Pharmacology Biochemistry & Behavior, Vol. 41, pp. 177–182. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/92 $5.00 + .00

Locomotor Bias Produced by Intra-Accumbens Injection of Dopamine Agonists and Antagonists

CLAUDE MESSIER, OULAYA MRABET* AND CLAUDE DESTRADE†

School of Psychology, University of Ottawa, 275 Nicholas St., Room 215 Vanier, Ottawa, Ontario, K1H 8M5, Canada
†Laboratoire de Neurosciences Comportementales et Cognitives, URA CNRS No. 339
Université de Bordeaux I, ave. des Facultés, 33405 Talence Cedex, France
**Département de Physiologie, Université de Kénitra, Morocco*

Received 18 March 1991

MESSIER, C., O. MRABET AND C. DESTRADE. *Locomotor bias produced by intra-accumbens injection of dopamine agonists and antagonists*. PHARMACOL BIOCHEM BEHAV **41**(1) 177–182, 1992.—Several experiments have shown that the dopamine (DA) receptors in the nucleus accumbens control the intensity of locomotor activity; however, there are several contradictory results concerning the role of the accumbens in the regulation of the direction of locomotion. To further evaluate the contribution of dopaminergic function in the accumbens to the direction of locomotion, we first compared the effect on the direction of locomotor activity of unilateral intra-accumbens injections of the nonspecific DA antagonist haloperidol, the specific D-1 antagonist SCH-23390, the specific D-2 antagonist metoclopramide. In the second part of the experiment, we examined the effect on the direction of locomotor activity of unilateral intra-accumbens injections of the non-specific DA agonist apomorphine, the specific D-1 agonist SKF-38393, the specific D-2 agonist LY-171555, and the combination of SKF-38393 and LY-171555. Haloperidol, metoclopramide and to a lesser extent, SCH-23393 together with peripheral amphetamine injections produced a locomotor bias that resulted in ipsilateral turning. Apomorphine, LY-171555 or the combination of SKF-38393 and LY-171555 (but not SKF-38393 alone) produced a locomotor bias that resulted in contralateral turning. No significant locomotor bias was produced by intra-accumbens injection of the various vehicles. These results suggest that the bilateral DA organization thought to exist in the nigro-striatal pathway for the control of locomotion may also be true for the mesolimbic dopamine system.

Apomorphine Dopamine Haloperidol Metoclopramide Nucleus accumbens LY-171555 SCH-23390 SKF-38393 Turning

SEVERAL experiments have shown that the dopamine (DA) receptors in the nucleus accumbens control the intensity of locomotor activity. Bilateral intra-accumbens injection of amphetamine (39), 6,7-ADTN (2) or ergometrine (30) increase locomotor activity. The locomotion increase produced by peripheral amphetamine is blocked by bilateral intra-accumbens haloperidol injection (31). Bilateral lesion of the nucleus accumbens produces an hypoactivity and prevents the amphetamine-induced hyperactivity. (17, 20, 21, 24).

While the role of the nucleus accumbens in locomotion is well-established, there are several contradictory results concerning the role of the accumbens in the regulation of the direction of locomotion. A series of experiments have shown that in animals with 6-OHDA lesions of the ventral tegmental area, intra-accumbens injection of either apomorphine or pergolide did not produce any locomotor asymmetry (14). Similarly, peripheral injections of either apomorphine or amphetamine in animals with unilateral 6-OHDA lesion of the nucleus accumbens did not produce any locomotor asymmetry (8,18).

However, contralateral locomotor asymmetry was produced in animals with a 6-OHDA lesion of the medial forebrain bundle by an intra-accumbens injection of apomorphine. This asymmetry was attenuated by a peripheral injection of haloperidol (38). In unlesioned animals, unilateral intra-accumbens injection of either amphetamine (5), ergometrine (30) or apomorphine (28) produced a contralateral locomotor bias, while unilateral intra-accumbens injection of haloperidol produced an ipsilateral locomotor bias (28). Recently, we have shown that unilateral intra-accumbens injection of either conjugated dopamine (DA linked to bovine serum albumin via glutaraldehyde) or polyclonal anti-anti-conjugated dopamine antibodies also produced an ipsilateral locomotor bias (29). To further evaluate the contribution of dopaminergic function in the accumbens to the direction of locomotion, we examined the effect of intra-accumbens injections of specific DA agonists and antagonists.

We first compared the effect on the direction of locomotor activity of unilateral intra-accumbens injections of the nonspecific DA antagonist haloperidol, the specific D-1 antagonist SCH-23390, the specific D-2 antagonist metoclopramide. In the second part of the experiment, we examined the effect on the direction of locomotor activity of unilateral intra-accumbens injections of the nonspecific DA agonist apomorphine, the specific D-1 agonist SKF-38393, the specific D-2 agonist LY-171555, and the combination of SKF-38393 and LY-171555.

