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Stimulation of glutamate receptors in the intermediate/caudal striatum induces contralateral turning

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Abstract

The aim of the present study was to investigate the role of striatal NMDA, kainate and AMPA receptors in the turning behaviour of rats. *N*-methyl-D-aspartate (NMDA, 500 ng/0.5 μl), kainic acid (50 ng/0.5 μl) or α-amino-3-hydroxy-5-methyl-4-isoxasole-propionic acid (AMPA, 1000 ng/0.5 μl), injected into the intermediate and caudal parts of the caudate-putamen, induced contralateral head turns and rotations. This effect was delayed or was not observed after administration of the compounds into the globus pallidus. The antagonist of non-NMDA receptors, 6,7-dinitroquinoxaline-2,3-dione (DNQX, 1000 ng/0.5 μl), antagonized the contralateral head turns and rotations induced by AMPA (1000 ng/0.5 μl) or kainic acid (50 ng/0.5 μl), and evoked per se (2000 ng/0.5 μl) the ipsilateral head turns and rotations. The NMDA receptor antagonist, (±)-2-amino-5-phosphonopentanoic acid (AP5, 1000 ng/0.5 μl), induced mainly ipsilateral head turns and rotations; when injected in a dose of 500 ng/0.5 μl, it inhibited the contralateral head turns and rotations after NMDA. The results seem to suggest that the contralateral head turns and rotations induced by stimulation of NMDA, AMPA and kainate receptors in the intermediate and caudal parts of the caudate-putamen may result from activation of the γ-aminobutyrate (GABA)-ergic strionigral pathway.

Keywords: NMDA receptor; Non-NMDA receptor; Contralateral turning; Strionigral pathway

1. Introduction

Excitatory amino acid receptors have been postulated to play an important role in Parkinson's disease, as well as in the motor behavior of animals (Riederer et al., 1992; Schmidt et al., 1992). It was found that antagonists of NMDA receptors have a beneficial effect in many experimental models of Parkinson's disease, or in models of the neuroleptic-induced parkinsonism. When injected systemically, these compounds inhibit the neuroleptic- or reserpine-induced catalepsy and akinesia (Carlsson and Carlsson, 1989a, b; Elliott et al., 1990; Klockgether and Turski, 1990; Mehta and Ticku 1990; Schmidt et al., 1991, 1992; Kretschmer et al., 1992; Verma and Kulkarni, 1992; Maj et al., 1993) as well as the reserpine-induced rigidity (Klockgether and Turski, 1990; Ossowska et al., 1994). Moreover, they enhance the antagonistic effect of l-3,4-dihydroxyphenylalanine (l-DOPA) on the reserpine-induced akinesia and rigidity (Klockgether and Turski, 1990; Maj et al., 1993) and increase the number of contralateral rotations induced by l-DOPA in 6-hydroxydopamine-lesioned rats (Morelli and Di Chiara, 1990; Löschmann et al., 1991). It has been postulated that the caudate-putamen, that receives a massive glutamatergic input from the cerebral cortex (Fonnum, 1984), is one of the structures responsible for the 'antiparkinsonian effect' of antagonists of NMDA receptors in animals (Yoshida et al., 1991, 1994;, Schmidt et al., 1992). This concept stems mainly from the finding that (±)-2-amino-5-phosphonopentanoic acid (AP5), a competitive antagonist of NMDA receptors, injected into the rostral part of the caudate-putamen, inhibits the haloperidol-induced catalepsy (Yoshida et al., 1991, 1994). In line with these results, NMDA injected into the rostral region of the caudate-putamen induces akinesia (Schmidt and Bury, 1988) and muscle rigidity (Klockgether and Turski, 1993). However, Turski et al. (1990) found that (−)-2-amino-7-phosphonoheptanoic acid

