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Rotational Bias in Intact Rats Following Intrastriatal Injections of Dopaminergic Drugs

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SMITH, I. D., M. A. SUTTON AND R. J. BENINGER. *Rotational bias in intact rats following intrastriatal injections of dopaminergic drugs.* PHARMACOL BIOCHEM BEHAV **58**(2) 431–441, 1997.—Following unilateral 6-OHDA lesions of the striatum, systemic dopamine agonists produce rotation due to receptor supersensitivity. Rotation following intrastriatal dopamine agonists in intact rats also has been reported, although these studies are few and contradictory. Dorsal striatal injection (0.5 μl) of the direct dopamine agonist apomorphine failed to caused rotation. In addition, neither the D1 agonist SKF 81297, the cAMP analogue Sp-cAMPS, nor the D2 agonist quinpirole affected rotation. In contrast, the dopamine releaser amphetamine (1.1, 10.9, 108.7 mM) caused significant contralateral rotation. This effect was reversed by coinjection of the D1 antagonist SCH 23390 (3.1 mM) but not by the D2 antagonist eticlopride. Rotation was also reversed by TTX coinjections (100 μM) but not by the NMDA antagonist AP7 or the kainate/AMPA antagonist CNQX. Thus, direct dopamine agonists in the striatum failed to cause behavioral asymmetry, whereas amphetamine induced contralateral rotation. This effect is mediated primarily by D1 receptors and requires concurrent neuronal activation that appears to be independent of glutamate receptor stimulation. These results are consistent with studies of Fos induction in normosensitive animals following dopamine agonists and are discussed in terms of changes in basal ganglia output pathway activity. © 1997 Elsevier Science Inc.

Dopamine Rotation Striatum D1 D2 Glutamate Amphetamine

ROTATION in rats has long been used as a behavioral measure of dopamine receptor stimulation in the basal ganglia. The striatum is the principal input nucleus of this region, receiving glutamatergic projections from the cerebral cortex and ascending dopaminergic fibers from the substantia nigra pars compacta. Studies of experimental Parkinsonism have shown that this region plays a role in the control of voluntary movement. Rats with unilateral depletion of striatal dopamine will rotate toward the side with lower dopamine receptor stimulation (17,54). The dorsal striatum has been implicated in this behavior pattern. The dorsal striatum receives glutamatergic afferents (49) from both sensory and motor areas of the cerebral cortex (31), and neurons in the dorsolateral striatum respond to limb and body movement (9). Moreover, recent studies have shown that dorsal striatal injections of glutamate receptor agonists in unlesioned rats cause movement asymmetry away from the side of the injection and that this contralateral rotation depends on concurrent dopamine receptor stimulation (5,42,47,48,52). In addition, contralateral rotation has been recorded following intrastriatal injections of caffeine (25), neuropeptide Y (35), the muscarinic agonist carbachol (32), and the γ-aminobutyric acid (GABA)-A antagonist bicuculline (32,47).

Although dopamine agonist injections into the supersensitive dopamine-depleted striatum will cause contralateral rotation (16,50), the effects of striatal dopamine agonists in intact rats remain unclear. Most investigators have found no rotation with either direct or indirect dopamine agonist injections (18,26,32,50), thereby casting doubt on the simple maxim that an imbalance in dopamine receptor stimulation causes locomotor asymmetry. However, recent reports have indicated that amphetamine injections into the striatum are effective in causing a rotational bias (35), suggesting that releasing endogenous dopamine stores might be more effective than exogenous receptor agonists in producing reliable behavioral effects.

The neuromodulatory effects of dopamine may occur by altering concurrent glutamate receptor stimulation. Thus, coapplication of dopamine can augment glutamate-mediated excitation (12,13), and decreases in cortical glutamate input drastically reduce the excitatory response of striatal cells to amphetamine application (52). The behavioral relevance of

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this interaction has been suggested by a study showing that a glutamate antagonist injection into the nucleus accumbens blocks amphetamine-induced place-preference conditioning (29). The role of glutamate–dopamine interaction in unconditioned behavior such as locomotor asymmetry and activity, however, is not fully understood.