METHOD

Subjects

Subjects were 12–16-week-old male Balb/c mice (IFFA-CREDO, Lyon, France). They were housed individually in a

temperature-controlled room on 12/12-h light/dark cycle with ad lib water and food.

Surgery

A stainless steel guide cannula was stereotaxically implanted 1 mm over the nucleus accumbens under sodium thiopental anesthesia (100 mg/kg). The following coordinates from bregma were chosen for the injection site: AP = 1.7 mm, L = 1.6 mm, 3.9 mm below the surface of the skull. The guide cannula (o.d.: 0.45 mm; i.d.: 0.24 mm; length = 8 mm), was lowered at a 12° angle in order to avoid the lateral ventricle and was attached to the skull using acrylic dental cement and jeweler screws. Injections were made using a 9 mm injection cannula (o.d.: 0.23 mm; i.d.: 0.12 mm) inserted into the guide cannula so that the tip of the injection cannula was situated in the nucleus accumbens. This procedure was used in order to prevent lesions prior to the behavioral test. Animals were given 10 days of postoperative recovery, during which the mice were handled daily.

Injected Substances

D-Amphetamine sulfate (0.3 mg/ml; Sigma) was dissolved in 0.9% saline solution. Haloperidol injections consisted of the commercial injectable preparation Haldol (5 mg/ml, Janssen). SKF-38393-A (7 mg/ml) was first dissolved in sodium metabisulfite and then diluted in 10^{-2} M NaCl. Quinpirole hydrochloride LY-171555 (20 mg/ml) and metoclopramide monohydrochloride (30 mg/ml, Sigma) were dissolved in 10^{-2} M NaCl. SCH-23390 (5 mg/ml) was first dissolved in dimethyl formamide (DMF) and was diluted to the final concentration with 10^{-2} M NaCl; sodium hydroxide was added to eliminate precipitation. Dosage of the various drugs were selected after pilot studies or in reference to previous studies (26).

Behavioral Procedure

Mice were placed in hemispheric glass bowls (diameter: 20 cm; height: 8 cm) and the number and the direction (ipsi- or contralateral to the injection site) of complete body rotations made by the mice were recorded by direct observation. The rotations were scored as ipsilateral when the animal turned towards the side of the brain implanted with the guide cannula and as contralateral when the animal turned away from the side of the brain implanted with the guide cannula. Baseline measures were taken for 20 min: 10 min before and 10 min after the insertion of the injection cannula. A polyethylene tubing (o.d.: 0.70 mm; i.d.: 0.30 mm) was attached to the injection cannula at one end and to a 5 μl Hamilton syringe at the other end. The Hamilton syringe was attached to an automatic micropump delivery apparatus (Roucaire, Perfusor VI) set to deliver 0.15 μl/min. After this 20-min period, unilateral intra-accumbens injection of the various substances was started and the animals were continuously observed for two 15-min periods. A first group of mice received a 1 μl intra-accumbens injection of either haloperidol (n = 10, 5 μg, 1.33×10^{-2} μM), SCH-23390 (n = 6, 5 μg, 1.54×10^{-2} μM), metoclopramide (n = 7, 30 μg, 0.1 μM), the SCH-23390 vehicle (n = 6) or 0.9% saline solution (n = 7). All the animals were given two peripheral amphetamine injections (2 mg/kg, IP): the first one was given immediately before the start of the intra-accumbens injection and the second one was given 15 min later. Amphetamine injections were used in order to raise the general activity levels of the animals.

A second group of mice received a 1 μl intra-accumbens injection of either apomorphine (n = 10, 17 μg, 6.36×10^{-2} μM) or the vehicle (n = 5). A third group of mice received a 0.5 μl intra-accumbens injection of either SKF-38393 (n = 9, 3.5 μg, 1.19×10^{-2} μM), LY-171555 (n = 9, 10 μg, 3.91×10^{-2} μM) or the combination of the previous doses of SKF-38393 and LY-171555 (together in 0.5 μl, n = 9). To test the effect of the SKF-38393 and LY-171555 vehicles, 16 of the 27 animals that had received intra-accumbens injections of specific DA agonists three weeks before were assigned to two groups that received an intra-accumbens injection of either the SKF-38393 or the LY-171555 vehicle. None of the animals receiving intra-accumbens injections of DA agonists or their vehicles were given peripheral amphetamine injections. Complete rotations were recorded by direct observation during a 20-min baseline period (10 min before and 10 min after the insertion of the injection cannula) After this period, the animals were observed for two additional 15-min periods.

