an influence of mGluRs on the striopallidal pathway, the effect of MPEP or of the agonist of group II mGluRs, DCG-IV, on the proenkephalin (PENK) mRNA expression in the dorso-lateral striatum was examined by an in situ hybridization. Repeated MPEP (6×10 mg/kg ip) administration did not influence PENK expression in naïve rats, but diminished that increased by haloperidol. In contrast, repeated DCG-IV (3×1 nmol/4 μl icv) injections enhanced both the control and the haloperidol-increased levels of PENK expression.

The obtained results suggest that blockade of group I mGluRs, or stimulation of group II mGluRs may be important to ameliorate parkinsonian symptoms. Striatal mGluRs may contribute to at least some of these effects.

Keywords: Metabotropic glutamate receptors – Antiparkinsonian-like effects – Striatum

Introduction

The primary cause of Parkinson's disease is degeneration of dopaminergic neurons in the substantia nigra pars compacta, which results in a dramatic decrease in dopamine content in the corpus striatum. This effect triggers a number of secondary neuronal alterations which contribute to the complex mechanisms underlying parkinsonian symptoms.

Dopaminergic terminals of the nigrostriatal pathway end on medium-size spiny GABAergic neurons which form striopallidal ("indirect") and strionigral ("direct") pathways (Gerfen, 1992; for ref. see Blandini et al., 2000). It has been postulated that a loss of dopamine in the course of Parkinson's disease leads to functional imbalance between these two efferents (the "indirect" pathway is disinhibited and the "direct" one is inhibited) (Gerfen, 1992; for ref. see Blandini et al., 2000), and finally to overactivation of glutamatergic neurotransmission (Klockgether and Turski, 1989). In accordance with this view, glutamate released in excess from corticostriatal or thalamostriatal terminals activates the striopallidal GABAergic pathway, which successively leads to inhibition of pallidosubthalamic GABA-ergic neurons, activation of subthalamopallidal and subthalamonigral glutamatergic projections, and overstimulation of GABA-ergic basal ganglia outputs: the nigro- and pallidothalamic pathways (Klockgether and Turski, 1989; Gerfen, 1992; for ref. see Blandini et al., 2000).

The role of the enhanced glutamatergic function in the appearence of parkinsonian symptoms has been corroborated by the findings that the well-known antiparkinsonian drugs amantadine and memantine, are uncompetitive antagonists of N-methyl-D-aspartate (NMDA) receptors. Moreover, the newly synthetized selective and potent NMDA receptor antagonists are effective in amelioration of parkinsonian-like symptoms in animal, rodent models (for ref.

see Ossowska, 1994; Ossowska et al., 1994; Konieczny et al., 1999). However, since the most effective of these compounds produce a number of serious side-effects (Andiné et al., 1999), a search for other antiglutamatergic agents devoid of such an undesirable activity is necessary.

Ligands of metabotropic, G protein-coupled glutamate receptors (mGluRs) seem to be good candidates for new antiparkinsonian drugs. These receptors have been divided into 3 groups. Group I includes 2 receptors (mGluR1 and 5) whose stimulation activates phospolipase C and phosphoinositide hydrolysis, and increases neuronal excitability. In contrast, stimulation of group II (mGluR2 and 3) and III receptors (mGluR4, 6, 7 and 8) decreases adenylate cyclase activity, cAMP level and neuronal activity, as well as glutamate release (Nicoletti et al., 1996; cf. Schoepp et al., 1999). Therefore putative antiparkinsonian agents are sought among compounds which inhibit glutamate-induced neuronal excitation i.e. among antagonists of stimulatory (group I) receptors, or agonists of inhibitory (group II and III) receptors.