The present study investigated the ability of both direct and indirect dopamine agonists injected into the dorsal striatum to cause rotation in rats. Molecular cloning experiments have described at least 5 dopamine receptor subtypes (D1–D5) that can be classified into D1 (D1, D5) and D2 (D2, D3, D4) subgroups by their affinity to standard binding ligands (45). In the present study, agonists and antagonists specific to D1 and D2 receptors were used to clarify the role of dopamine receptor subtypes in the intact animal in locomotor activation. The involvement of glutamate receptor subtypes N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate in amphetamine-mediated behaviors was examined.

METHODS

Animals and Surgery

Male Wistar rats (Charles River, Canada) were caged individually in a climate-controlled environment and given free access to food and water. All animal procedures were in accordance with the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care and relevant university policy and were approved by the Queen's University Animal Care Committee.

Rats were anesthetized with halothane (1.5–4%) and implanted unilaterally with a 23-gauge guide cannula (0.6 mm outer diameter) in the dorsal striatum (A −0.3 mm, L 3.0 mm, V 3.5 mm) according to Paxinos and Watson (39). At the same time, an arborite chip was affixed to the skull with dental cement for attachment to a rotometer apparatus. Rats were allowed to recover for 5 days before the 13-day experimental protocol began.

Apparatus

The rotometer was a rotating disk with a single slot that moved past 4 infrared beams oriented in equal 90° intervals. Photocell beam breaks were recorded on an experimenter-controlled circuit board connected to a Macintosh microcomputer. A sliding, pivoting stainless steel rotometer lead was clipped to the arborite chip in the rat's skull mount, allowing free movement around the experimental chamber. Any postural turns involving the head or circling locomotor activity were registered and recorded as beam breaks. Data were stored as the number of full turns in each direction occurring in 1-min bins over a 20-min recording session. To register a full turn, a sequence of 5 beam breaks must have occurred in one direction. The rat and rotometer was located in a plastic cylinder, 45 cm in diameter × 30 cm high, inside a sound-attenuated, ventilated and illuminated box.

Procedure

The procedure consisted of a 13-day protocol of 7 rotation activity recording sessions; sessions were separated by 2 days. For dose–response tests of drug effects (SKF 81297, Sp-cAMPS, quinpirole, apomorphine, amphetamine), there were no injections before the first and seventh sessions and saline injections before the second and sixth sessions. Three drug doses were given in a counterbalanced order over the third, fourth and fifth sessions. For the 2 experiments testing amphetamine effect reversal, the saline sessions were replaced by a single dose of amphetamine alone (20 μg). In the case of D1 and D2 antagonist testing, 4 sessions separated initial and final amphetamine injections and consisted of counterbalanced injections of SCH 23390 and eticlopride alone and in a mixture with amphetamine. This method resulted in a total of 8 treatment sessions for this experiment. In the cases of eticlopride doses and glutamate antagonist testing, mixtures of the agonist and various antagonists [eticlopride, AP7, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), tetrodotoxin (TTX)] were administered in a counterbalanced order over the third, fourth and fifth sessions. The treatments for each session in 8 experiments, including doses of the various drugs administered, are summarized in Table 1.

As an index of rotational behavior, a ratio was calculated for each animal over each session. This measure is the number of full turns made ipsilateral to the injection side divided by the total number of full turns. Thus, a ratio of 0.5 would indicate a nondirectionally biased session, and a lower or higher ratio would indicate contralateral or ipsilateral rotation, respectively. For comparison, contralateral full turns were also recorded and analyzed. The total number of full turns over a session was analyzed as a measure of overall locomotor activity.

Following the complete protocol, some rats were observed in the experimental chamber for 20 min to describe qualitative aspects of their behavior. These observations were made in 2 groups of rats: 1 group following no injection and injections of apomorphine and 1 group following no injection and injections of quinpirole.

Central Injections, Drugs and Histology

Injections of 0.5 μl of fluid were made through vinyl tubing attached to a 30-gauge cannula (0.3 mm outer dimater, 0.15 mm inner diameter) extending 1 mm below the guide cannula (V 4.5 mm). Injections were made with an infusion pump over a 30-s period, and the cannula was left in place for an additional 30 s to allow for drug diffusion. Rats were unrestrained during injections.