Data Analysis

The number of ipsi- and contralateral rotations were transformed by dividing the number of ipsilateral rotations by the total number of rotations (both ipsi- and contralateral). The results was multiplied by 100 to give the percentage of ipsilateral rotations. For each experiments, the percentage of ipsilateral rotations made by the animals in each group during the 10-min period before the insertion of the injection cannula was compared to the percentage of ipsilateral rotations made during the 10-min period after the insertion of the injection cannula using *t*-tests. In all cases, no difference was found and consequently the data for these two periods (baseline period) were combined for subsequent analysis. The percentage of ipsilateral rotations were analyzed using a two-way analysis of variance (19) with groups as one factor and time periods as the repeated factor. Spjotvol and Stolin's (SPS) generalization of Tukey's HSD test was used to evaluate pairwise comparisons between the percentage of ipsilateral rotations made during the baseline time period and the percentage of ipsilateral rotations made during the subsequent time periods. These tests were performed in order to detect significant departure from the baseline percentage of ipsilateral rotations.

SPS tests were also used to evaluate pairwise comparisons between the percentage of ipsilateral rotations made by the various groups within each time period. These tests were performed in order to detect if the injected substance produced a significant change in the percentage of ipsilateral rotations as compared to vehicle injection.

Histology

Animals were perfused with 10% formalin solution through the ascending aorta under sodium thiopental anesthesia. The brains were removed and kept in a solution containing 10% formalin and 30% saccharose for at least 7 days. Sixty μm cryostat sections were made and were mounted on glass slides and thionin-stained.

RESULTS

Four animals were discarded due to inaccurate placements: haloperidol (n = 2); apomorphine (n = 2). It is important to note that the discarded animals which had either low cannula placements in the olfactory tubercle or higher placements in the anterior caudate nucleus failed to show any locomotor bias in response to the drug treatments.

DA Antagonists

Figure 1 presents the cannula placements for all animals. The data of the two groups that were injected with the two vehicles

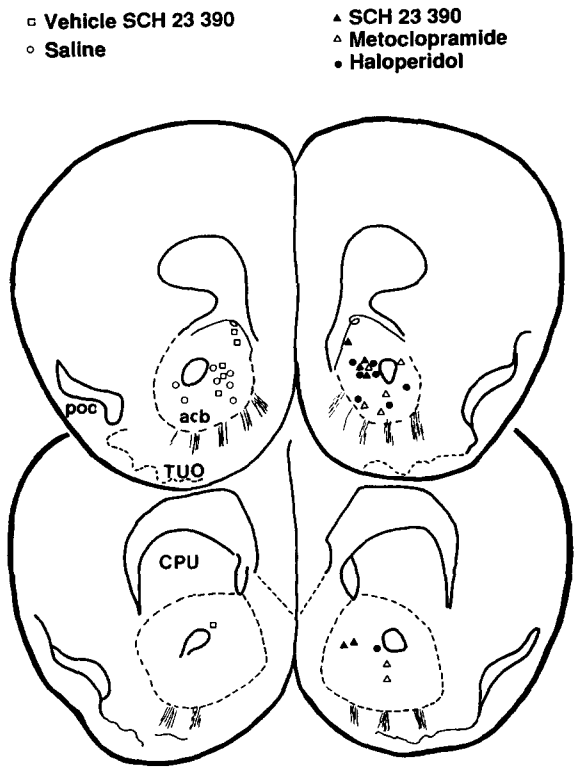

FIG. 1. Cannula placements for animals that received an intra-accumbens injection of either haloperidol (filled circles), SCH-23390 (filled triangles), metoclopramide (open triangles), SCH-23390 vehicle (open squares) or saline (open circles). Abbreviations: acb: nucleus accumbens, CPu: caudate putamen, TUO: olfactory tubercle, POC: primary olfactory cortex.

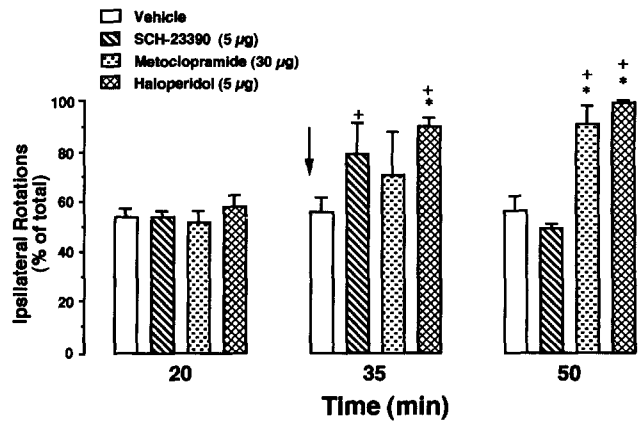

FIG. 2. Effect of intra-accumbens injection of either haloperidol, SCH-23390, metoclopramide or vehicle on the percentage of ipsilateral rotations. The arrow indicates the start of the intra-accumbens injection. The line on each bar indicates the standard error of the mean. Subcutaneous amphetamine injection (2 mg/kg) were given to all animals 20 and 35 min after the start of the experiment. Probabilities associated with pairwise SPS tests are indicated as follows: comparison between the various substances and vehicle $*p<0.05$; intra-group comparison of the preinjection period to each of the postinjection periods $+p<0.05$.

were analyzed first. Since there was no overall significant difference between the percentage of ipsilateral rotations made by these two groups, $F(1,11)=0.29$, their results were combined for subsequent analysis.

