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

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Summary. The aim of the study was to examine the effect of antagonists of the NMDA receptor on the parkinsonian-like muscle rigidity in rats. Reserpine and haloperidol increased the muscle resistance of the hind foot to passive movements, as well as the reflex electromyographic (EMG) activity in the gastrocnemius and tibialis anterior muscles. MK-801 (0.32–1.28 mg/kg sc), an uncompetitive antagonist of the NMDA receptor, and L-701,324 (5–40 mg/kg ip), an antagonist of the glycine site, reduced the muscle tone and the reflex EMG activity enhanced by reserpine or haloperidol. AP-5 (2 and 5 μg/ 0.5 μl), a competitive antagonist of the NMDA receptor, and 5,7-dichlorokynurenic acid (1.0–4.5 μg/0.5 μl), the glycine site antagonist injected bilaterally into the rostral striatum, inhibited the muscle rigidity induced by haloperidol. In contrast, AP-5, injected alone bilaterally into the intermediate-caudal striatum induced muscle rigidity. The present results suggest that: (1) the inhibitory effect of the NMDA receptor antagonists on the parkinsonian-like muscle rigidity depends, at least partly, on their action on the rostral striatum; (2) the blockade of NMDA receptors in the intermediate-caudal striatum may reduce the beneficial impact of these compounds.

Keywords: Parkinsonian-like muscle rigidity – NMDA receptor antagonists – Striatum

It is generally accepted that main symptoms of Parkinson's disease (akinesia, rigidity) result from degeneration of dopaminergic nigrostriatal neurons, which leads to a loss of dopamine in the striatum. On the other hand, parkinsonian symptoms which occur during the course of neuroleptic therapy are believed to be caused by the blockade of striatal dopaminergic receptors. Recently, it has been suggested that the primary striatal dopaminergic hypofunction results in a secondary hyperactivity of glutamatergic neurotransmission. A number of authors have postulated that in Parkinson's disease at least three glutamatergic pathways are hyperactive: corticostriatal, subthalamopal-

lidal and subthalamonigral ones (for ref. see Ossowska, 1994). This concept presupposes that not only dopaminomimetics, but also antagonists of glutamatergic receptors may be beneficial to the treatment of this disease. Moreover, it has been suggested that the striatum, globus pallidus and substantia nigra pars reticulata may be responsible for their effects (for ref. see Ossowska, 1994). In fact, numerous studies which were carried out during the last few years have shown that antagonists of the NMDA receptor exhibit antiparkinsonian properties. The NMDA receptor is a heterooligomeric ionotropic receptor which is permeable mainly for calcium ions. At the NMDA receptor complex, at least a few binding sites influencing its function have been found. It has been shown that competitive and uncompetitive antagonists – channel blockers – of the NMDA receptor are effective in animal models of parkinsonian akinesia, i.e. in the neuroleptic-induced catalepsy or reserpine-induced akinesia (for ref. see Ossowska, 1994). After systemic administration, antagonists of the modulatory glycine binding site (7-chlorokynurenic acid, 5,7-dichlorokynurenic acid) which poorly penetrate into the brain did not exhibit any beneficial effects in animal models of parkinsonism (Maj et al., 1994). However after intrastriatal injections, 7-chlokynurenic acid and the partial agonist of the glycine site, R-(+)-HA-966, inhibited the neuroleptic-induced catalepsy or reserpine-induced akinesia (Carrol et al., 1995; Kretschmer et al., 1995). Moreover, some uncompetitive antagonists of the NMDA receptor, amantadine, memantine and budipine, are used to ameliorate parkinsonian symptoms in humans (for ref. see Ossowska, 1994).

In contrast to akinesia, the influence of NMDA receptor antagonists on muscle rigidity has not been thoroughly examined. It is well-known that parkinsonian rigidity, defined as an increase in the muscle resistance in response to passive movements, depends on the reflex activity. It has been found that in Parkinson's disease there occurs an increase in the amplitude of a long-latency electromyographic (EMG) stretch reflex response and a reflex EMG shortening reaction. This rise leads to an enhanced co-activation of antagonistic muscles in response to passive movements. Parkinsonian patients also have difficulty in relaxing muscles, thus showing an EMG tonic activity at rest (Lee, 1989). Animal studies have shown that the uncompetitive antagonist of the NMDA receptor complex MK-801 and the competitive antagonist of this receptor CPP inhibit the tonic EMG resting activity induced by the monoamine-depleting compound – reserpine (Klockgether and Turski, 1990). Another competitive antagonist, CGP 37849, has been found to diminish the muscle resistance enhanced by haloperidol (Maj, personal communication).

The aim of the present study was to examine the influence of antagonists of the NMDA receptor complex acting on its different binding sites on muscle rigidity in animal models of parkinsonism. The muscle rigidity of the parkinsonian type was induced by reserpine and haloperidol. Reserpine depletes dopamine in terminals of the nigrostriatal pathway, and is therefore commonly used to induce symptoms of Parkinson's disease. Haloperidol, a classic neuroleptic, blocks dopamine D2 receptors in the striatum and is used to evoke the drug-induced parkinsonism.

Methods

Mechanomyogram

Muscle tone was estimated as a resistance developed by the rat's hind foot during its passive flexion and extension in the ankle joint. The resistance was recorded with a force sensor (mechanical moment, torque). The experiment consisted of up-and-down movements of the foot (30 s apart), which flexed and extended it in the ankle joint by 25 deg with a velocity of 100 deg/s. The maximum resistance (MMGmax) of the hindlimb muscles developed in response to each up-and-down movement was estimated.

