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Crucial role of the accumbens nucleus in the neurotransmitter interactions regulating motor control in mice

A. Svensson, M. L. Carlsson, and **A. Carlsson**

Department of Pharmacology, University of Göteborg, Sweden

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Summary. Previous work, based on systemic drug administration, has shown that neurotransmitter interactions between dopaminergic, adrenergic, glutamatergic and cholinergic systems are involved in locomotor control in mice. In an attemp to identify the target sites in the brain of these interactions, we have started a series of experiments, where the drugs are administered intracerebrally in mice.

The locomotor threshold doses of the competitive NMDA antagonist AP-5 and the noncompetitive NMDA antagonist MK-801 were investigated by means of local application in the accumbens nucleus of monoamine-depleted and monoaminergically intact mice, respectively. The threshold dose of AP-5 was lower in depleted than in intact animals, whereas the threshold dose of MK-801 was lower in monoaminergically intact than monoamine-depleted mice.

The locomotor effects of AP-5 and the AMPA-kainate receptor antagonist CNQX were registered in monaomine-depleted mice after local application in the accumbens or entopedunular nucleus (= medial pallidum). Both AP-5 and CNQX stimulated locomotor activity in the accumbens, but had no effects in the entopedunular nucleus.

We have previously shown synergistic interactions with regard to locomotor stimulation in monoamine-depleted mice, between an NMDA antagonist and an α_2-adrenoceptor agonist or a dopamine D1 agonist (all drugs given systemically). In the present study the α_2-adrenoceptor agonist α-methyl-noradrenaline was applied intracerebrally in combination with a subthreshold dose of MK-801 given intraperitoneally: Locomotor stimulation was produced after α-methyl-noradrenaline injection into the accumbens nucleus, but not after injection into the dorsal striatum, prefrontal cortex or thalamus. Likewise, local application of the D1 agonist SKF 38393, in combination with a subthreshold dose of MK-801 given intraperitoneally, point to an important role of the accumbens nucleus in motor control.

Previous experiments based on systemic drug administration have also shown a synergistic interaction between a muscarine antagonist and an α_2-

adrenoceptor agonist in monoamine-depleted mice. Local application of the muscarine antagonist methscopolamine, in combination with the α_2-adrenoceptor agonist clonidine given intraperitoneally, showed that the striatum, in this case both the ventral and dorsal parts of the striatum, is an important target for the muscarine antagonist.

Unilateral injection of AP-5 into the accumbens nucleus of mice induces rotational behaviour: Previous findings have shown that the rotation is ipsilateral in monoaminergically intact animals, whereas monoamine-depleted animals rotate contralaterally. In addition, these findings have shown that dopamine D2 receptor stimulation seems to determine whether AP-5 will induce ipsilateral or contralateral rotation. In the present study we report further evidence for a crucial role of the D2 receptor in this respect.

Finally, the rotational effects of AP-5 injected into the dorsal striatum or hippocampus were investigated: As after AP-5 application into the accumbens nucleus, monoaminergically intact mice rotated ipsilaterally, whereas monoamine-depleted animals rotated contralaterally, following AP-5 application in the dorsal striatum or the hippocampus.

The present data show that the accumbens nucleus has an important role in motor control. Both glutamatergic, muscarine cholinergic, dopaminergic and α-adrenergic systems are involved in the control of motor functions in the accumbens nucleus.

Keywords: Accumbens nucleus, α-adrenoceptors, dopamine receptors, dorsal striatum, entopedunular nucleus, glutamate receptors, hippocampus, locomotion, mouse, muscarine receptors, rotation.

Introduction

Previous work in our laboratory has shown that glutamate blockade by means of systemic administration of the non-competitive NMDA antagonist MK-801 reverses the akinesia induced by reserpine and α-methyl-tyrosine in mice (Carlsson and Carlsson, 1989a). In an attempt to identify the target site(s) of the glutamate antagonist, we started a series of experiments injecting drugs intracerebrally in mice. We found that stimulation of locomotor activity was produced in monoamine-depleted mice when the competitive NMDA antagonist AP-5 (5 μg) was injected into the accumbens nucleus, but not when injected into the dorsal striatum. Systemic treatment with the α_2-adrenergic agonist clonidine potentiated the locomotor effects of intra-accumbens AP-5. Following local application of AP-5 in combination with systemic administration of clonidine, locomotor stimulation was also produced when AP-5 was injected into the dorsal striatum but not the prefrontal cortex (Svensson and Carlsson, 1992). These data suggest that the glutamatergic projections to the striatum, especially the ventral striatum, are inhibitory on behaviour.

Figure 1 shows parts of the circuitry which link the basal ganglia with the cerebral cortex and thalamus. Practically all areas of the cerebral cortex project to the striatum. The neocortex projects to the dorsal striatum, i.e. the caudate nucleus and putamen, whereas the allocortex, cingulate and prefrontal cortices project to the ventral striatum, i.e. mainly the accumbens nucleus