The percentage of ipsilateral rotations made by animals that received either the nonspecific DA antagonist haloperidol, the specific D-1 antagonist SCH-23390, the specific D-2 antagonist metoclopramide or vehicle are presented in Fig. 2. There was an overall difference between the percentage of ipsilateral rotations made by the four groups, $F(3,30)=7.07$, $p<0.001$, an overall significant effect of time, $F(2,60)=12.8$, $p<0.005$ and a significant interaction between group and time, $F(6,60)=5.02$, $p<0.0003$.

There was an overall difference between the percentage of ipsilateral rotations made at the various time periods by the animals that received haloperidol, $F(2,60)=11.98$, $p<0.001$, SCH-23390, $F(2,60)=5.05$, $p<0.009$, metoclopramide, $F(2,60)=8.54$, $p<0.001$, but not the vehicles, $F(2,60)=0.06$. SPS tests showed that the animals that received haloperidol made a significantly greater percentage of ipsilateral rotations during the first and second 15-min period that followed the start of the intra-accumbens injection than during the 20-min preinjection period. The animals that received SCH-23390 made a significantly greater percentage of ipsilateral rotations during the first but not during the second 15-min period while the animals that received metoclopramide made a significantly greater percentage of ipsilateral rotations during the second but not during the first 15-min period.

There was an overall significant difference between the percentage of ipsilateral rotations made by the various groups during the two 15-min periods that followed the start of the intra-accumbens injection, $F(3,86)=4.36$ and 13.22 respectively, $p<0.005$, but not during the 20-min preinjection period, $F(3,86)=0.15$. SPS tests showed that the animals that received haloperidol made a significantly greater percentage of ipsilateral rotations than the control animals for each of the postinjection periods, while the animals that received metoclopramide made a significantly greater percentage of ipsilateral rotations than the control animals only during the last 15-min postinjection period. No difference was found between the control and SCH-23390 animals.

These results show that the intra-accumbens injection of haloperidol and metoclopramide together with peripheral amphetamine injections produced a locomotor bias that resulted in ipsilateral turning. This locomotor bias was greater than the one produced by vehicle injections and was not due to a preexisting locomotor bias in these animals. No significant locomotor bias was produced by intra-accumbens vehicle injections.

The results also show that the locomotor bias produced by intra-accumbens SCH-23390 injections was relatively small. Because of the absence in the present experiment of dose-response data, it is not possible to conclude about their relative efficacy. However, at the doses tested, the nonspecific DA antagonist haloperidol induced a more consistent locomotor bias than the specific antagonists SCH-23390 and metoclopramide.

DA Agonists

Figure 3 presents the cannula placements for all animals. Figure 4 presents the percentage of ipsilateral rotations made by animals that received either the nonspecific DA agonist apomorphine, the specific D-1 agonist SKF-38393, or the specific D-2

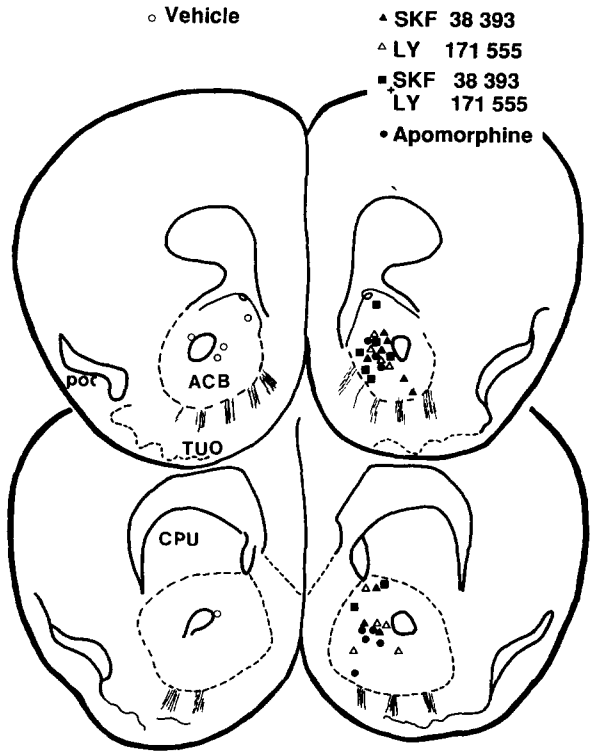

FIG. 3. Cannula placements for animals that received an intra-accumbens injection of either apomorphine (filled circles), SKF-38393 (filled triangles), LY-171555 (open triangles) or the combination of SKF-38393 and LY-171555 (squares). Animals that received the apomorphine vehicle are presented on the left side (open circles). Abbreviations are the same as in Fig. 1.