Electromyogram

Two pairs of flexible, stainless-steel wire electrodes were inserted percutaneously into two antagonistic muscles of the ankle joint – the gastrocnemius and tibialis anterior, and the EMG activity was recorded. For the sake of quantification, the EMG activity was rectified and averaged with a time constant of 20 ms for each movement. The following components were estimated: (1) the level of the EMG activity recorded before the start of each movement as a measure of the resting EMG activity; (2) the maximum amplitude measured within a period of 0–20 ms after the start of a movement, corresponding to the short-latency reflex response; (3) 3 amplitudes measured within a period of 20–340 ms, corresponding to long-latency reflex responses.

Results

Reserpine in a dose of 10 mg/kg ip, as well as haloperidol in doses of 0.5–10 mg/kg ip induced muscle rigidity. Both those drugs increased muscle resistance to a passive flexion and extension of the hind foot in the ankle joint (Lorenc-Koci et al., 1995; 1996). Both the drugs studied also increased the resting EMG activity, as well as the long-latency EMG reflex responses to movements in the gastrocnemius and tibialis anterior muscles (Lorenc-Koci et al., 1995; 1996). Reserpine additionally increased the EMG short-latency reflex activity. In contrast, haloperidol decreased the short-latency EMG reflex response in the gastrocnemius and tibialis muscles.

Systemic injections of NMDA receptor antagonists

The uncompetitive antagonist of the NMDA receptor complex dizocilpine (MK-801), in doses of 0.32–1.28 mg/kg sc, inhibited in a dose-dependent manner the muscle resistance, as well as the resting and long-latency EMG reflex activity enhanced by reserpine (10 mg/kg ip) (Ossowska et al., 1994, 1996).

The highly selective full antagonist of the glycine modulatory site of the NMDA receptor complex, which penetrates well through the blood-brain barrier, L-701,324 (Merck, Sharp and Dohme; 7-chloro-4-hydroxy-3(3-phenoxy)phenylquinoline-2-(1H)-one) administered in doses of 10–40 mg/kg ip inhibited the muscle resistance increased by haloperidol (5 mg/kg ip). A lower dose of L-701,324 (5 mg/kg ip) diminished the muscle rigidity induced by a lower dose of haloperidol (1 mg/kg ip). A dose of 2.5 mg/kg ip of L-701,324 also tended to diminish the muscle tone increased by haloperidol (1 mg/kg ip), however, this effect was insignificant.

L-701,324 in doses of 10–40 mg/kg also diminished the resting EMG activity, as well as the long-latency EMG reflex activity increased by haloperidol (5 mg/kg ip). Moreover, it either did not affect or even enhanced the inhibitory influence of haloperidol on the short-latency reflex EMG activity. L-701,324 in lower doses of 2.5–5 mg/kg also tended to decrease the resting EMG activity and the long-latency EMG reflex activity in normal control animals or in animals pretreated with haloperidol (1 mg/kg).

However, even in the lowest doses of 2.5–5 mg/kg ip, L-701,324 induced ataxia and disturbed the performance of a rotarod test in rats. Joint administration of L-701,324 (2.5–5 mg/kg ip) and haloperidol (0.5 or 1 mg/kg ip) also strongly disturbed the performance of that test.

Intrastriatal injections of NMDA receptor antagonists

5,7-dichlorokynurenic acid (DCKA) was injected bilaterally in doses of 1–4.5 μg/0.5 μl into the rostral region of the striatum. Such treatment inhibited the muscle resistance increased by haloperidol (2.5 mg/kg ip). Moreover, DCKA inhibited long-latency EMG reflex responses in the gastrocnemius muscle during a passive flexion and in the tibialis anterior during a passive extension of the foot.

(±)-2-amino-5-phosphonopentanoic acid (AP-5), a competitive antagonist of NMDA receptor – injected bilaterally (2 and 5 μg/0.5 μl) into the same region of the striatum also diminished the muscle resistance increased by haloperidol (1 mg/kg ip). However, when injected bilaterally in the same doses into the intermediate-caudal region of the striatum of rats non-pretreated with haloperidol, AP-5 *per se* induced muscle rigidity (Ossowska and Konieczny, 1996).

Conclusions

The present results seem to suggest that reserpine and haloperidol induce muscle rigidity resembling that seen in Parkinson's disease. Characteristic features of the parkinsonian-like rigidity induced by these compounds are: an increase in the muscle resistance in response to passive movements, as well as a rise in the resting EMG activity and long-latency EMG reflex responses.

The blockade of different binding sites at the NMDA receptor complex may be very important for the inhibitory effect of drugs on the parkinsonian rigidity. This antiparkinsonian action seems to be shared by both uncompetitive and competitive antagonists, as well as by antagonists of the modulatory glycine site.

The inhibitory effect of different antagonists of the NMDA receptor complex on the muscle rigidity depends, at least partly, on the blockade of NMDA receptors in the rostral region of the striatum. However, the blockade of NMDA receptors in the intermediate-caudal region of the striatum induces an opposite effect (muscle rigidity) which, in turn, may reduce the beneficial impact of NMDA receptor antagonists after their systemic administration. A search for compounds that may specifically block NMDA receptors in the rostral region of the striatum should be carried on.

A number of earlier animal experiments, as well as observations concerning humans suggest that both competitive and uncompetitive antagonists of NMDA receptors exhibit serious side-effects including psychoses, memory impairment, disturbance of motor coordination and balance, as well as vacuolisation and neuronal degeneration (for ref. see Ossowska, 1994). The present study indicates that potent antagonists of the glycine site which penetrate well the blood-brain barrier, are not devoid, either, of side-effects and may induce ataxia.

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