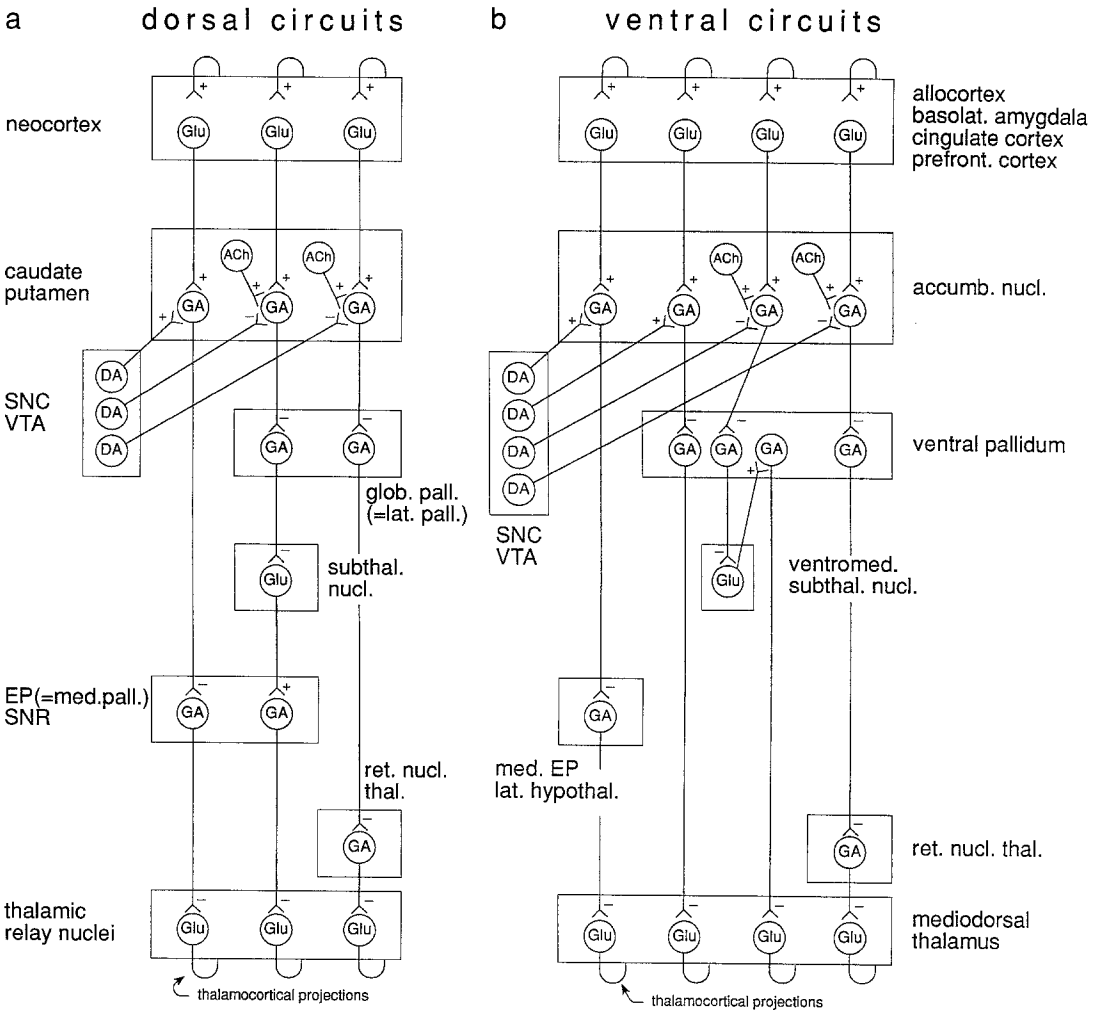

Fig. 1. Schematic circuit diagrams comparing the cortico-striato-thalamo-cortical feedback circuits of the dorsal and ventral striatum. **a** The feedback circuits of the caudate-putamen. Shown are one positive feedback circuit, encompassing two gabaergic neurones between the caudate-putamen and the thalamic relay nuclei, and two negative feedback circuits, encompassing three gabaergic neurones between the caudate-putamen and the thalamic relay nuclei. **b** The feedback circuits of the accumbens nucleus. Shown are two positive feedback circuits, encompassing two gabaergic neurones between the accumbens nucleus and the mediodorsal thalamus, and two negative feedback circuits, encompassing three gabaergic neurones between the accumbens nucleus and the mediodorsal thalamus. The transmitter of the neurones projecting from the lateral hypothalamus to the thalamus is uncertain. The negative feedback circuit via the subthalamic nucleus is hypothetical: There are reciprocal connections between the ventral pallidum and the ventromedial subthalamic nucleus, but the exact organization of these connections is uncertain. Abbreviations: *EP* entopeduncular nucleus, *ret nucl thal* reticular nucleus of the thalamus, *SNC* pars compacta of the substantia nigra, *SNR* pars reticulata of the substantia nigra, *VTA* ventral tegmental area, *ACh* acetylcholine, *DA* dopamine, *GA* gaba, γ-aminobutyric acid, *Glu* glutamate

and parts of the olfactory tubercle (Heimer et al., 1985). Projections from the dorsal and ventral striatum go to different relay nuclei of the thalamus via the dorsal and ventral pallidum, respectively. Finally, thalamic projections back to the cerebral cortex close the circuits. There is evidence that these feedback circuits are arranged in parallel, i.e. the topographical organization is maintained throughout the circuit (Alexander et al., 1986; Alexander and Crutcher, 1990; Alheid and Heimer, 1988). According to this view, the basal ganglia appear to be capable of participating in a number of functions, including motor, cognitive and "limbic" functions.

The feedback circuits related to the dorsal striatum are shown in Fig. 1 a. There are two types of pathways between the caudate-putamen and the thalamus, the so-called direct pathway, which contains two gabaergic neurones, and the so-called indirect pathway, which contains three gaba neurones. The direct pathway goes via the entopeduncular nucleus (the rodent equivalent of the medial pallidum in primates; Morgan, 1927) or the pars reticulata of the substantia nigra. The indirect pathway goes via the globus pallidus (= the lateral segment of the globus pallidus in primates), subthalamic nucleus and entopeduncular nucleus or pars reticulata of the substantia nigra. There is also another chain of three gaba neurones between the caudate-putamen and thalamus, i.e. an "indirect" pathway, which goes via the globus pallidus and the reticular nucleus of the thalamus (Parent, 1991). The direct pathway appears to form part of a positive cortico-striato-thalamo-cortical feedback circuit, whereas the two indirect pathways appear to form parts of corresponding negative feedback circuits.

The dopaminergic projections to the striatum seem to excite the direct pathway and inhibit the indirect pathways, which will result in decresed inhibition of thalamic relay nuclei, increased cortical arousal and behavioural stimulation. Consequently, dopamine seems to stimulate behavioural functions through both types of pathways. The glutamatergic, corticostriatal projections excite both the direct and the indirect pathways, which can result both in decreased and increased inhibition of the thalamus. Glutamate seems thus capable both to facilitate and inhibit behavioural programs (Alexander and Crutcher, 1990; Bernath and Zigmond, 1989; Gerfen et al., 1990; Girault et al., 1986; Penney and Young, 1986). However, also the dopaminergic system seems to have a possibility both to stimulate and inhibit psychomotor functions: Recent findings showing that the D3 antagonist U 99194A stimulates locomotor activity in rats, suggest that postsynaptic dopamine D3 receptors are inhibitory on behaviour (Waters et al., 1993).

The neuroanatomy of the dorsal striatum is more accurately mapped than the ventral striatum, but the principal organization and connections seem to be analogous (Heimer et al., 1985). For instance, there seems to be both "direct" and "indirect" striatothalamic pathways, and accordingly both positive and negative cortico-striato-thalamo-cortical feedback circuits. However, since the functions of both the medial and lateral pallidum seem to be mixed in the ventral pallidum, the organization of the ventral feedback circuits is yet not as well understood as that of the dorsal circuits (Heimer et al., 1985). In Fig. 1b the putative feedback circuits of the accumbens nucleus are compared

with those of the dorsal striatum (for refs see Alheid and Heimer, 1988; Heimer et al., 1985; Nauta, 1989).

The findings that systemic or intra-accumbens glutamate blockade results in behavioural stimulation suggest that the negative feedback circuits are the more active of the two types of circuits. However, measurements of rotational behaviour following unilateral injections of glutamate antagonists in mice with various dopaminergic tone suggest that the positive feedback circuit also influences behavioural functions. A unilateral injection of the competitive NMDA antagonist AP-5 caused the animals to rotate. The rotation was predominantly ipsilateral in monoaminergically intact animals, whereas the rotation in monoamine-depleted mice was exclusively contralateral (Svensson et al., 1992a). This shift in the direction of rotation was apparently due to lack of dopamine receptor stimulation, because in monoamine-depleted animals treated with the mixed dopamine agonist apomorphine, AP-5 caused the animals to rotate predominantly ipsilaterally (Svensson et al., unpublished findings).

These data can be interpreted in the following way: The unilateral AP-5 injection into the accumbens nucleus of monoamine-depleted mice reduces the activity in the indirect, inhibitory pathways on the AP-5-treated side. Hence, an asymmetrical stimulation of locomotor activity is induced, which gives rise to a turning behaviour directed away from the AP-5-injected side (contralateral turning). This finding is in line with the rotational behaviour induced by asymmetrical activation of the mesencephalostriatal dopaminergic system: In this case the animals turn away from the side where the dopaminergic activity is highest (Ungerstedt, 1971a,b; Colle and Wise, 1991; Miller and Beninger, 1991).