Drug freebases were dissolved in either saline (d-amphetamine, eticlopride, SKF 81297, Sp-cAMPS, quinpirole, AP7; Research Biochemicals International) or a saline solution buffered with NaOH [CNQX (Tocris Cookson), TTX (Sigma)]. The pH of all solutions was adjusted to 7–8 with 1 M NaOH or 1 M HCl. Solutions were injected at room temperature. Apomorphine and amphetamine solutions were mixed immediately prior to injections.

After behavioral testing was completed, rats were killed through inhalation of CO_2. Brains were extracted and stored in a 10% formalin solution for at least 10 days. To verify cannula injection sites, coronal sections of brain tissue (60 μm) were sliced on a freezing-stage microtome, mounted and stained with thionine.

Statistics

Statistical analyses for each experiment consisted of a single-factor repeated measures analysis of variance (ANOVA) for overall treatment effects. Changes in both rotation ratio and total full turns were analyzed in the same manner. The Geisser–Greenhouse adjusted degrees of freedom for repeated measures designs were used, although, for clarity, unadjusted degrees of freedom are presented in the Results section. Changes in behavioral measures between the first and

TABLE 1

DRUG DOSES AND TREATMENT PROTOCOL FOR EACH SESSION FOR 8 EXPERIMENTS

Exp. #	*n*	1	2	3	4	5	6	7	8
1	10	NI	Saline	SKF 0.19 μg (1 mM)*	SKF 1.9 μg (10 mM)	SKF 18.6 μg (100 mM)	Saline	NI	
2	13	NI	Saline	Sp-cAMPS 0.05 μg (0.11 mM)	Sp-cAMPS 0.5 μg (1.1 mM)	Sp-cAMPS 5 μg (11.2 mM)	Saline	NI	
3	12	NI	Saline	QUIN 0.1 μg (0.78 mM)	QUIN 1 μg (7.8 mM)	QUIN 10 μg (78.2 mM)	Saline	NI	
4	9	NI	Saline	APO 0.1 μg (0.66 mM)	APO 1 μg (6.6 mM)	APO 10 μg (65.8 mM)	Saline	NI	
5	10	NI	Saline	AMPH 0.8 μg (1.09 mM)	AMPH 4 μg (10.9 mM)	AMPH 20 μg (108.7 mM)	Saline	NI	
6	11	NI	AMPH 20 μg (108.7 mM)	ETIC 1 μg (5.3 mM)	AMPH+ETIC	SCH 0.5 μg (3.1 mM)	AMPH+SCH	AMPH 20 μg (108.7 mM)	NI
7	11	NI	AMPH 20 μg (108.7 mM)	AMPH+ETIC 0.1 μg (0.53 mM)	AMPH+ETIC 1 μg (5.3 mM)	AMPH+ETIC 10 μg (53.8 mM)	AMPH 20 μg (108.7 mM)	NI	
8	10	NI	AMPH 20 μg (108.7 mM)	AMPH+CNQX 29 ng (250 μM)	AMPH+AP7 0.1 μg (0.9 mM)	AMPH+TTX 16 ng (100 mM)	AMPH 20 μg (108.7 mM)	NI	

*Drug doses indicated as absolute quantity injected in 0.5 μl and as concentration. NI, no injection; SKF, SKF 81297; QUIN, quinpirole; APO, apomorphine; AMPH amphetamine; ETIC, eticlopride; SCH, SCH 23390. Drug treatments 3,4 and 5 administered in a counterbalanced order across sessions.

final no-injection sessions were examined with a correlated *t*-test. If no difference was found in these measures, values were averaged before the ANOVA was performed. To test drug doses against a single control measure, the two saline injections were also compared using a correlated *t*-test and collapsed into a single mean if no difference was found. Similarly, the two baseline amphetamine sessions in the reversal studies (experiments 6 and 7) were compared and, if no differences were found, were collapsed into a single control mean against which antagonist coinjections were tested. Dunnett's *t*-tests were used as post hoc tests of drug effects by comparing control conditions against subsequent amphetamine injections or amphetamine/antagonist coinjections. In the cases of testing the initial efficacy of drug doses (SKF 81297, Sp-cAMPS, quinpirole, apomorphine, amphetamine), Dunnett's tests incorporated the saline vehicle session as the control. Experiments testing the reversal of agonist effects used the amphetamine session as the control.