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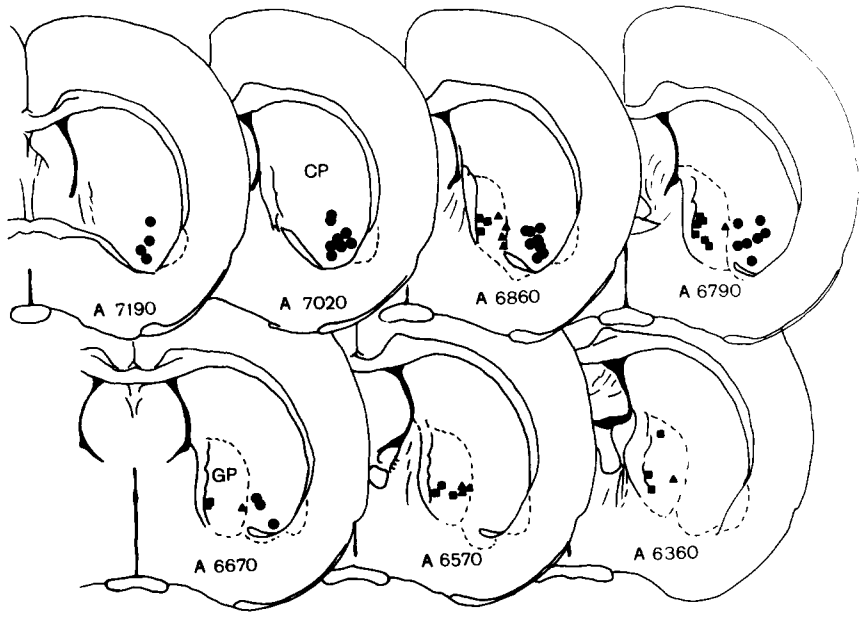


Fig. 1. Localization of cannula tips on frontal sections of the rat brain. Filled circles – cannula tips located in the ventrolateral part of the intermediate and caudal regions of the caudate-putamen (CP). Filled squares – cannula tips in the central part of the globus pallidus (GP). Filled triangles – cannula tips in the lateral part of the globus pallidus (GP). A – anterior plane, according to König and Klippel (1963).

(AP7), another competitive antagonist of NMDA receptors, injected directly into intermediate and caudal regions of the striatum, induces catalepsy and muscle rigidity, and that these symptoms are antagonized by NMDA. All the above-mentioned results suggest that NMDA receptors located in rostral and caudal regions of the caudate-putamen may play an opposite role in animal models of Parkinson's disease.