In contrast to monoamine-depleted mice, monoaminergically intact animals rotated predominantly towards the injected side (ipsilateral turning), following a unilateral injection of AP-5 into the accumbens nucleus. Consequently, this effect can not be explained in terms of interference with the indirect pathways. Hence, we suggest that in animals with intact monoaminergic systems the balance between the two types of pathways is shifted in favour of the direct, stimulant pathways, perhaps owing to the excitatoy dopaminergic input to these pathways. In this case the loss of glutamatergic tone in the positive feedback circuits, following treatment with AP-5 in the accumbens, should reduce the stimulant influence on the thalamus, and this should lead to a relatively higher activity in the positive feedback circuits on the intact side, and accordingly ipsilateral rotation. However, it might well be a postural rather than locomotor phenomenon that is responsible for the rotation in the monominergically intact mice: Since these animals have spontaneous locomotor activity, inducing a postural asymmetry would be sufficient to produce turning behaviour. In contrast, the turning behaviour in monoamine-depleted mice, whose baseline motor activity is practically zero, must be dependent on stimulation of locomotor activity.

This duality of the effect of intra-accumbens AP-5, which is dependent on the monoaminergic tone, was further investigated using dopamine D1 and D2 receptor agonists in order to elucidate the interactions between glutamate and

dopamine. (In this paper, D2 generally refers to the whole D2 receptor family comprising the D2, D3 and D4 receptor subtypes. Likewise, D1 refers to D1 = D1A and D5= D1B.) The D2 receptor agonist quinpirole reversed the contralateral rotation induced by AP-5 in monoamine-depleted animals into ipsilateral rotation. In contrast, in monoamine-depleted mice treated with the dopamine D1 receptor agonist SKF 38393, AP-5 still induced contralateral turning (Svensson et al., 1992a). These findings suggest that glutamate in the accumbens both can stimulate and inhibit motor functions, and that interactions with dopamine D2 receptors are crucial for the balance between glutamatergic stimulation and inhibition of behaviour. The notion that glutamate has a dual function is also suported by experiments with systemic drug administration: MK-801 increased the locomotor stimulation produced by SKF 38393 in monoamine-depleted mice but decreased the effects of quinpirole (Svensson et al., 1992b).

In the present paper we report further data supporting the notion that dopamine D2 receptors modulate the behavioural effects of glutamatergic neurotransmission in the accumbens nucleus. Furthermore, the interactions between central catecholaminergic and glutamatergic systems have been investigated in monoamine-depleted mice by means of local application of the dopamine D1 agonist SKF 38393 or the α_2-adrenoceptor agonist α-methyl-noradrenaline in combination with the NMDA receptor antagonist MK-801. Moreover, motor effects of locally applied glutamate antagonists in the accumbens nucleus, dorsal striatum, entopeduncular nucleus and hippocampus are described.

Methods

Animals

Male albino mice of the NMRI strain weighing 18–20 g were purchased from ALAB, Sollentuna.

Systemically administered drugs

Reserpine (Sigma) was dissolved in a few drops of glacial acetic acid and a 5.5% glucose solution. Dizocilpine hydrogen maleate (MK-801; Research Biochemicals Inc), Ketamine hydrochloride (Sigma), α-methyl-para-tyrosine methylester hydrochloride (α-MT; Sigma), quinpirole hydrochloride (Research Biochemicals Inc), 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine hydrochloride (SKF 38393; Research Biochemicals Inc), raclopride tartrate (generously supplied by Prof S Ahlenius at Astra Läkemedel AB) and (S)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol hydrochloride (SCH 23390; Research Biochemicals Inc) were dissolved in physiological saline. The commercially obtained solution of xylazine chloride (Rompun vet.; Bayer) was diluted to 0.75 mg/ml with physiological saline. The drugs were injected intraperitoneally (ip), with the exception of SCH 23390 and raclopride which were injected subcutaneously (sc). The injection volumes were 10 ml/kg, except for reserpine which was given in a volume of 20 ml/kg.

Intracerebrally administered drugs

DL-2-amino-5-phosphonopentanoic acid (AP-5; Sigma), and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; Tocris Neuramin) were dissolved in an aqueous solution of NaOH and diluted with distilled water. Dizocilpine hydrogen maleate (MK-801; Research Bioche-

micals Inc), methscopolamine nitrate (Pharmacia), 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1 H-3-benzazepine hydrochloride (SKF 38393; Research Biochemicals Inc) and (+/−)-α-methyl-noradrenaline hydrochloride (Research Biochemicals Inc) were dissolved in distilled water. Methylene blue (20 μg/μl; Sigma) was added to the solutions to make it possible to locate the injection sites anatomically. Finally the solutions were adjusted to neutral pH and isotonicity by adding NaOH or HCl and NaCl, respectively. To prevent oxidation the solution of α-methyl-noradrenaline was not neutralized completely; in this case final pH was adjusted to approximately 6.5.

Surgery and intracerebral injections

Stereotaxic surgery was performed under ketamine (approximately 150 mg/kg) and xylazine (approximately 7.5 mg/kg) anaesthesia. Guide cannulas (diameter 0.60 mm, length 17 mm) were implanted unilaterally and fixed to the skull, the tips of the cannulas reaching just above the surface of the brain. The animals were allowed three to four days of recovery following the surgery.

Using injection cannulas (diameter 0.40 mm) AP-5, MK-801, CNQX, methscopolamine, α-methyl-noradrenaline or SKF 38393 were injected in a volume of 0.1 μl (if not otherwise stated) into the accumbens nucleus, dorsal striatum, entopeduncular nucleus, thalamus, prefrontal cortex or hippocampus of the freely moving animals.

After completion of the locomotor recordings the animals were decapitated and the brains were sectioned on a freezing sledge microtome and only animals with stained injection sites within the following coordinates, according to the atlas of Slotnick and Leonard (1975), were included in the study: I. The accumbens nucleus: Anterior/Posterior (A/P) 0.5–1.3 mm anterior to bregma, Lateral (L) 0.4–1.4 mm (on the right or on the left and right side) and Vertical (V) 4.0–4.8 mm. II. The dorsal striatum: A/P 0.4 mm anterior to bregma – 0.8 mm posterior to bregma, L 1.8–2.7 mm (right) and V 2.1–3.4 mm. III. The entopeduncular nucleus: A/P 1.3–1.8 mm posterior to bregma, L 1.9–2.7 mm (right) and V 4.0–4.5 mm. IV. The thalamus: A/P 1.7–2.5 mm posterior to bregma, L 1.0–1.4 mm (right) and V 2.8–3.2 mm. V. The prefrontal cortex: A/P 1.7–2.3 mm anterior to bregma, L 0.7–1.4 mm (right) and V 1.4–1.8 mm. VI. The hippocampus (rostral part): A/P 0.8–1.4 mm posterior to bregma, L 0.6–1.2 mm (right) and V 1.3–2.2 mm.

Locomotor recording

Locomotor activity was measured by means of one of the following equipments: 1. Electronic motility meters (M/P 40 Fc, Motron Products, Stockholm) with 40 photoconductive sensors (5 rows × 8, centre-centre distance 40 mm). 2. Circular tracks, 5 cm wide and 1 m in circumference, the inner and outer walls being plastic cylinders, 15 and 25 cm high, respectively; the number of turns (= meters) the animals cover was registered by means of infra-red detectors. 3. Circular open fields, surrounded by a plastic cylinder, diameter 25 cm, where the animals wee videotaped for 20 min and the number of complete rotations was counted manually.