RESULTS

Histological examination of brains from rats in the 7 experiments revealed that of the 87 animals used in this study, 75 cannula placements were suitable for data analysis. Of the 12 rats excluded from the analyses, 5 cannula placements were located dorsal to the corpus callosum. Seven animals in various experiments had considerable lesioned tissue that surrounded the guide cannula tract and affected substantial portions of the dorsal striatum. The remaining rats had injection sites located in the dorsal striatum and exhibited minimal gliosis in the region of the injection tip, and the surrounding neuropil was judged to be intact. Figure 1 illustrates the location of the cannula placements for each study and shows a photomicrograph of a representative section from the brain of a rat that received 2 injections of saline and 3 doses of amphetamine.

For each experiment, the turning ratio and total full turn means of the initial and final no-injection sessions were compared with a correlated *t*-test. In addition, the initial and final saline sessions (experiments 1–5) or amphetamine sessions (experiments 6–8) were compared. No significant differences were found between any of these 14 comparisons, and each pair of means was averaged to provide single control measures for use in the ANOVAs of treatment effects. These averaged control values are presented in the figures showing turning ratios and in Table 2 showing the total full turns for each treatment in 8 experiments. Table 2 also shows contralateral full turns for each session and indicates significant treatment and post hoc drug effects for both contralateral and total full turns.

Direct Dopamine Agonists

Intrastriatal injections of the full D1 agonist SKF 81297 at 3 doses [0.19, 1.9, 18.6 μg (1, 10, 100 mM)] failed to alter rotational behavior [$F(4, 40) < 1, p > 0.05$, Fig. 2a] or overall locomotor activity [$F(4, 40) = 1.22, p > 0.05$]. Similarly, injections of the protein kinase A activator Sp-cAMPS [0.05, 0.5, 5 μg (0.11, 1.1, 11.2 mM)] did not have a significant effect on rotation [$F(4, 52) < 1, p > 0.05$, Fig. 2b] or on total full turns [$F(4, 52) = 1.18, p > 0.05$].

Injections of the D2 agonist quinpirole [0.1, 1, 10 μg (0.78, 7.8, 78.2 mM)] also failed to cause a rotation bias [$F(4, 48) < 1$, $p > 0.05$, Fig. 2c]. However, intrastriatal quinpirole did affect overall locomotor activity [$F(4, 48) = 8.51, p < 0.01$], causing a significant decrease in total full turns at the high dose as compared with saline ($t = 3.95, p < 0.01$, Table 2). This effect was dose dependent, with the 10-μg dose resulting in significantly fewer full turns than either the 1 μg ($p < 0.01$) or 0.1 μg ($p < 0.01$) dose.

Injections of the full dopamine agonist apomorphine [0.1, 1, 10 μg (0.66, 6.6, 65.8 mM)] into the dorsal striatum showed a profile similar to that of quinpirole, causing no significant rotation bias [$F(4, 36) < 1, p > 0.05$, Fig. 2d], but resulting in a significant, dose-dependent decrease in locomotor activity [$F(4, 36) = 3.92, p < 0.05$]. The 10-μg dose of apomorphine