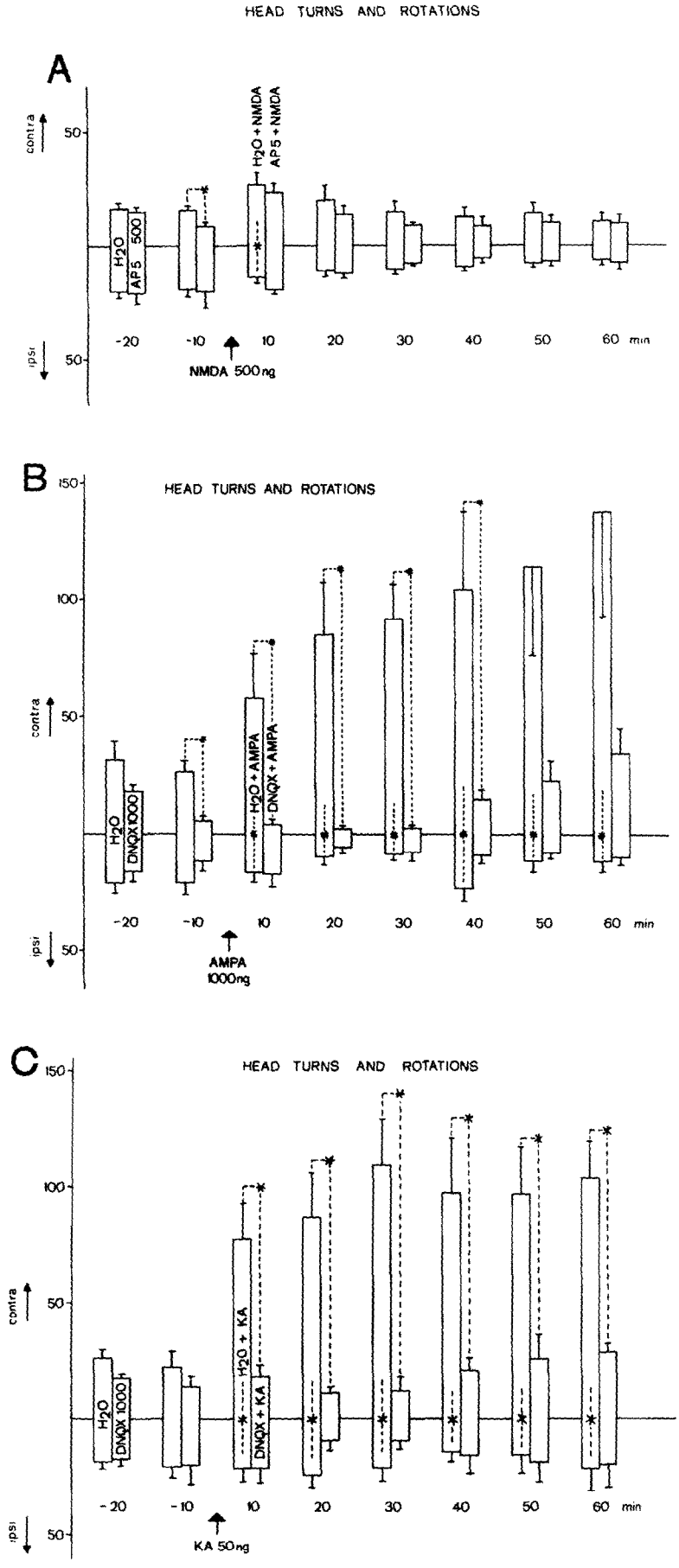
In contrast to NMDA, the role of non-NMDA receptors in parkinsonian symptoms seems to be unclear. Some authors (Klockgether et al., 1991; Löschmann et al., 1991) reported that 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(*F*)quinoxaline (NBQX), an antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors, enhances the antiparkinsonian effect of l-DOPA in reserpine- or 6-hydroxydopamine-treated rats and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys. However, other authors did not find any antiparkinsonian effect of NBQX in MPTP-treated monkeys, or even showed an increasing effect of the compound on the raclopride-induced catalepsy in rats (Luquin et al., 1993; Papa et al., 1993). Furthermore, Klockgether et al. (1991) and Klockgether and Turski (1993) did not demonstrate any involvement of non-NMDA receptors located in the rostral or caudal part of the caudate-putamen in akinesia and muscle rigidity.

In the present study we continued our previous research (Ossowska and Wolfarth, 1994) and examined the influence of agonists and antagonists of NMDA and non-NMDA receptors, injected unilaterally into the intermediate and caudal regions of the caudate-putamen, in the turning behaviour which is commonly accepted as a model for studying pathophysiologic mechanisms of Parkinson's disease.

2. Materials and methods

The experiment was performed on male Wistar rats, implanted unilaterally and chronically with stainless steel guide cannulas (0.4 mm o.d.) under pentobarbital anaesthesia (Vetbutal, Biowet, Poland). Approximately one week after the surgery, the animals were injected with drugs using an inner cannula (0.3 mm o.d.) protruding 0.6 mm from the guide cannula. The tips of the inner cannulas were aimed at the ventrolateral part of the intermediate and caudal regions of the caudate-putamen (A = 7190–6670; L = 3.4; H = −0.6 to −1.7) or into the central (A = 6860–6360; L = 2.0; H = −1.0

Fig. 2. Head turns and rotations induced by unilateral intrastriatal NMDA (A), AMPA (B) and kainic acid (KA) (C) injections. Antagonism shown by AP5 (A) and DNQX (B,C). NMDA was injected 20 min after AP5. AMPA or kainic acid was injected 20 min after DNQX (big black arrows). Doses are given as ng/0.5 μl. Ordinate – the total number of contralateral (contra) or ipsilateral (ipsi) head turns and rotations; the results are presented as the mean and S.E.M.; the number of animals: H_2O + NMDA – $n = 12$, AP5 + NMDA – $n = 6$; H_2O + AMPA – $n = 7$, DNQX + AMPA – $n = 6$, H_2O + KA – $n = 6$, DNQX + KA – $n = 6$; an asterisk denotes a statistically significant difference at $P < 0.05$ between the total number of contra- and ipsilateral head turns and rotations, or between groups.