Antiparkinsonian-like effects of blockade of group I mGluRs, and activation of group II mGluRs in animal models

Putative antiparkinsonian drugs are frequently screened in different rodent models of parkinsonism. Their antiparkinsonian properties are postulated when these compounds produce rotational behavior in rats unilaterally lesioned with 6-hydroxydopamine, or when they antagonize the behavioral symptoms induced by neuroleptics or reserpine. The catalepsy or hypolocomotion induced by neuroleptics or reserpine seem to reflect parkinsonian akinesia rather than other parkinsonian symptoms. Moreover, our earlier studies postulated that neuroleptics and reserpine may model parkinsonian muscle rigidity (Lorenc-Koci et al., 1995; 1996). The muscle rigidity present in the course of Parkinson's disease is characterized by an increase in muscle resistance of a patient's extremities, estimated during their passive displacement, as well as by enhancement of the resting and reflex EMG activities in the examined muscles (Lee, 1989). We observed that haloperidol or reserpine increased both muscle resistance of a rat's hind leg, developed in response to its passive extension and flexion at the ankle joint, and the EMG activity recorded before (resting activity) and during (reflex-related activity) its passive movements (Lorenc-Koci et al., 1995; 1996). Moreover, the above-mentioned effects were inhibited by some antiparkinsonian agents (L-DOPA, pramipexol) (Lorenc-Koci and Wolfarth, 1999; Wardas et al., 2001).

Our recent studies (Konieczny et al., 1998) showed for the first time that drugs acting on mGluRs may be important to the treatment of parkinsonian muscle rigidity. We found that the selective agonist of group II mGluRs, (+)-2-aminobicyclo[3.1.0]-hexane-2,6-dicarboxylate monohydrate (LY 354,740), injected in doses of 5 and 10 mg/kg ip 60 min after haloperidol (1 mg/kg ip) administration diminished in a dose-dependent manner both muscle resistance and the EMG activity enhanced by that neuroleptic in rats (Konieczny et al., 1998). In contrast, LY 354,740 administered alone in a dose of 10 mg/kg did not affect muscle tension of rats (Konieczny et al., 1998).

In a subsequent study, Bradley et al. (2000) reported that LY 354,740 dose-dependently decreased the haloperidol-induced catalepsy, which suggested that stimulation of group II mGluRs may be important to amelioration of parkinsonian akinesia. This view was further supported by another study which showed that (2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV), another agonist of those receptors, administered intraventricularly diminished the reserpine-induced akinesia (Dawson et al., 2000).

Recent studies predicted also the role of mGluR5 blockade in antiparkinsonian effects. First, Spooren et al. (2000) reported that 2-methyl-6-(phenylethynyl)pyridine (MPEP), a selective, non-competitive antagonist of those receptors, which crosses easily the blood-brain barrier, produced ipsilateral rotations in unilaterally 6-hydroxydopamine-lesioned rats. However, the latter effect was fairly weak and MPEP inhibited the rotational behavior induced by dopaminomimetics (Spooren et al., 2000). Therefore the latter authors concluded that MPEP, either given alone or in combination with dopaminomimetics, may not have a great impact on the treatment of parkinsonian symptoms in humans.

However, our most recent study in which haloperidol was used as a model compound showed that MPEP may actually be important to amelioration of both parkinsonian akinesia and muscle rigidity (Ossowska et al., 2001). In the latter study, haloperidol was used in doses of 0.25, 0.5 and 1 mg/kg ip to induce hypolocomotion, catalepsy and muscle rigidity, respectively. Locomotor activity was estimated by an

open-field test, catalepsy – by a 9-cm cork test. As before, muscle rigidity was measured as increased resistance of a hind leg to passive extension and flexion at the ankle joint. Additionally, increases in electromyographic activity were recorded in the gastrocnemius and tibialis anterior muscles. MPEP (1.0–10 mg/kg ip) inhibited the haloperidol-induced muscle rigidity, electromyographic activity, hypolocomotion and catalepsy (Ossowska et al., 2001).

Spooren et al. (2000) reported that MPEP in doses exhibiting antiparkinsonian-like properties did not induce ataxia, nor did it increase locomotor activity in rats. Our study (Ossowska et al., 2001) supports the latter finding and also shows that this compound does not produce myorelaxation. The lack of all the above-mentioned effects suggests that MPEP may be devoid of serious side-effects and promises well for the future regarding human therapy.