Monoamine depletion

In order to effectively reduce central dopaminergic neurotransmission some mice in the present study were pretreated with the monoamine depleter reserpine and the catecholamine synthesis-inhibitor α-MT. Reserpine (10 mg/kg) was administered 20 hours and α-MT (500 mg/kg) 2 hours before locomotor registration. One hour following reserpine administration and throughout the experiment the ambient temperature was held at 26°C. In addition, the animals were kept warm on electric pads until the locomotor registration commenced.

Statistics

Mann-Whitney U-test was used throughout for comparisons between groups.

Results

Doses of AP-5 and MK-801: intact vs. monoamine-depleted animals

Figure 2 shows that the doses of the NMDA antagonists AP-5 and MK-801 required to produce locomotor stimulation were different in monoamine-depleted mice and monoaminergically intact mice. 0.1 μg of the competitive NMDA antagonist AP-5 injected bilaterally into the accumbens nucleus stimulated locomotor activity in monoamine-depleted mice but not in monoaminergically intact mice (Fig. 2a). Also 2.5 μg AP-5 was without effect in monoaminergically intact mice (not shown). However, when higher doses of AP-5 (7 and 10 μg) were given, a behavioural stimulation was produced also in intact animals (Fig. 2b).

Likewise, the effects of a low dose of the noncompetitive NMDA antagonist MK-801 (dizocilpine) were compared in monoamine-depleted and monoaminergically intact animals. 0.3 μg of MK-801 injected bilaterally into the accumbens nucleus produced a significant locomotor stimulation in intact mice, but was ineffective in monoamine-depleted mice (Fig. 2c). However, when 1.5 μg of MK-801 was given, a clear-cut locomotor stimulation was produced in monoamine-depleted animals (Fig. 2d. In this experiment locomotor activity was measured in the circular tracks instead of the electronic motility meters which otherwise were used in this experiment series, because

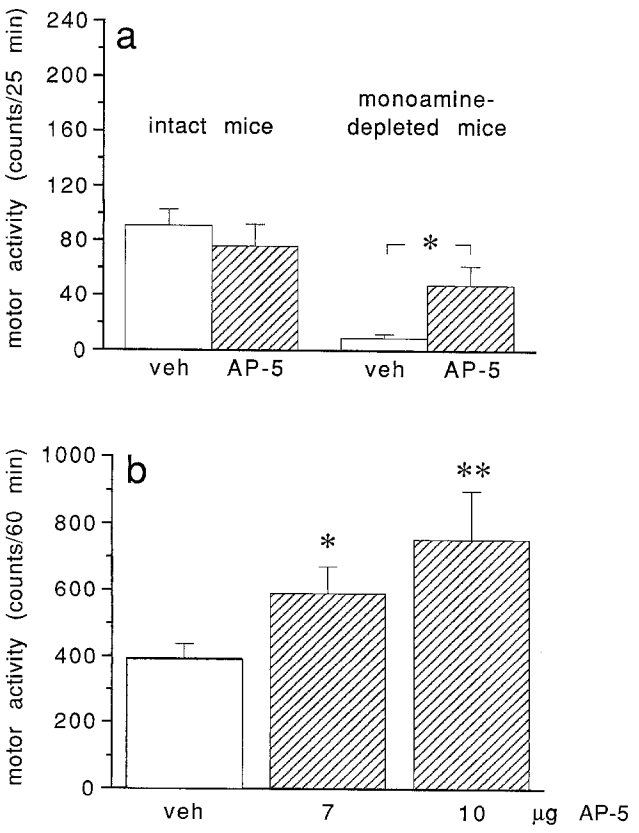

Fig. 2a, b

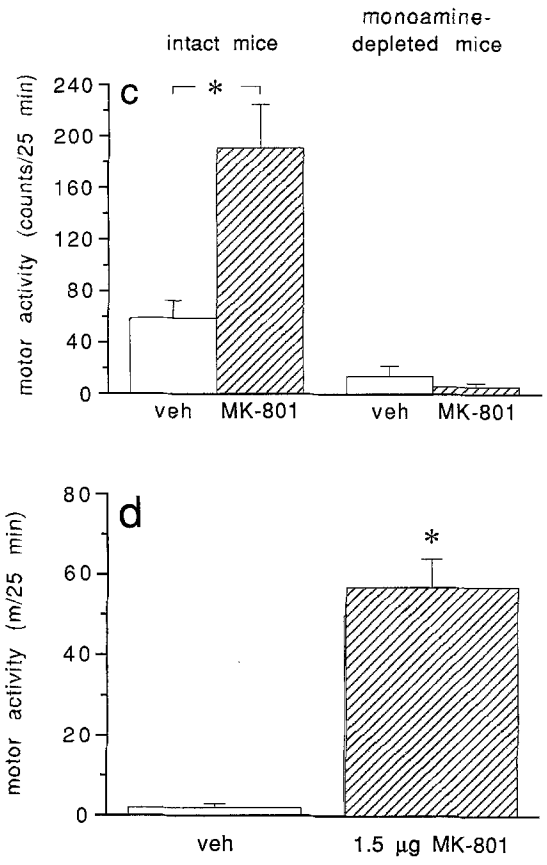

Fig. 2. **a** Effects on locomotor activity of AP-5 injected bilaterally into the accumbens nucleus of monoaminergically intact mice, habituated during 60 min, and monoamine-depleted mice. Locomotor activity was recorded in the motility meters for 25 min, beginning 5 min after the injection of AP-5 (0.1 µg) or vehicle. Shown are the means ± sem, n = 7–9. *P < 0.02. (These data have previously been published by Carlsson, 1993.) **b** Effects on locomotor activity of AP-5 injected bilaterally into the accumbens nucleus of monoaminergically intact mice (non-habituated). Locomotor activity was recorded for 60 min, beginning immediately after the injection of AP-5 (7 µg in 0.1 µl or 10 µg in 0.15 µl) or vehicle. Shown are the means ± sem, n = 5–6. *p < 0.05, **p < 0.01 vs. vehicle. **c** Effects of MK-801 injected bilaterally into the accumbens nucleus of monoaminergically intact mice, habituated during 60 min, and monoamine-depleted mice. Locomotor activity was recorded in the motility meters for 25 min, beginning 5 min after the injection of MK-801 (0.3 µg) or vehicle. Shown are the means ± sem, n = 6–12. *p < 0.02. (These data have previously been published by Carlsson, 1993.) **d** Effects on locomotor activity of MK-801 injected bilaterally into the accumbens nucleus of monoamine-depleted mice. MK-801 (1.5 µg, injection volume 0.3 µl) was administered 5 min before the animals were placed in the circular tracks where locomotor activity was registered for 25 min. Shown are the means ± sem, n = 4–5. *p < 0.05 vs. vehicle