HEAD TURNS AND ROTATIONS
A
contra
ipsi
50
H2O
AP5 500
H2O + NMDA
AP5 + NMDA
-20
-10
10
20
30
40
50
60 min
NMDA 500 ng
B
HEAD TURNS AND ROTATIONS
150
100
H2O
DNQX 1000
H2O + AMPA
DNQX + AMPA
AMPA 1000 ng
C
HEAD TURNS AND ROTATIONS
H2O + KA
DNQX + KA
KA 50 ng

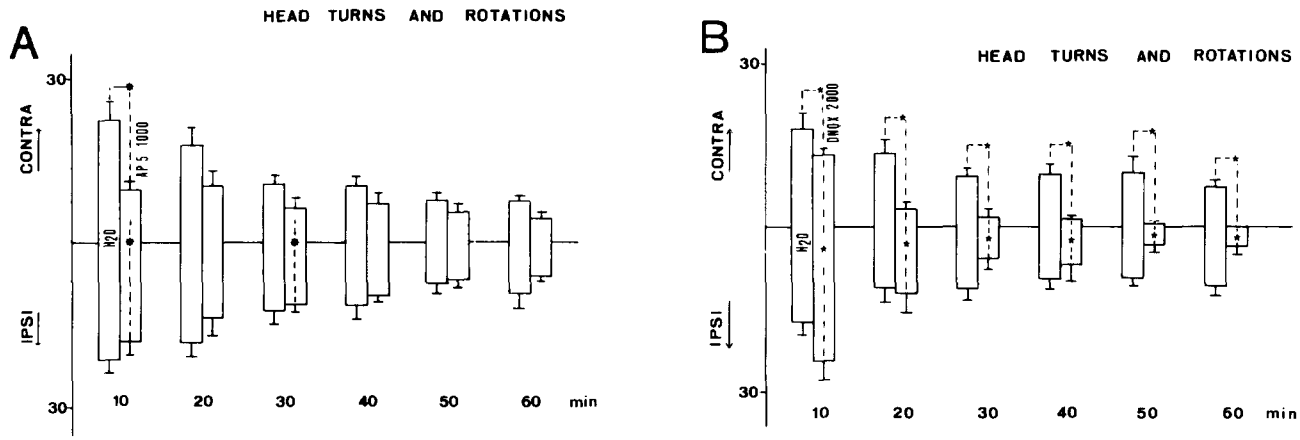


Fig. 3. Head turns and rotations induced by unilateral intrastriatal AP5 (A) and DNQX (B) injections. Doses are given in ng/0.5 μl. The number of animals: H_2O – $n = 10$, AP5 – $n = 8$, DNQX – $n = 9$. For further explanations see Fig. 2.

to −1.2) or lateral part of the globus pallidus (A = 6860–6360; L = 2.4–2.8; H = −1.0 to −1.2) using the stereotaxic atlas of König and Klippel (1963) (Fig. 1). Injection of a volume of 0.5 μl lasted 2.0 min, and the inner cannula was withdrawn 1 min after its termination.

N-Methyl-D-aspartate (NMDA, RBI, 500 ng), α-amino-3-hydroxy-5-methyl-4-isoxasole-propionic acid (AMPA, RBI, 1000 ng) and 6,7-dinitroquinoxaline-2,3-dione (DNQX, RBI, 1000 or 2000 ng) were dissolved in small amounts of 1 N NaOH, diluted with redistilled water, and the pH was balanced with 1 N HCl to a final pH of 6–7. Kainic acid (Sigma, 50 ng) and (±)-2-amino-5-phosphonopentanoic acid (AP5, RBI, 500 or 1000 ng) were dissolved in distilled water. Redistilled water was used as control injection.