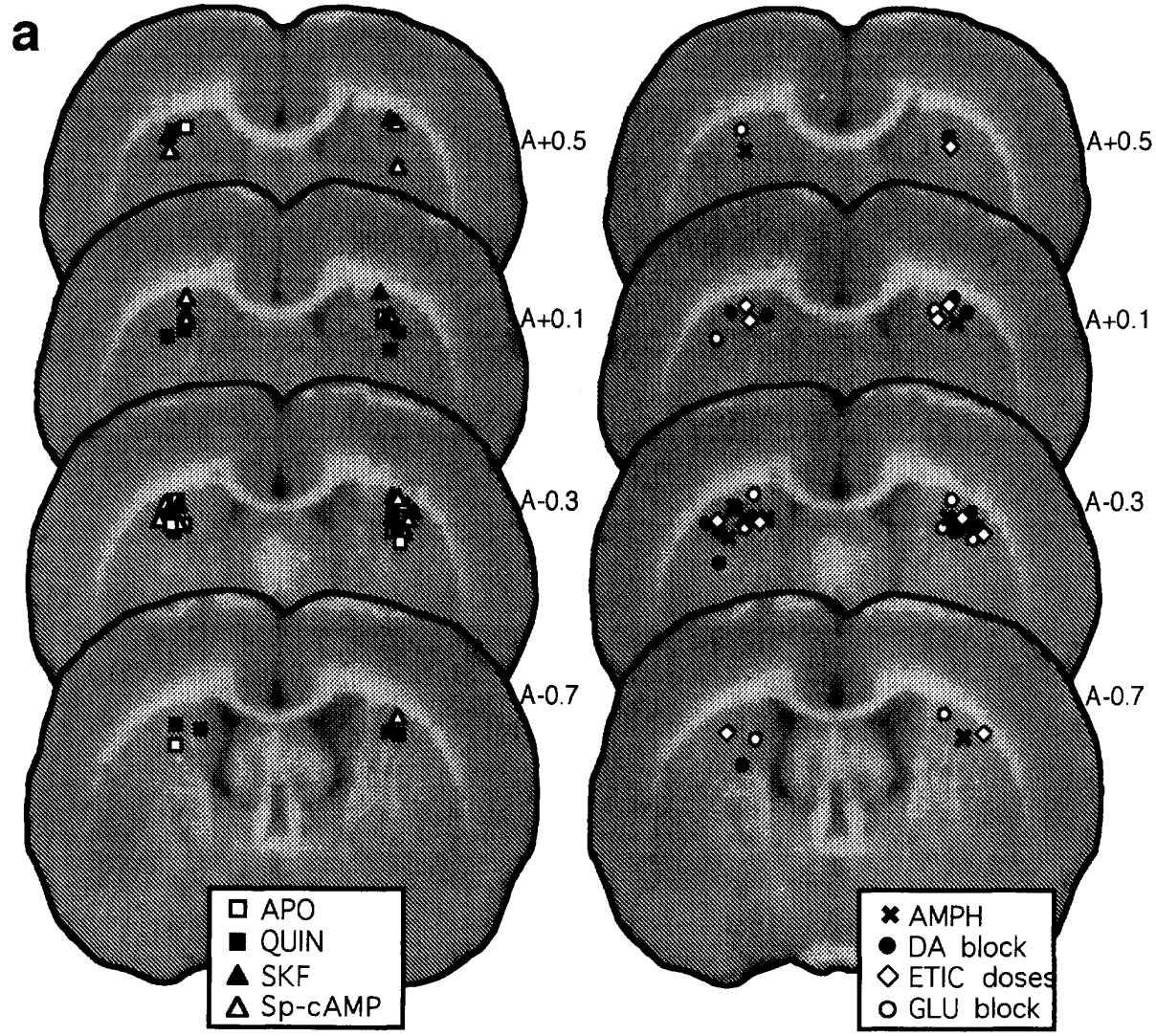

FIG. 1. Location of cannulae placements in the dorsal striatum. a: A schematic drawing showing the placement of cannulae for 8 experiments. Dose–response studies for the following compounds are represented in the left panel: APO, apomorphine; QUIN, quinpirole; SKF, SKF 81297. The right panel indicates placements for the following experiments: AMPH, amphetamine dose response; DA block, amphetamine coinjected with eticlopride and SCH 23390; ETIC doses, amphetamine coinjected with three doses of eticlopride; GLU block, amphetamine coinjected with AP7, CNQX and TTX. b: Representative coronal section of rat brain near anterior −0.3 from bregma, showing cannula tract in the dorsal striatum. This section was taken from a rat in which two 0.5-μl saline injections and three 0.5-μl injections of amphetamine at three doses were made, with 1 day between each injection.