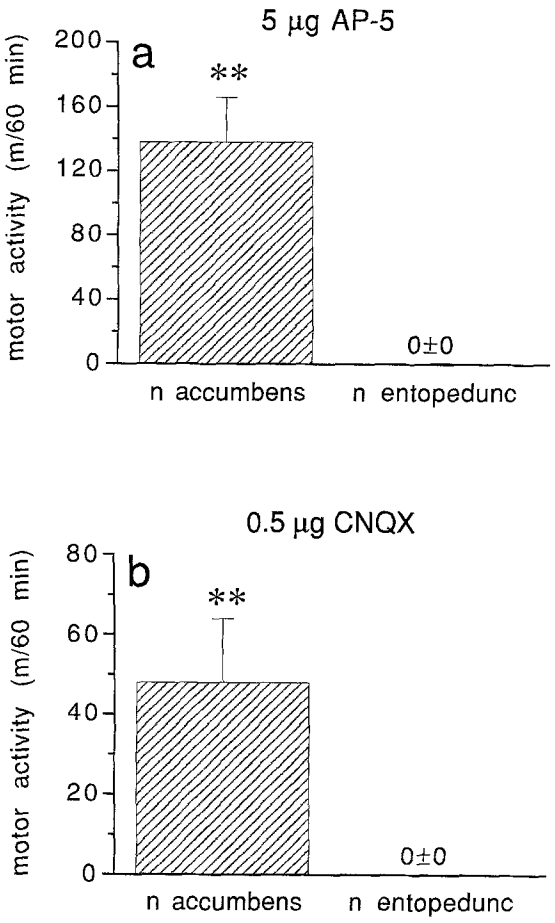

Fig. 3. **a** Effects of AP-5 injected into the accumbens nucleus or entopedunular nucleus of monoamine-depleted mice. 10 min after the injection of AP-5 (5 µg) the animals were placed in the circular tracks and locomotor activity was recorded for 60 min. Shown are the means ± sem, n = 4–8. **p < 0.01 vs. the entopedunular nucleus. **b** Effects of CNQX injected into the accumbens nucleus or entopedunular nucleus of monoamine-depleted mice. 30 min after the injection of CNQX (0.5 µg, injection volume 0.3 µl) the animals were placed in the circular tracks and locomotor activity was recorded for 60 min. Shown are the means ± sem, n = 5–8. **p < 0.01 vs. the entopedunular nucleus

monoamine-depleted mice treated with high doses of MK-801 have an inclination to get stuck in the corners of the motility meters; Carlsson and Carlsson, 1989b).

Effects of AP-5 and CNQX: accumbens nucleus vs. entopeduncular nucleus

The importance for locomotor activity of the glutamatergic neurotransmission in the entopeduncular nucleus was investigated in monoamine-depleted mice using AP-5 and the AMPA-kainate receptor antagonist CNQX. Both AP-5 (5 µg) and CNQX (0.5 µg) stimulated locomotor activity when injected into the accumbens nucleus but not when injected into the entopeduncular nucleus (Fig. 3a and b).

Intracerebral injections of α-methyl-noradrenaline and SKF 38393

In the following series of experiments monoamine-depleted, akinetic mice received a subthreshold locomotor stimulant dose of MK-801 intraperitoneally in combination with intracerebral injections of the α_2-adrenergic agonist α-methyl-noradrenaline or the dopamine D1 agonist SKF 38393.

Under these conditions 1 or 2 μg α-methyl-noradrenaline produced behavioural stimulation when injected into the accumbens nucleus but not the dorsal striatum (Fig. 4a). No behavioural stimulation was induced by injection of α-methyl-noradrenaline into the prefrontal cortex or the thalamus (Fig. 4b). In the case of the dopamine D1 agonist SKF 38393 (4 μg), the locomotor stimulation was significantly larger after injection into the accumbens than the dorsal striatum (Fig. 4c).

Intracerebral injections of methscopolamine

In Fig. 5 are shown the locomotor effects of intracerebral administration of the muscarine antagonist methscopolamine in combination with intraperitoneal administration of the α_2-adrenergic agonist clonidine in monoamine-depleted, akinetic mice. Injection of a high dose of methscopolamine (60 μg) produced locomotor stimulation when injected into the dorsal striatum, but not when injected into the prefrontal cortex (Fig. 5a). To compare the effects in the dorsal striatum with those in the accumbens, a series of experiments were performed using successively decreasing doses of methscopolamine, but the drug was equally effective in both injection sites (not shown). Given in a dose of 3 μg there was no statistical difference between the effects elicited in the two injection sites, although the drug appeared to produce larger effects in the accumbens nucleus (Fig. 5b).

Effects of glutamate blockade on rotational behaviour

To confirm the crucial role of dopamine D2 receptors for the direction of the rotation induced by intra-accumbens AP-5 (see Introduction), the rotation following 2.5 μg AP-5 was studied in monoaminergically intact mice, pretreated with the selective dopamine D1 receptor antagonist SCH 23390 or the D2 antagonist raclopride, each antagonist given in two different doses. (The lower dose of SCH 23390 and raclopride, respectively, reduced locomotor activity by approximately 50% in intact, non-habituated mice; Martin et al., 1993). Given in these lower doses, SCH 23390 had no obvious effect on the direction of the rotation induced by AP-5, whereas raclopride reduced the ipsilateral rotation and increased the contralateral rotation. Following a higher dose of raclopride, which did not reduce the total number of turns, AP-5 induced almost exclusively contralateral rotation. Following the higher dose of SCH 23390, which reduced the overall locomotor activity, AP-5 induced both ipsilateral and contralateral rotation (Fig. 6a).

In Fig. 6b are shown the effects on rotational behaviour of AP-5 injected into the dorsal striatum of monoamine-depleted and monoaminergically in-