As a rule, each animal was given one intrastructural injection. Two successive injections were made to one animal only when the influence of an antagonist on the effect of an agonist was examined (Fig. 2A, B and C).

The number of contralateral and ipsilateral rotations and head turns was estimated by an observer during 10-min periods. Head turns, i.e. ipsi- or contralateral head movements, were counted when an animal did not make any locomotor movements. Rotations were estimated as the turning of the whole body 360° around a vertical axis. The duration of a single head turn or single full rotation was not taken into consideration. The total number of head turns and rotations is given in the figures.

After completion of the experiment, all the rats were killed by an overdose of pentobarbital, their brains were removed, and localization of all the injection cannula tips was checked histologically (Fig. 1).

Statistical evaluation of differences between groups was carried out by means of Student's *t*-test for independent variables, and for differences between contralateral and ipsilateral turns by Student's *t*-test for dependent variables.

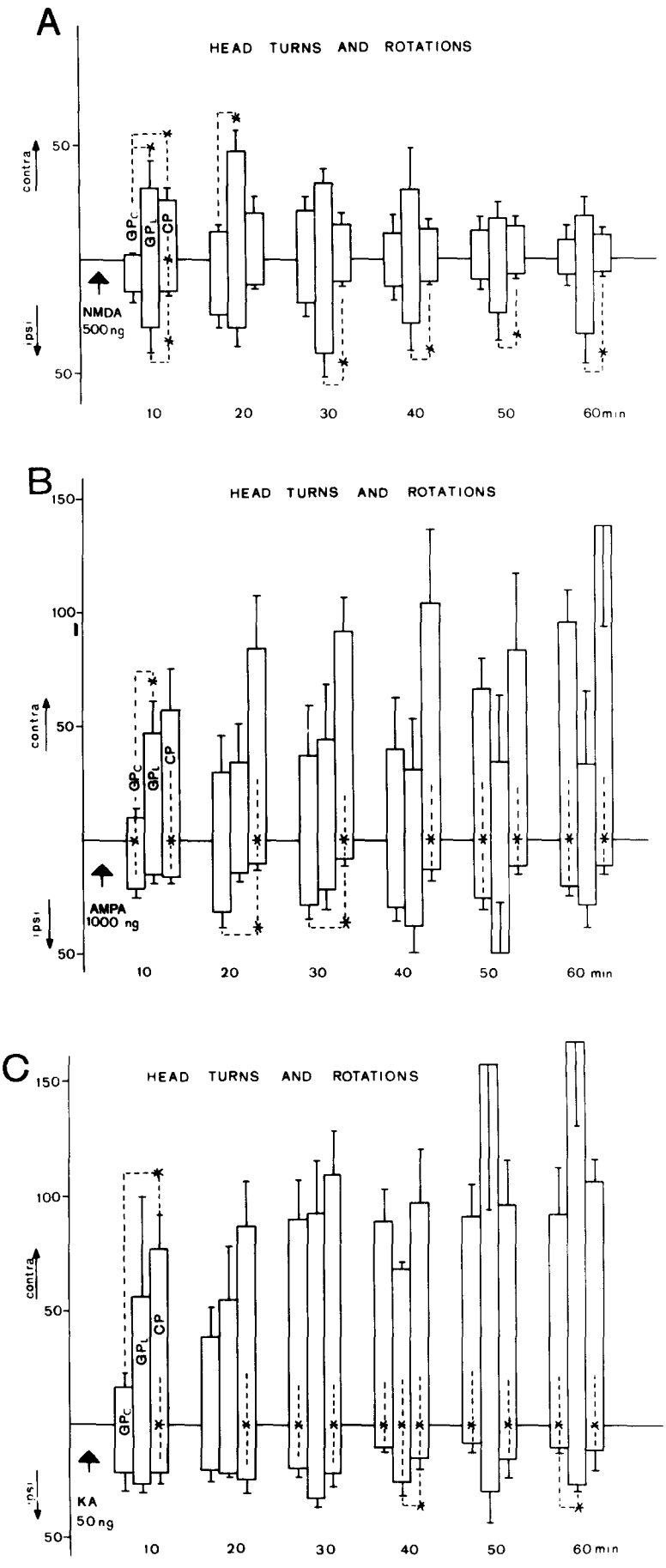
3. Results

3.1. Intrastriatal injections

Unilateral control injections of redistilled water into the ventrolateral part of intermediate and caudal regions of the caudate-putamen did not induce any turning behaviour in the rats (Fig. 2A, B and C; Fig. 3A and B). The sum of contralateral head turns and rotations did not differ significantly from the sum of ipsilateral ones.

NMDA (500 ng/0.5 μl) injected into the same region induced weak contralateral turning. This consisted mainly of contralateral head turns, but a small number of contralateral rotations was also observed. The locomotor activity of animals was not visibly changed. Contralateral head turns represented approx. 91% of the whole of contralateral head turns and rotations. This effect was transient and clearly visible only during the first 10 min after the injection (Fig. 2A). Moreover, the region in which NMDA injections were effective was limited to the area adjoining the globus pallidus (A = 6860–6790) (Fig. 1). Injections directed outside this