agonist LY-171555, the combination of SKF-38393 and LY-171555 or apomorphine vehicle.

The results of the animals that received apomorphine or its vehicle were analyzed separately. The was an overall difference between the percentage of ipsilateral rotations made by the two

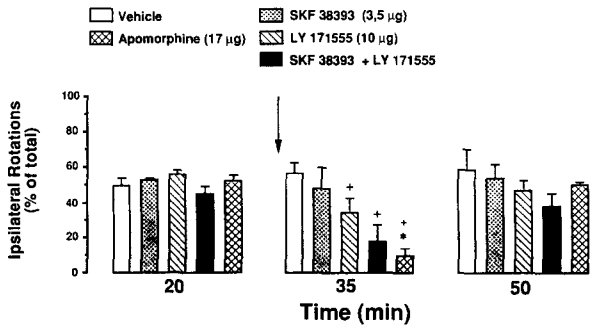

FIG. 4. Effect of intra-accumbens injection of either apomorphine, SKF-38393, LY-171555, the combination of SKF-38393 and LY-171555 or apomorphine vehicle on the percentage of ipsilateral rotations. The line on each bar indicates the standard error of the mean. No amphetamine injections were given. Probabilities associated with pairwise SPS tests are indicated as follows: comparison between apomorphine and apomorphine vehicle $*p<0.05$; intra-group comparison of the preinjection period to each of the postinjection periods $+p<0.05$.

TABLE 1

EFFECT OF INTRA-ACCUMBENS INJECTION OF EITHER THE SKF-38393 VEHICLE OR THE LY-171555 VEHICLE ON THE PERCENTAGE OF IPSILATERAL ROTATIONS (MEAN ± S.E.M.)

	Time		
Group	20	35	50
SKF-38393 vehicle	54.46 ± 5.06	54.82 ± 3.88	49.35 ± 4.51
LY-171555 vehicle	47.76 ± 4.45	45.93 ± 4.38	49.50 ± 4.9

groups, $F(1,11)=12.11$, $p<0.01$, an overall significant effect of time, $F(2,22)=12.44$, $p<0.001$, and a significant interaction between groups and time, $F(2,22)=14.58$, $p<0.0001$. There was an overall difference between the percentage of ipsilateral rotations made during the various time periods by the animals that received apomorphine, $F(2,22)=33.96$, $p<0.001$, but not by the animals that received the vehicle, $F(2,22)=0.73$. SPS tests showed that animals that received an intra-accumbens injection of apomorphine made a significantly smaller percentage of ipsilateral rotations during the first (but not the second) postinjection period than during the 20-min preinjection period. There was an overall significant difference between the percentage of ipsilateral rotations made by the two groups during the first 15-min period, $F(1,31)=39.03$, $p<0.001$, that followed the start of the intra-accumbens injection but not during the 20-min preinjection period, $F(1,31)=1.24$, nor during the last 15-min postinjection period, $F(1,31)=0.12$.

The results of the animals that received SKF-38393, LY-171555 or the combination of the two drugs were analyzed separately. There was no overall difference between the percentage of ipsilateral rotations made by the three groups, $F(2,24)=3.3$, $p=0.054$, and no significant interaction between groups and time, $F(4,48)=1.02$. However, there was a significant effect of time, $F(2,48)=8.03$, $p<0.001$. There was an overall difference between the percentage of ipsilateral rotations made at the various time periods by the animals that received LY-171555, $F(2,48)=33.96$, $p<0.001$, the combination of LY-171555 and SKF-38393, $F(2,48)=5.9$, $p<0.005$, but not SKF-38393, $F(2,48)=0.37$. SPS tests showed that animals that received an intra-accumbens injection of LY-171555 or the combination of LY-171555 and SKF-38393 made a significantly smaller percentage of ipsilateral rotations during the first (but not the second) postinjection periods as compared to baseline.

Finally, the results of the 16 animals that received either the SKF-38393 or LY-171555 vehicle three weeks after receiving intra-accumbens injections of specific DA agonists were analyzed separately and are presented in Table 1. The results of the analysis showed that there was no significant overall difference between group, $F(1,14)=0.8$, time periods, $F(2,28)=0.23$ and no interaction between group and time, $F(2,28)=2.04$.