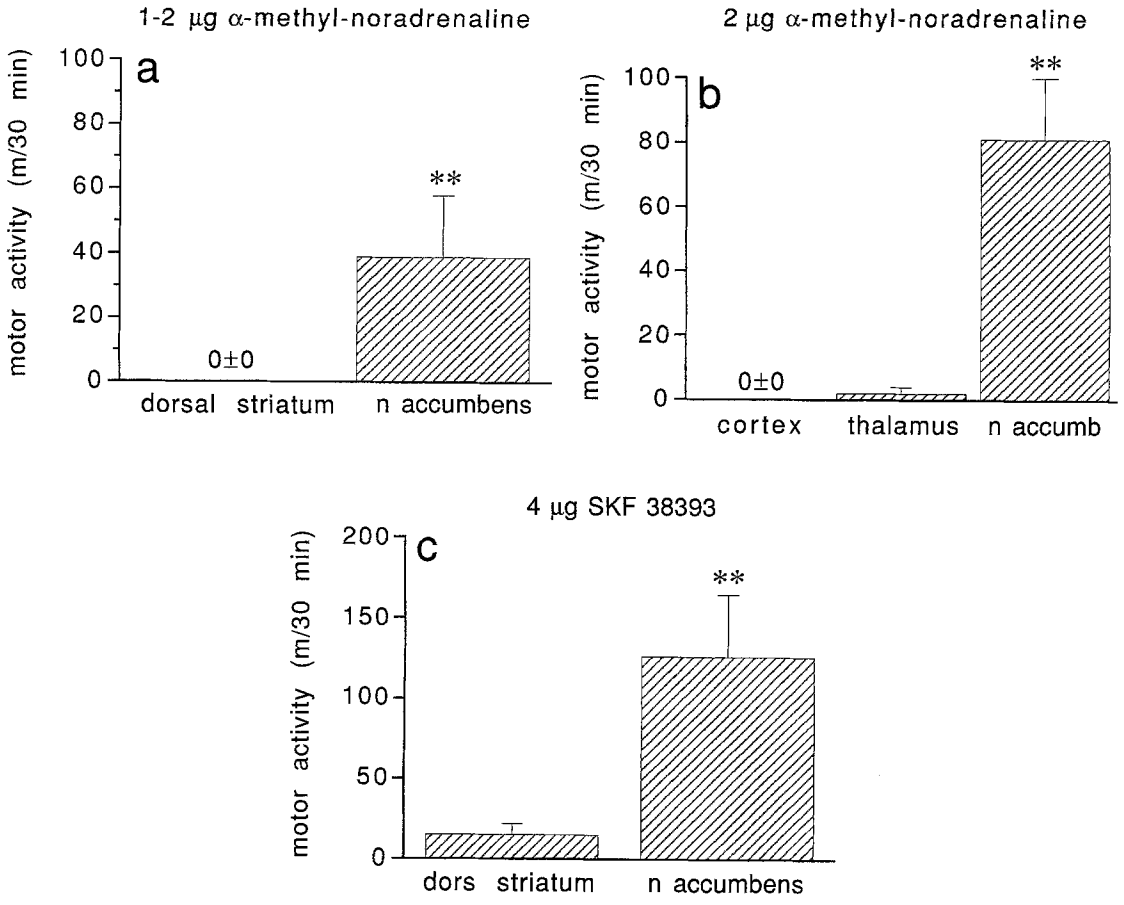

Fig. 4. **a** Effects on locomotor activity of α-methyl-noradrenaline injected unilaterally into the accumbens nucleus or dorsal striatum of monoamine-depleted mice pretreated with a subthreshold dose of MK-801 given ip. MK-801 (0.25 mg/kg) was administered 60 min and α-methyl-noradrenaline 5 min before the animals were placed in the circular tracks where locomotor activity was registered for 30 min. Four animals in each group received 1 μg α-methyl-noradrenaline (injection volume 0.1 μl) and 4 animals received 2 μg α-methyl-noradrenaline (injection volume 0.2 μl). Shown are the means ± sem, n = 8. **p < 0.01 vs. the dorsal striatum. **b** Effects on locomotor activity of α-methyl-noradrenaline injected unilaterally into the accumbens nucleus, thalamus or prefrontal cortex of monoamine-depleted mice pretreated with a subthreshold dose of MK-801 given ip. MK-801 (0.25 mg/kg) was given 60 min and α-methyl-noradrenaline (2 μg, injection volume 0.2 μl) was administered 5 min before the animals were placed in the circular tracks where locomotor activity was registered for 30 min. Shown are the means ± sem, n = 4–6. **p < 0.01 vs. the thalamus and prefrontal cortex. **c** Effects on locomotor activity of SKF 38393 injected into the accumbens nucleus or dorsal striatum of monoamine-depleted mice pretreated with a subthreshold dose of MK-801 ip. MK-801 (1 mg/kg) was administrered 60 min and SKF 38393 (4 μg) immediately before the animals were placed in the circular tracks where locomotor activity was registered for 30 min. Shown are the means ± sem, n = 6–7. **p < 0.01 vs. the dorsal striatum

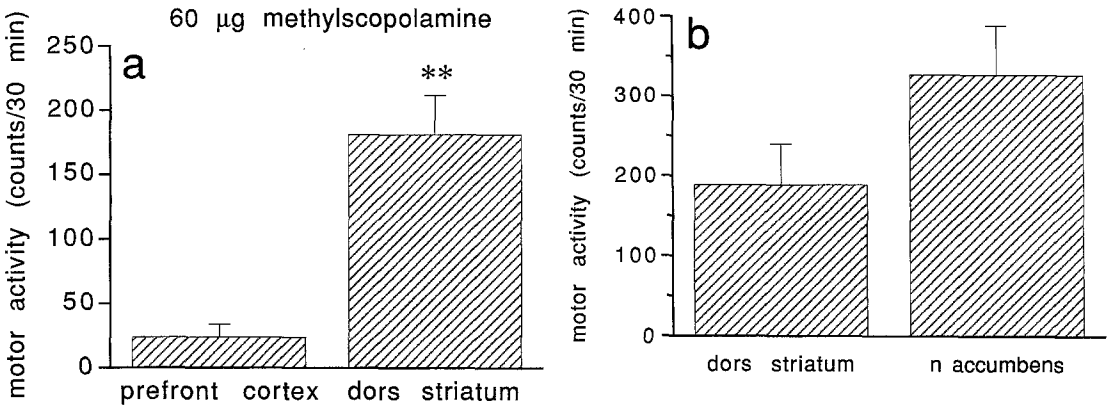

Fig. 5. a Effects on locomotor activity of methscopolamine injected into the dorsal striatum or prefrontal cortex of monoamine-depleted mice treated with clonidine ip. Methscopolamine (60 µg) and clonidine (1 mg/kg) were given immediately before the animals were placed in the motility meters where locomotor activity was registered for 30 min. Shown are the means ± sem, n = 5–6. ** $p < 0.01$ vs. the prefrontal cortex. **b** Effects on locomotor activity of methscopolamine injected into the accumbens nucleus or dorsal striatum of monoamine-depleted mice treated with clonidine ip. Methscopolamine (3 µg) and clonidine (1 mg/kg) were given immediately before the animals were placed in the motility meters where locomotor activity was registered for 30 min. Shown are the means ± sem, n = 6–8

tact mice. The direction of rotation was the same as following AP-5 treatment in the accumbens nucleus: monoaminergically intact mice rotatated predominantly ipsilaterally, whereas monoamine-depleted mice rotated exclusively contralaterally.

Finally are shown the effects on rotational behaviour of AP-5 treatment in the rostral part of hippocampus (Fig. 6c). Also in the hippocampus predominantly ipsilateral rotation was observed in monoaminergically intact mice. In monoamine-depleted mice the rotation was predominantly contralateral, and this contralateral rotation was increased by intraperitoneal administration of clonidine.

Discussion

The potency of AP-5 and MK-801 is differently affected by monoamine depletion

When the locomotor effects in monoaminergically intact mice, produced by intra-accumbens injections of low doses of AP-5 and MK-801, were compared with the effects in monoamine-depleted mice, it was observed that monoamine depletion reduced the threshold dose for locomotor stimulation of the competitive antagonist AP-5, but raised the threshold dose of the non-competitive antagonist MK-801.

Likewise, previous observations of systemic administration of NMDA antagonists showed that monoamine depletion affects the potencies of competitive vs. non-competitive NMDA antagonists differently. The threshold