The role of the subthalamo-nigral pathway in antiparkinsonian-like effects of mGluR ligands

Several brain structures may be responsible for the above-mentioned antiparkinsonian-like effects of mGluR ligands. The subthalamic nucleus and its glutamatergic efferents to the substantia nigra pars reticulata, as well as to the internal part of the globus pallidus seem to be the first candidates. An overactivity of these pathways takes place in Parkinson's disease and is generally accepted to be crucial for the appearance of parkinsonian symptoms (Klockgether and Turski, 1989; Bergman et al., 1990; cf. Ossowska, 1994; cf. Blandini et al., 2000). A possible role of group II mGluRs that are related to this system was postulated by Bradley et al. (2000) and Dawson et al. (2000). Using whole-cell-patch-clamp recordings, Bradley et al. (2000) found that LY 354,740 (which probably acts via mGluR2/3 autoreceptors localized on subthalamonigral terminals) reduced the excitation of nigral neurons induced by stimulation of the latter pathway (Bradley et al., 2000). The significance of this effect for antiparkinsonian-like properties of agonists of group II mGluRs was confirmed by a decrease in the reserpine-induced akinesia, evoked by DCG-IV administered directly into the substantia nigra pars reticulata (Dawson et al., 2000). The blockade of mGluR5 of the subthalamic nucleus also seemed important, since MPEP was found to inhibit directly the neuronal activity of that structure, increased by stimulation of group I mGluRs (Awad et al., 2000).

The role of the striatum in antiparkinsonian-like effects of mGluR ligands

MGluRs localized in the striatum are also likely to contribute to antiparkinsonian effects. Receptors belonging to groups I and II are present in the striatum. The highest expression has been found for mGluR5 which is also considerably bigger in this structure than in other basal ganglia regions (Testa et al., 1994). Striatal mGluR1 are less abundant. Receptors of group I are localized on the majority of striatal neurons (Kerner et al., 1997; Thallaksen-Greene et al., 1998; Testa et al., 1994; 1995). The expression of group II mGluRs is low to moderate in this structure, but at least some of them are localized presynaptically on glutamatergic cortico/thalamo-striatal terminals (Testa et al., 1994; Neki et al., 1996; Petralia et al., 1996). The latter receptors act as autoreceptors, since their stimulation by selective agonists decreases glutamate release in the striatum (Battaglia et al., 1997; Cozzi et al., 1997).

It has been suggested that a loss of striatal dopamine in Parkinson's disease increases stimulatory influence of glutamate, released from the cortico- and/or thalamostriatal terminals, on striatal projection neurons (Gerfen et al., 1992). In line with this view, injection of NMDA receptor antagonists into the striatum diminishes parkinsonian-like symptoms in animals (Yoshida et al., 1994; Ossowska and Konieczny, 1996; Kretschmer and Schmidt, 1996; Kaur and Starr, 1997; Lorenc-Koci et al., 1998). Similarly, a recent study has shown that (S)-4-carboxy-3-hydroxyphenylglycine ((S)-4C3HPG), a mixed group I antagonist and a group II agonist of mGluRs, administered intrastriatally counteracts the haloperidol-induced muscle rigidity in rats (Lorenc-Koci et al., 2001).

Our results (Ossowska et al., 2002) show that (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA), a potent and selective mGluR1 antagonist, injected bilaterally in doses of 7.5–15 μg/0.5 μl into the striatum or nucleus accumbens diminishes the haloperidol-induced muscle rigidity. In contrast, (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC; 7.5–15 μg/0.5 μl), a selective group II agonist, injected bilaterally into the same striatal region is ineffective (Ossowska et al., 2002). These results seem to suggest that the blockade of striatal group I mGluRs, but not stimulation of group II mGluRs in the striatum may be important to antiparkinsonian-like effects.