These results show that the intra-accumbens injection of either apomorphine, LY-171555 or the combination of SKF-38393 and LY-171555 (but not of SKF-38393 alone) produced a locomotor bias that resulted in contralateral turning and that this locomotor bias was not due to a preexisting locomotor bias in these animals. The results also show that no significant locomotor bias was produced by intra-accumbens injection of the various vehicles.

DISCUSSION

The present results show that unilateral intra-accumbens injection of various DA agonists and antagonists resulted in a lo-

comotor bias. These results raise a number of issues that need to be further discussed.

In our experiments, mice were placed into an hemispheric bowl and observed visually. Some authors have criticized the use of spherical containers to observe locomotor bias: they consider that rotational behavior in those conditions are artificial because the animals tend to follow spontaneously the side of the container (4,42). In general, it seems easier to induce a circling behavior in a spherical recipient than in a square one or in an open field (15). In the present experiments, our interest was the measure of direction of locomotion not its absolute intensity. For this type of measure, we have obtained similar results using an hemispheric glass bowl or a plastic square container (unpublished observations).

Other studies have shown that rodents have a slight but measurable lateralization of their orienting and locomotor behavior [reviewed in (3)]. This tendency can be accentuated by peripheral injections of DA agonists (10). Moreover, the locomotor bias appears to be correlated somehow with striatal dopaminergic activity (36).

In our experiments, the influence of this variable was controlled by the preinjection observational period. No systematic lateralization was observed before or after the injection cannula was inserted. The absence of a systematic bias during that period suggest that the locomotor bias observed after the injection was started was not due to preexisting locomotor bias.

Several authors have reviewed extensively the literature on locomotor asymmetry (7, 11, 32). In these reviews, the effects of unilateral manipulations of the basal ganglia (including lesion and electrical or pharmacological stimulation) on the direction of locomotion are described. In general, unilateral lesion of the nigrostriatal dopaminergic system produces, in the rat, a locomotor bias resulting in spontaneous rotations ipsilateral to the lesioned side. This locomotor bias is enhanced by systemic injections of amphetamine (16,40). Similarly, injections of dopamine antagonists in the ventral striatum also produces rotations ipsilateral to the injection site when peripheral amphetamine or apomorphine are administered (22). Other experiments have shown that electrical stimulation of the substantia nigra (1), caudate nucleus (6) and globus pallidus (13) produces rotations contralateral to the stimulated side. These observations and others (9) argue in favor of a model of asymmetry in locomotion based on the asymmetry of basal ganglia dopamine systems.

On the other hand, some results do not fit very well with this model. For example, there appears to be a relationship between locomotion asymmetry and lateralized striatal dopamine activity in male rats but it is not found in female rats (34). Unilateral 6-OHDA lesions of the striatum sometimes paradoxically produces in some individual rats, contralateral asymmetry (35). Unilateral electrical stimulation of the substantia nigra in the rat produces ipsilateral or contralateral rotations depending on the lateral or medial placement of the electrode (41). Similar results were obtained by Gratton and Wise (12) and were interpreted as the indication of inter-individual differences rather than the indication of a placement difference. These individual differences do not invalidate the DA balance model if several animals are observed. However, these differences suggest either more variability in the DA system functional organization or the existence of two functional DA systems on each side of the brain, these systems being more or less in equilibrium.

Our results are consistent in a general way with the DA balance model. They also tend to show that the bilateral DA organization thought to exist for the nigro-striatal pathway may also be true for the mesolimbic and mesocortical (26,27) dopamine systems.

Because of the absence in the present experiments of dose-response data, it is not possible to directly evaluate the relative contribution of D-1 and D-2 receptors in the nucleus accumbens to the locomotor bias observed. However, the consistent pattern observed is the relative inability of D-1 specific drugs to produce an important effect compared to D-2 specific drugs, while the strongest and most consistent effects are observed with the nonspecific agonist or antagonist or with a combination of D-1 and D-2 DA agonists. This synergism between DA agonists has been described previously for locomotion and stereotypy (33,37) and may reflect a functional interaction between D-1 and D-2 receptors (22, 23, 25, 43). More research will be needed to confirm the role of dopamine receptors in the nucleus accumbens in the directionality of locomotor activity.

ACKNOWLEDGEMENTS

This research was supported by grants to the URA No. 339 from the CNRS and from the University of Bordeaux I. O.M. was supported by a fellowship from the Morocco government. C.M. was a postdoctoral fellow of the Fonds pour la Recherche en Santé du Québec during the course of this investigation. We acknowledge the kind gift of SKF-38393 from Smith Kline and French, UK, of LY-171555 from Lilly Research Laboratories, Indianapolis, USA and of SCH-23390 from Schering Co., USA.