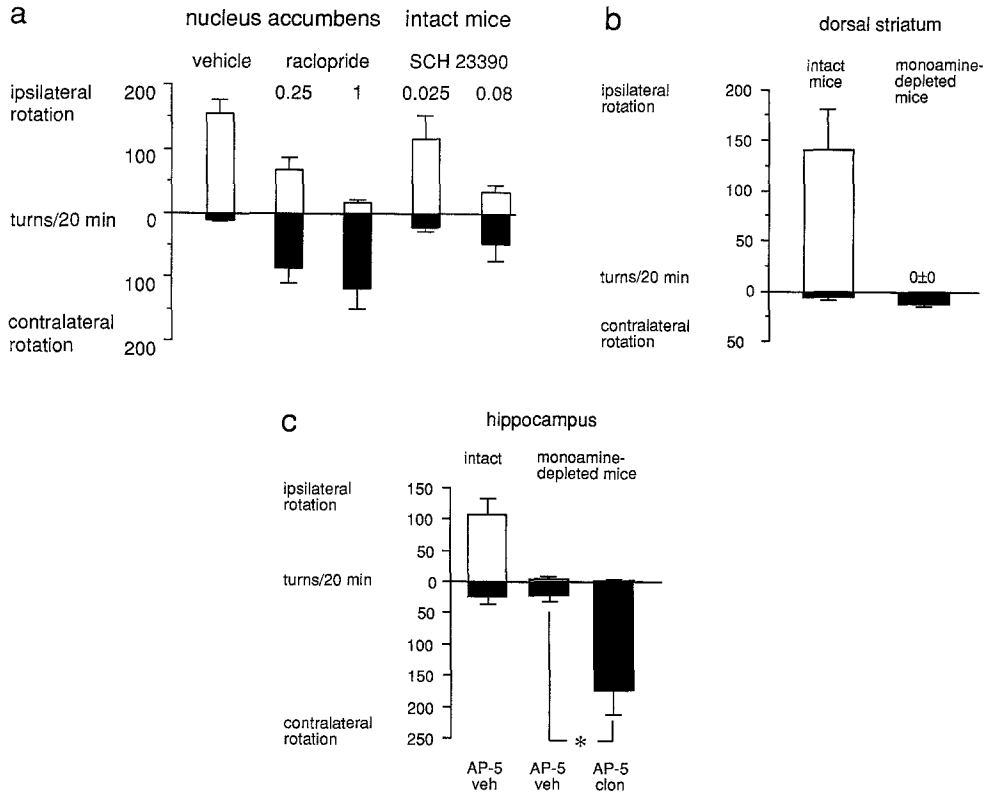

Fig. 6. **a** Effects on rotational behaviour induced by a unilateral injection of AP-5 into the accumbens nucleus of monoaminergically intact mice pretreated with either SCH 23390 or raclopride. SCH 23390 (experiment 1: 0.025 mg/kg, exp 2: 0.08 mg/kg) was administered 5 min and raclopride (exp 1: 0.25 mg/kg, exp 2: 1 mg/kg) 20 min before recording of locomotor activity. Immediately after the injection of AP-5 (2.5 μg) the animals were placed in the circular open fields and videotaped for 20 min. The number of complete rotations was counted manually. Shown are the means ± sem, n = 5–6. **b** Effects on rotational behaviour of AP-5 injected unilaterally into the dorsal striatum of monoaminergically intact and monoamine-depleted mice. All intact mice received 10 μg of AP-5 (injection volume 0.15 μl). Three monoamine-depleted mice received 10 μg (0.15 μl) and two monoamine-depleted mice received 20 μg (0.3 μl) AP-5. AP-5 was given immediately before the animals were placed in the open fields and video-taped for 20 min. Shown are the means ± sem, n = 5–8. **c** Effects on rotational behaviour of AP-5 injected unilaterally into the hippocampus of monoaminergically intact mice, monoamine-depleted mice and monoamine-depleted mice treated with clonidine ip. AP-5 (10 μg; injection volume 0.2 μl) and clonidine (1 mg/kg) were given immediately before the animals were placed in the open fields and video-taped for 20 min. Shown are the means ± sem, n = 4–5. *$p < 0.05$

locomotor stimulant dose of MK-801 was considerably higher in monoamine-depleted than intact mice (Carlsson and Carlsson, 1989a; Svensson et al., 1991). In contrast, the potencies of the competitive NMDA antagonists D-CPPene and CGS 19755 were approximately in the same magnitude in monoamine-depleted and inctact animals (Carlsson and Svensson, 1990b; Svensson et al., 1991; Carlsson, 1993).

These phenomena could hypothetically be explained as follows: The striatal gabaergic neurones pertaining to the indirect pathways (see Introduction) appear to have a higher baseline activity than the corresponding neurones of the direct pathways (Chevalier and Deniau, 1990; Côté and Crutcher, 1991; Carlsson, 1993). Thus the glutamate concentration is assumed to be higher in the corticostriatal synapses of the indirect pathways than the direct pathways (Carlsson, 1993). This assumed difference in glutamate concentration might affect the interactions between the NMDA receptor complex and its ligands in the following manner: The binding of competitive NMDA antagonists is inhibited by the endogenous ligand glutamate (Murphy et al., 1987, 1988), whereas the binding of non-competitive NMDA antagonists, which gain access to the binding site in the ion channel only when the receptor is stimulated, is enhanced by NMDA receptor agonists, a phenomenon designated use dependency (Kemp et al., 1987; Lodge and Johnson, 1990).

According to the so-called filter hypothesis (Carlsson, 1988), a reduction of the dopaminergic input to the indirect pathways, brought about by monoamine depletion, would result in a decreased activity in the corticostriatal neurones. Some experimental support for such a notion is provided by the finding by Reid et al. (1990) showing that striatal glutamate release is decreased by 6-hydroxy-dopamine treatment in rats. Thus, in monoamine-depleted animals, where the striatal synaptic glutamate concentration presumably is lowered, it would be easier for a competitive but more difficult for a non-competitive NMDA antagonist to bind to its receptor. In other words, the threshold dose of a competitive NMDA antagonist would be decreased, whereas the reverse would be true for a non-competitive NMDA antagonist.

The entopeduncular nucleus

The entopeduncular nucleus, which corresponds to the medial segment of the globus pallidus in primates (Morgan, 1927), receives a glutamatergic projection (Albin et al., 1989) from the subthalamic nucleus which, at least in primates, is important for psychomotor control: Injections of glutamate antagonists into the medial pallidum (Robertson et al., 1989; Graham et al., 1990) or lesions of the subthalamic nucleus (Bergman et al., 1990) produced locomotor stimulation in primates. Similar effects in patients with Parkinson's disease are reported after a stereotactic lesion in the medial pallidum, by means of Leksell's posteroventral pallidotomy, which improved both rigidity, tremor and hypokinesia (Laitinen et al., 1992). In contrast, in the present study in mice, no locomotor stimulation was found after administration of the NMDA antagonist AP-5 into the entopedunular nucleus. A recent autoradiographic study shows that the density of non-NMDA receptors is higher than the density of NMDA receptors in the entopedunular nucleus of the rat (Albin et al., 1992). Therefore, we have also investigated the effects of the AMPA-kainate receptor antagonist CNQX injected into the entopedunular nucleus, but no locomotor stimulation was observed. This discrepancy be-

tween the findings in primates and our findings in mice supports the notion that the dramatic influence of the subthalamic nucleus on motor functions might be confined to primates (Parent, 1990). However, in contrast to the present findings locomotor stimulation has been reported after injection of CNQX (Brotchie et al., 1990) and the AMPA antagonist NBQX (Klockgether et al., 1991) into the entopedunular nucleus of rats.

Intracerebral injections of α-methyl-noradrenaline, SKF 38393 and methscopolamine

Previous experiments with systemic drug administration have shown that glutamate antagonists have a capacity for reinforcing the locomotor stimulant properties of catecholaminergic agonists and muscarinic antagonists. In mice rendered akinetic by means of monoamine depletion, NMDA antagonists interact synergistically with α_2-adrenergic agonists to promote behavioural activation (Carlsson and Carlsson, 1989b; Carlsson and Svensson, 1990b). Likewise, MK-801 interacts synergistically with the muscarine receptor antagonist atropine in monoamine-depleted mice (Carlsson and Svensson, 1990a). Synergistic interactions with regard to motor stimulation have also been observed between muscarine antagonists and α_2-adrenergic agonists in monoamine-depleted mice (Carlsson and Carlsson, 1989c; Carlsson et al., 1991). In the case of the dopaminergic system, the interactions with NMDA antagonists are complex: In general the behavioural effects of a dopamine D1 agonist are reinforced by MK-801, whereas the effects of a D2 agonist are counteracted (Svensson et al., 1992b). However, the baseline motor activity induced by the dopaminergic agonist is also important for the pattern of interactions. This was especially evident in experiments with the mixed dopaminergic agonist apomorphine: When a subthreshold locomotor stimulant dose of apomorphine was used, MK-801 potentiated the behavioural effects, whereas the effects of a per se active dose of apomorphine were counteracted by MK-801 (Svensson et al., 1992b).