Fig. 4. Head turns and rotations induced by unilateral intrapallidal and intrastriatal NMDA (A), AMPA (B) and kainic acid (KA) (C) injections. GPc – injection into the central part of the globus pallidus; GPl – injection into the lateral part of the globus pallidus; CP – injection into the caudate-putamen. The number of animals: NMDA injected into the GPc – $n = 6$, into the GPl – $n = 4$, into the CP – $n = 12$, AMPA injected into the GPc – $n = 5$, into the GPl – $n = 5$, into the CP – $n = 7$, kainic acid injected into the GPc – $n = 6$, into the GPl – $n = 3$, into the CP – $n = 6$. For further explanations see Fig. 2.


A
HEAD TURNS AND ROTATIONS
contra
ipsi
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NMDA
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region were ineffective. The contralateral turning behaviour induced by NMDA was blocked by a previous (20 min earlier) unilateral injection of the competitive antagonist of NMDA receptors, AP5 (500 ng/0.5 μl) (Fig. 2A). A prior injection of AP5 did not change the ratio between the number of head turns and rotations.

AMPA (1000 ng/0.5 μl) and kainic acid (50 ng/0.5 μl), injected into the caudate-putamen, induced strong contralateral turning (Fig. 2B and C). Like the behaviour evoked by NMDA, the latter behaviour also consisted mainly of contralateral head turns (approx. 95–97% of the total number of head turns and rotations). AMPA and kainic acid evoked such behaviour after administration into a larger region of the striatum than did NMDA injections (A = 7190–6670). The locomotor activity of these animals was slightly increased. The contralateral head turns and rotations induced by AMPA and kainic acid were antagonized by pretreatment (20 min earlier) with the competitive antagonist of non-NMDA receptors, DNQX (1000 ng/0.5 μl) (Fig. 2B and C). After joint injections of DNQX with AMPA or kainic acid, the ratio between the contralateral head turns and rotations was similar to that seen after injections of AMPA or kainic acid alone.

AP5 (500 and 1000 ng/0.5 μl) or DNQX (2000 ng/0.5 μl), injected alone into the above-mentioned region of the caudate-putamen, resulted in the prevalence of ipsilateral head turns and rotations (Fig. 2A; Fig. 3A and B). The contribution of ipsilateral head turns to the total number of ipsilateral head turns and rotations was approx. 79–88% after DNQX, and 85–90% after AP5. After such treatments, the animals were motionless and some were cataleptic, hence the absolute number of ipsilateral rotations was very low (approx. 4 during 10 min). Moreover, it often happened that a rat froze in an ipsilateral head and body turn for a longer period of time.