REFERENCES

1. Arbuthnott, G. W.; Ungerstedt, U. Turning behaviour induced by electrical stimulation of nigro-neostriatal system of the rat. Exp. Neurol. 47:162–172; 1975.
2. Arnt, J. Neuroleptic inhibition of 6,7-ADTN-induced hyperactivity after injection into the nucleus accumbens. Specificity and comparison with other models. Eur. J. Pharmacol. 90:47–55; 1983.
3. Carlson, J. N.; Glick, S. D. Cerebral lateralization as a source of inter-individual differences in behavior. Experientia 45:788–798; 1989.
4. Cohn, M. L.; Cohn, M. Barrel rotation induced by somatostatin in the nonlesioned rat. Brain Res. 96:138–141; 1975.
5. Colle, L. M.; Wise, R. A. Nucleus accumbens contributes to the direction of dopamine-dependent circling. Soc. Neurosci. Abstr. 14: 662; 1988.
6. Cools, A. R. Chemical and electrical stimulation of the caudate nucleus in freely moving cats: the role of dopamine. Brain Res. 58: 437–451; 1973.
7. Dankova, J.; Bédard, P.; Langelier, P.; Poirier, L. J. Dopaminergic agents and circling behaviour. Gen. Pharmacol. 9:295–302; 1978.
8. Elkhawad, A. O.; Woodruff, G. N. Studies on the behavioural pharmacology of a cyclic analogue of dopamine following its injection into the brains of conscious rats. Br. J. Pharmacol. 54:107–114; 1975.
9. Freed, C. R.; Yamamoto, B. K. Regional brain dopamine metabolism: a marker for the speed, direction and posture of moving animals. Science 229:62–65; 1985.
10. Glick, S. D.; Hinds, P. A.; Baird, J. L. Two kinds of nigrostriatal asymmetry: relationship to dopaminergic drug sensitivity and 6-hydroxydopamine lesion effects in Long-Evans rats. Brain Res. 450: 334–341; 1988.
11. Glick, S. D.; Jerussi, T. P.; Fleisher, L. N. Turning in circles: the neuropharmacology of rotation. Life Sci. 18:889–896; 1976.
12. Gratton, A.; Wise, R. A. Mapping of contraversive and ipsiversive circling response to ventral tegmental and substantia nigra electrical stimulation. Physiol. Behav. 35:61–65; 1985.
13. Hassler, R.; Dieckmann, G. Locomotor movements in opposite direction by stimulation of pallidum or of putamen. J. Neurol. Sci. 8:189–195; 1968.