A question arises as to the reason of ineffectiveness of the above mentioned group II agonist towards the haloperidol-induced muscle rigidity. It may be due to the fact that acute haloperidol administration does not increase striatal extracellular glutamate level (Daly and Moghaddam, 1993; Gołembiowska, unpublished). Agonists of group II mGluRs have been found to potently inhibit glutamate release in brain structures only when it has been earlier increased by veratridine or phencyclidine (Battaglia et al., 1997; Moghaddam and Adams, 1998). They either do not influence basal extracellular levels of this amino acid, or diminish them only inperceptibly (Battaglia et al., 1997; Cozzi et al., 1997; Moghaddam and Adams, 1998). Such a differential influence of these compounds on the basal versus stimulated levels of glutamate has been explained by characteristic, perisynaptic (outside of the normal zone of the synapse) localization of group II mGluRs (Ohishi et al., 1994; Shigemoto et al., 1997), which allows activation of these receptors only when the level of glutamate in the synapse is pathologically high (Scanziani et al., 1997).

The influence of mGluR ligands on the expression of proenkephalin (PENK) in the striatum

It is well known that repeated haloperidol administration activates the striopallidal pathway which mimics a pathological mechanism working in the course of Parkinson's disease. This alteration is usually estimated by an increased expression of proenkephalin (PENK) – a neuropeptide which is co-localized with GABA in this projection (Angulo et al., 1990; Noailles et al., 1996; Mavridis and Besson, 1999). Therefore drugs that reverse the haloperidol-enhanced striatal PENK expression are predicted to exhibit antiparkinsonian properties.

The above model was also used to examine the influence of mGluR ligands on activity of the striopallidal pathway (Ossowska et al., unpublished). Haloperidol was administered in a dose of 1.5 mg/kg sc 3 times, at 3-hour intervals. MPEP (10 mg/kg ip) was injected 6 times, at 1.5-hour intervals. Rats were decapitated 2 h after the last haloperidol injection (0.5 h after the last MPEP injection). The PENK mRNA expression was estimated in the dorso-lateral striatum by an in situ hybridization. The experiment showed that repeated MPEP administration diminished the haloperidol-increased PENK expression in the region studied.

A similar experiment was carried out to determine the influence of DCG-IV, a group II agonist on the striopallidal pathway. Haloperidol (1.5 mg/kg sc) and DCG-IV (1 nmol/4 μl icv) were administered 3 times at 3-hour intervals. Each injection of DCG-IV was carried out 2 h after haloperidol. The rats were decapitated 3 h after the last haloperidol injection (1 h after the last DCG-IV injection). DCG-IV enhanced both the control and the haloperidol-increased PENK mRNA expression in the dorso-lateral striatum.

The above results support the view that the blockade of striatal group I mGluRs (mGluR5) by MPEP inhibits the pathologically activated striopallidal pathway, which may contribute to antiparkinsonian-like effects of this compound. The present study does not fully explain the involvement of group II mGluRs localized in the striatum in antiparkinsonian-like effects of agonists of these receptors. The lack of an inhibitory effect of DCG-IV on PENK expression may speak against such a role. However, it is noteworthy that DCG-IV in higher doses acts as an NMDA receptor agonist (Kwak et al., 1996), this action possibly contributing to the above-mentioned enhancement of PENK expression induced by this compound (Beckstead, 1995). Further studies with more selective agents are necessary to clarify this issue.

Conclusions

The present review of the literature data and our own results suggest that:

(1) an antiparkinsonian effect of drugs may be produced by the blockade of group I (mGluR1 and 5), or stimulation of group II (mGluR2 and/or 3) metabotropic glutamate receptors. This conclusion is based on the findings that selective ligands of these receptors, administered systemically or intracerebrally ameliorate parkinsonian-like symptoms in animals;
(2) striatal receptors belonging to group I seem to be important to the antiparkinsonian effects, since (a) intrastriatal injection of AIDA – a selective antagonist of mGluR1 – diminishes the haloperidol-induced muscle rigidity and (b) systemic administration of MPEP – a selective antagonist of mGluR5 – normalizes the activity of the striopallidal pathwy overstimulated by haloperidol;
(3) group II mGluRs in the striatum do not seem to be involved in parkinsonism, since their selective agonists administered either intrastriatally or intraventricularly

do not antagonize the haloperidol-induced muscle rigidity or the activation of the striopallidal pathway. These receptors localized in other extrastriatal regions such as, e.g., the subthalamo-nigro/pallidal system, are more likely to contribute to antiparkinsonian effects of drugs.

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