3.2. Intrapallidal injections

In contrast to intrastriatal injections, NMDA (500 ng/0.5 μl), administered unilaterally into central or lateral regions of the globus pallidus, did not induce contralateral turning (Fig. 4A). The sum of contralateral head turns and rotations did not differ significantly from the sum of ipsilateral ones. However, an insignificant tendency to ipsilateral turning behaviour was observed in rats during the first 20 min after administration to the central part of the globus pallidus (Fig. 4A).

AMPA (1000 ng/0.5 μl), administered into the central part of the globus pallidus, induced weak ipsilateral head turns (82%) and rotations (18%) immediately after the completion of injection. Afterwards, the ipsilateral turning disappeared and changed into contralateral head turns (96%) and rotations (4%) at 50 and 60 min after injection. AMPA, injected into the lateral part of the globus pallidus, did not induce any distinct turning; however, a faint tendency towards contralateral head turns (83%) and rotations (17%) during the first 20 min was observed (Fig. 4B).

Kainic acid (50 ng/0.5 μl) induced a potent contralateral turning behaviour after administration into both central and lateral parts of the globus pallidus. The contribution of head turns to the total number of head turns and rotations was similar to that observed after kainic acid injections into the caudate-putamen (93–97%). However, in comparison to that of intrastriatal injections, this effect was delayed and statistically significant not earlier than 30–40 min after injection (Fig. 4C).

4. Discussion

The present results suggest that stimulation of NMDA receptors (by NMDA) and non-NMDA ones (by kainic acid and AMPA) in the ventrolateral part of the intermediate and caudal regions of the caudate-putamen results in contralateral turning behaviour. On the contrary, blockade of NMDA receptors (by AP5) and non-NMDA ones (by DNQX) in this region leads to ipsilateral turning.

A question arises as to which striatal neuronal output system is responsible for these effects. It is well known that the caudate-putamen is a source of two main γ-aminobutyrate (GABA)-ergic output systems: striopallidal and strionigral (Nagy et al., 1978; Fonnum et al., 1978; Staines et al., 1980; Araki et al., 1985; Kita and Kitai, 1988; Reiner and Anderson, 1990). The anatomical data obtained with rats and cats indicate that both these pathways originate in the entire (rostral to caudal) region of the caudate-putamen (Grofová, 1975; Araki et al., 1985; Penny et al., 1986; Beckstead and Cruz, 1986). In the intermediate and caudal parts of the caudate and putamen there exist a number of neurons of the GABAergic strionigral pathway (Grofová, 1975; Araki et al., 1985; Beckstead and Cruz, 1986). In contrast, neurons of the striopallidal pathway (leading to the external segment of the globus pallidus) were reported to be infrequent in the caudal region of those nuclei (Beckstead and Cruz, 1986). Behavioural studies showed that stimulation of GABAergic receptors in the substantia nigra pars reticulata by muscimol injected into this structure induced contralateral rotations, whereas the blockade of those receptors by GABA receptor antagonists produced ipsilateral turning (Wolfarth et al., 1981; Coward, 1982; Scheel-Krüger, 1986). It was also shown that injections of dynorphin and substance P, which is known to co-localize with GABA in the same strionigral neurons, into the substantia nigra pars reticulata also induced contralateral

rotations (for references see Reiner and Anderson, 1990). Therefore it is likely that the contralateral head turns and rotations induced by injections of NMDA, kainic acid and AMPA into the intermediate and caudal striatal regions result from activation of the strionigral GABAergic pathway and enhancement of the GABAergic transmission in the substantia nigra pars reticulata. In line with this concept, antagonists of NMDA and non-NMDA receptors, AP5 and DNQX, seem to inhibit this pathway. This conclusion is supported by the results of recent binding studies which show that a part of striatal NMDA and non-NMDA receptors are present on strionigral neurons (Tallaksen-Greene et al., 1992). It cannot be excluded that NMDA and non-NMDA receptor agonists and antagonists, administered into the caudal region of the caudate-putamen, also affect some neurons of the GABAergic striopallidal pathway, yet this does not seem very likely. It was found that stimulation of GABAergic receptors in the globus pallidus (which can mimic activation of the GABAergic striopallidal pathway) induced ipsilateral turning, and their blockade, contralateral turning (Scheel-Krüger, 1986). Therefore it is assumed that direct stimulation of NMDA and non-NMDA receptors located on striopallidal neurons should induce ipsilateral turning, i.e. an effect opposite to that shown in the present study.