14. Herrera-Marschitz, M.; Forster, C.; Ungerstedt, U. Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats II. The striatum of the rat is heterogeneously organized for rotational behavior. Acta Physiol. Scand. 125:529–535; 1985.
15. Jerussi, T. P.; Glick, T. D. Drug-induced rotation in rats without lesions: Behavioral and neurochemical indices of a normal asymmetry in nigrostriatal function. Psychopharmacology (Berlin) 47:249–260; 1976.
16. Kafetzopoulos, E.; Vlaha, V.; Konitsiotis, S. Different patterns of rotational behavior in rats after dorsal and ventral striatal lesions with ibotenic acid. Pharmacol. Biochem. Behav. 29:403–408; 1987.
17. Kelly, P. H.; Roberts, D. C. S. Effects of amphetamine and apomorphine on locomotor activity after 6-OHDA and electrolytic lesions of the nucleus accumbens septi. Pharmacol. Biochem. Behav. 19:137–143; 1983.
18. Kelly, P. H.; Seviour, P. W.; Iversen, S. D. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. 94:507–522; 1975.
19. Kirk, R. E. Experimental design: Procedures for the behavioral sciences. Belmont, CA: Brooks/Cole; 1982.
20. Koob, G. F.; Riley, S. J.; Smith, S. C.; Robbins, T. W. Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. J. Comp. Physiol. Psychol. 92:717–727; 1978.
21. Koob, G. F.; Stinus, L.; Le Moal, M. Hyperactivity and hypoactivity produced by lesions to the mesolimbic dopamine system. Behav. Brain Res. 3:341–359; 1981.
22. Koshikawa, N.; Mori, E.; Maruyama, Y.; Yatsushige, N.; Kobayashi, M. Role of dopamine D-1 and D-2 receptors in the ventral striatum in the turning behaviour of rats. Eur. J. Pharmacol. 178: 233–237; 1990.
23. Koshikawa, N.; Tomiyama, K.; Omiya, K.; De Beltran, K. K.; Kobayashi, M. Dopamine D-1-receptor but not D-2-receptor stimulation of the dorsal striatum potentiates apomorphine-induced jaw movements in rats. Eur. J. Pharmacol. 178:189–194; 1990.
24. Kubos, K. L.; Moran, T. H.; Robinson, R. G. Differential and asymmetrical behavioral effects of electrolytic of 6-hydroxydopamine lesions in the nucleus accumbens. Brain Res. 401:147–151; 1987.
25. LaHoste, G. J.; Marshall, J. F. Nigral D1 and striatal D2 receptors mediate the behavioral effects of dopamine agonists. Behav. Brain Res. 38:233–242; 1990.
26. Morency, M. A.; Stewart, R. J.; Beninger, R. J. Effects of unilateral microinjections of sulpiride into the medial prefrontal cortex on circling behavior of rats. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 9:735–738; 1985.
27. Morency, M. A.; Stewart, R. J.; Beninger, R. J. Circling behavior following unilateral microinjections of cocaine into the medial prefrontal cortex: Dopaminergic or local anesthetic effect? J. Neurosci. 7:812–818; 1987.
28. Mrabet, O.; Messier, C.; Destrade, C. Unilateral intra-accumbens injection of a dopaminergic agonist and two dopaminergic antagonists produces circling in mice. C. R. Acad. Sci. (Paris) 309(III): 77–82; 1989.
29. Mrabet, O.; Messier, C.; Mons, N.; Destrade, C.; Geffard, M. Locomotor bias produced by intra-accumbens or intra-caudate injection of polyclonal dopamine antiidiotypic antibodies. J. Hirnforsch.; in press.
30. Pijnenburg, A. J. J. Ergometrine induced locomotor activity following intracerebral injection into the nucleus accumbens. Brain Res. 59:289–302; 1973.
31. Pijnenburg, A. J. J.; Honig, W. M. M.; Van Rossum, J. M. Inhibition of d-amphetamine-induced locomotor activity by injection of haloperidol into the nucleus accumbens of the rat. Psychopharmacologia 41:87–95; 1975.
32. Pycock, C. J. Turning behaviour in animals. Neuroscience 5:461–514; 1980.
33. Robertson, G. S.; Robertson, H. A. Synergistic effects of D1 and D2 dopamine agonists on turning on turning behaviour in rats. Brain Res. 384:387–390; 1986.
34. Robinson, T. E.; Becker, J. B.; Ramirez, V. D. Sex differences in amphetamine-elicited rotational behavior and the lateralization of striatal dopamine in rats. Brain Res. Bull. 5:539–545; 1980.
35. Shapiro, R. M.; Glick, S. D.; Camarota, N. A. A two-population model of rat rotational behavior: effects of unilateral nigrostriatal 6-hydroxydopamine on striatal neurochemistry and amphetamine-induced rotation. Brain Res. 426:323–331; 1987.
36. Shapiro, R. M.; Glick, S. D.; Hough, L. B. Striatal dopamine uptake asymmetrics and rotational behavior in unlesioned rats: revising the model? Psychopharmacology (Berlin) 89:25–30; 1986.
37. Starr, M. S.; Starr, B. S. Behavioral synergism between the dopamine agonists SKF 38393 and LY 171555 in dopamine-depleted mice: Antagonism by sulpiride reveals only stimulant postsynaptic D-2 receptors. Pharmacol. Biochem. Behav. 33:41–44; 1989.
38. Starr, M. S.; Summerhayes, M. Multifocal brain sites for apomorphine-induced circling and other stereotyped motor behaviours in the 6-hydroxydopamine-lesioned rat. Neurosci. Lett. 34:277–282; 1982.
39. Staton, D. M.; Solomon, P. R. Microinjection of d-amphetamine into the nucleus accumbens and caudate-putamen differentially affect stereotypy and locomotion in the rat. Physiol. Psychol. 12:159–162; 1984.
40. Ungerstedt, U. Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behavior. Acta Physiol. Scand. 367(Suppl.):69–93; 1971.
41. Vaccarino, F. J.; Franklin, K. B. Opposite locomotor asymmetries elicited from the medial and lateral SN by modulation of SN DA receptors. Pharmacol. Biochem. Behav. 21:73–77; 1984.
42. Watanabe, H.; Watanabe, K. Enhancement of apomorphine-induced rotational behaviour in rats following the combination of 6-hydroxydopamine and electrolytic lesions in the substantia nigra. Jpn. J. Pharmacol. 29:93–104; 1979.
43. Weick, B. G.; Walters, J. E. Effects of D1 and D2 dopamine receptor stimulation on the activity of substantia nigra pars reticulata neurons in 6-hydroxydopamine lesioned rats: D1/D2 coactivation induces potentiated responses. Brain Res. 405:234–246; 1987.