The mechanisms underlying these interactions are not known. However, they must be of postsynaptic origin, since they were observed in monoamine-depleted animals. In the case of D1 receptors, an interaction with NMDA receptors has been observed at the level of phosphorylation of DARPP-32 in rat striatal slices (Girault et al., 1990; Halpain et al., 1990).

Regarding the target site of the NMDA antagonist in the interaction with the adrenergic system, our experiments with intracerebral drug administration point to an important role of the striatal complex, especially the accumbens nucleus (Svensson and Carlsson, 1992). Hitherto no experimental data on the target site of the adrenergic agonists have been available. Therefore in the present study monoamine-depleted animals were treated with a subthreshold locomotor stimulant dose of MK-801 given intraperitoneally in combination with intracerebral injections of the α_2-adrenergic agonist α-methyl-noradrenaline. From these experiments it can be concluded that also in the interaction between an adrenergic agonist and glutamate, the accumbens nucleus plays an important role. No stimulant effects were observed following

injection of α-methyl-noradrenaline into the thalamus or prefrontal cortex, structures which are densely innervated with adrenergic fibres (Björklund and Lindvall, 1986). However, it is important to note that all parts of the thalamus or prefrontal cortex were not investigated in this study.

In the case of the interaction between the dopamine D1 agonist SKF 38393 and MK-801, the present data again point to an important role of the ventral rather than the dorsal striatum, as a target site for the D1 agonist. Other brain regions containing high densities of the D1 receptors remain to be investigated.

The experiments with intracerebral injections of the muscarine antagonist methscopolamine, in combination with systemic clonidine treatment, also focus on the striatal complex. In the case of cholinergic neurotransmission, the striatum rather than the prefrontal cortex seems to play an important role for motor functions. However, from the present experiments no conclusions can be drawn about the relative importance of the dorsal vs. the ventral striatum.

Effects of dopaminergic tone on the rotation induced by AP-5

The present findings from local application of AP-5, and previous findings from systemic administration of MK-801, which show a synergism between a dopamine D1 agonist and MK-801, but an antagonism between a dopamine D2 agonist and the NMDA antagonist (Svensson et al., 1992b), suggest that the responsiveness of the D1 receptors is suppressed by glutamate, whereas D2 receptors seem to operate in concert with the glutamatergic system, with respect to the control of psychomotor functions. It might thus be hypothesized that the striatal gabaergic neurones pertaining to the direct pathways (see Fig. 1) are principally equipped with D2 receptors, whereas the D1 receptors are principally involved in the indirect pathways. Experimental support for this hypothesis is also provided by work of Herrera-Marschitz and Ungerstedt (1987) showing that 1) rotation in 6-hydroxy-dopamine-treated rats induced by a D1 agonist was inhibited by the gaba antagonist picrotoxin, whereas the rotation induced by a D2 agonist was enhanced by picrotoxin and 2) non-lesioned animals unilaterally injected with intrastriatal picrotoxin rotated ipsilaterally after systemic treatment with a D1 agonist, whereas the rotation was contralateral after a D2 agonist. Since picrotoxin is an antagonist of an inhibitory neurotransmitter whereas AP-5 and MK-801 are antagonists of an excitatory transmitter, the effects of picrotoxin treatment should be the reverse of the effects of NMDA antagonist treatment, and this was actually the case. Against this interpretation of the striatal distribution of the dopamine D1 and D2 receptors stand data of Gerfen et al. (1990) showing that the majority of the rat substance P neurones, projecting from the caudate-putamen to the reticular part of the substatia nigra – the direct pathway, expresses mRNAs encoding the D1 receptor but no the D2 receptor, whereas the enkephalin neurones, projecting from the caudate-putamen to the globus pallidus – the indirect pathway, express mRNAs encoding the D2 receptor but not the D1 receptor. The organization seems to be the same in the ventral circuits; the accumbens substance P neurones express the D1 receptor,

whereas the accumbens enkephalin neurones express the D2 receptor (Le et al., 1991). However, a considerable degree of co-localization of D1 and D2 receptor mRNA in rat striatal cells has been reported (Meador-Woodruff et al., 1991). It is also important to note that subtypes of the D1 and D2 receptor population are studied with mRNA in situ hybridization, whereas the D1 and D2 receptor families rather than subtypes are studied with the pharmacological tools used in the present study.

Rotational behaviour after glutamate blockade in the dorsal striatum and hippocampus

Locomotor stimulation following a locally applied NMDA receptor antagonist in the dorsal striatum has previously been shown in rats (Schmidt, 1986) and mice (Svensson and Carlsson, 1992). As in the case of dopamine agonists (Pijnenburg et al., 1973; Johnels, 1982), locomotor activity is more easily induced when the NMDA antagonist is applied in the accumbens nucleus than in the dorsal striatum (Svensson and Carlsson, 1992). Locomotor stimulation following glutamate blockade in the dorsal striatum seems to be dependent on simultaneous stimulation of adrenergic and/or dopaminergic receptors, whereas locomotor activation following glutamate blockade in the accumbens nucleus is induced also in the virtually complete absence of catecholamines (Schmidt, 1986; Svensson and Carlsson, 1992). Not surprising, only weak rotation was observed in the present study following AP-5 injection into the dorsal striatum of monoamine-depleted mice. However, as in the case of the accumbens nucleus, the direction of the rotation was exclusively contralateral in depleted animals, whereas monoaminergically intact mice rotated predominantly ipsilaterally. The same shift in the direction of rotation was also observed after AP-5 application in the rostral part of hippocampus, suggesting that also in the dorsal striatum and hippocampus mechanisms similar to those in the accumbens are responsible for the balance between motor activation and inhibition following glutamate blockade. Moreover, in the case of glutamate blockade in the hippocampus, the motor effects might be mediated by the accumbens, since there is a projection from the hippocampus to the dorsomedial part of accumbens nucleus, at least in the rat (Kelley and Domesick, 1982).

Although only rotational behaviour, not locomotor activity, was measured following AP-5 treatment in the hippocampus, it seems that, at least in monoamine-depleted mice, a certain degree of locomotor stimulation was induced, since the baseline locomotor activity is practically zero in these animals. This finding is interesting since the hippocampally lesioned animal has been proposed as a model for schizophrenia (see Schmajuk, 1987). Also clinical data point to an important role of the hippocampus in schizophrenia: Using positron emission tomography with fluorodeoxyglucose, Tamminga et al. (1992) showed a reduced metabolic rate in the hippocampus of schizophrenic patients. The reduction in metabolic rate might be a consequence of reduced excitatory amino acid input: Loss of glutamate receptors, particularly of the kainate subtype, has been shown in the hippocampus of post mortem schizophrenic brains (Kerwin et al., 1990). Taken together, these findings

motivate further studies on the behavioural effects of glutamate blockade in the hippocampus.

Conclusion

The present data, based on local application of various receptor agonists and antagonists into mouse brain, show that the accumbens nucleus has an important role in the control of motor functions. Both glutamatergic, muscarine cholinergic, dopaminergic and α-adrenergic transmitter systems are involved in motor control in the accumbens nucleus.

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Authors' address: A. Svensson, Department of Pharmacology, Medicinaregatan 7, S-413 90 Göteborg, Sweden.

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