Another possibility examined by us was whether the contralateral turning induced by injections of NMDA and non-NMDA receptor agonists into the caudate-putamen results from diffusion of these compounds to the globus pallidus. The latter structure is known to send a massive GABAergic projection to the substantia nigra (Grofová, 1975; Araki et al., 1985). However, it does not seem likely that the above mentioned effect of NMDA, kainate and AMPA would stem from activation of the pallidonigral pathway. Injections of these compounds into any part of the globus pallidus either induced no clear-cut contralateral turning, or the effect was delayed. Moreover, injections directed into the central part of the globus pallidus tended to induce an opposite effect – ipsilateral head turns and rotations – immediately after their termination.

The turning behavior of rats is commonly used for studying pathophysiologic mechanisms of Parkinson's disease. In this model, substances that can be useful as antiparkinsonian drugs induce contralateral rotations (Morelli and Di Chiara, 1990; Löschmann et al., 1991). Therefore it is assumed that the contralateral turning induced by stimulation of excitatory amino acid receptors (NMDA and non-NMDA) located in the intermediate and caudal regions of the caudate-putamen may be regarded as an 'antiparkinsonian' effect, and the ipsilateral turning after their blockade as a 'proparkinsonian' effect. The above conclusion is in an agreement with that emerging from the study of Turski et al. (1990) who found that blockade of NMDA receptors in the same striatal region as that examined in the present study induced catalepsy and rigidity. Moreover, NMDA administered into this region counteracted both those symptoms induced by AP7 (Turski et al., 1990). However, there are findings suggesting that NMDA receptors located in more anterior parts of the caudate-putamen may play an opposite role. Namely, it has been shown that direct injection of the antagonist of NMDA receptors, AP5, into the anterior part of the caudate-putamen antagonizes the haloperidol catalepsy, i.e. induces an 'antiparkinsonian effect' (Yoshida et al., 1991, 1994). Moreover, NMDA injected into this region induced akinesia (Schmidt and Bury, 1988) and muscle rigidity (Klockgether and Turski, 1993). At present, a sharp definition of which output neuronal system is involved in these effects is not possible, since both the strionigral and striopallidal pathways originate in the anterior caudate-putamen (Grofová, 1975; Nagy et al., 1978; Beckstead and Cruz, 1986; Gerfen and Young, 1988). It may be assumed, however, that NMDA activates predominantly the striopallidal pathway in this region, whereas AP5 blocks the stimulatory influence of glutamic acid on it (Schmidt et al., 1992; Klockgether and Turski, 1993). This hypothesis is derived from the findings showing that activation of the striopallidal pathway, which leads to an increase in the GABAergic neurotransmission in the globus pallidus, results in akinesia, catalepsy and rigidity (Ossowska et al., 1984; Turski et al., 1984; Scheel-Krüger, 1986), whereas its inhibition causes an anticataleptic effect (Ossowska et al., 1984; Scheel-Krüger, 1986). On the basis of all the above experimental data, it can be suggested that stimulation of the two main striatal output pathways by glutamic acid via NMDA receptors leads to opposite effects. Stimulation of the striopallidal pathway by NMDA receptors results in experimental animal equivalents of parkinsonian symptoms (akinesia, catalepsy and rigidity), whereas stimulation of the strionigral pathway evokes 'antiparkinsonian' effects (attenuation of catalepsy and rigidity, contralateral rotations). Similarly, the effects of NMDA receptor antagonists on these two striatal output systems also seems to be opposed.

Summing up, it seems that excitatory amino acid receptors in the caudate-putamen may differently influence experimental animal equivalents of parkinsonian symptoms, depending on their localization on different striatal output pathways.

Acknowledgements

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