TABLE 2

EFFECTS OF INTRASTRIATAL DOPAMINERGIC DRUGS ON TOTAL AND CONTRALATERAL FULL TURNS (MEAN ± SEM) IN 20-MIN SESSIONS

Experiment	NI mean	SAL mean	Low dose*	Med. dose	High dose	
SKF 81297						
Total	14.0 ± 1.8	14.7 ± 2.2	17.2 ± 2.8	11.5 ± 2.3	14.4 ± 2.1	
Contra	6.4 ± 1.3	6.6 ± 1.3	8.9 ± 1.9	5.2 ± 1.3	6.2 ± 1.5	
Sp-cAMPS						
T	12.0 ± 1.6	12.4 ± 1.4	15.7 ± 2.0	14.2 ± 2.5	12.8 ± 2.0	
C	5.0 ± 0.8	5.4 ± 0.8	7.1 ± 1.5	6.9 ± 1.1	5.8 ± 1.2	
Quinpirole						
T†	15.7 ± 1.4	13.3 ± 1.2	12.9 ± 1.9	15.4 ± 2.5	5.1 ± 0.7§	
C†	6.9 ± 0.8	5.4 ± 0.7	5.8 ± 1.3	7.3 ± 1.3	2.5 ± 0.5§	
Apomorphine						
T†	16.6 ± 1.8	16.9 ± 1.8	16.6 ± 2.5	16.4 ± 2.9	9.0 ± 1.2§	
C	8.5 ± 1.2	8.8 ± 1.7	9.1 ± 2.0	7.7 ± 1.9	5.1 ± 1.2	
Amphetamine						
T	17.9 ± 1.9	14.7 ± 1.6	16.8 ± 3.0	16.3 ± 2.5	18.1 ± 2.5	
C†	8.3 ± 0.9	7.7 ± 1.5	8.0 ± 1.6	7.8 ± 1.2	12.1 ± 2.0§	
	NI mean	AMPH mean	Antagonist*	Antagonist	Antagonist	AMPH+SCH
AMPH+DA antagonists						
T	16.5 ± 1.8	18.0 ± 2.6	19.2 ± 2.6	17.9 ± 2.5	15.9 ± 2.3	16.9 ± 3.1
C‡	6.8 ± 0.9¶	11.6 ± 1.7	10.4 ± 1.7	10.5 ± 1.8	10.8 ± 1.9	7.5 ± 1.7¶
AMPH+ETIC doses						
T	19.5 ± 3.0	19.7 ± 2.7	20.1 ± 2.2	21.0 ± 2.7	18.5 ± 3.5	
C‡	8.9 ± 2.1¶	13.2 ± 2.4	12.9 ± 2.8	13.5 ± 2.5	10.7 ± 2.0	
AMPH+GLU antagonists						
T	14.1 ± 0.9	17.4 ± 1.9	17.4 ± 2.9	17.6 ± 3.0	18.5 ± 3.5	
C†	6.8 ± 0.7¶	10.3 ± 1.3	9.4 ± 1.4	10.2 ± 2.3	5.1 ± 1.0§	

*Counterbalanced agonist and antagonist treatments as indicated in Table 1.

NI: No Injection; SAL: saline; T: total full turns; C: contralateral full turns; AMPH: amphetamine; SCH: SCH 23390; ETIC: eticlopride; DA: dopamine; GLU: glutamate.

†p<.01, ‡p<.05 ANOVA main effect across sessions; §p<.01, ¶p<.05 vs. saline or AMPH control sessions.

caused significantly fewer total full turns than the mean of the saline control sessions ($t = 3.24, p < 0.01$).

To characterize further the effects of intrastriatal injections of high doses of apomorphine and quinpirole, visual observations were made in a small number of rats following these treatments. Rats injected with 10 μg apomorphine ($n = 4$) or 10 μg quinpirole ($n = 4$) exhibited hypolocomotion accompanied by mild orofacial stereotypy when compared with a no-injection condition. These behaviors had an onset of approximately 4 min following the injections and consisted primarily of vacuous chewing and sniffing. When placed on a catalepsy bar, the release and locomotor behavior of injected rats was similar to those in the no-injection sessions.

Amphetamine and Antagonists

In contrast to the failure of direct dopamine agonists to cause a rotational bias, injections of the indirect dopamine agonist amphetamine [0.8, 4, 20 μg (1.09, 10.9, 108.7 mM)] resulted in significant contralateral rotation [$F(4, 40) = 5.05$, $p < 0.01$, Fig. 3a]. The 20-μg dose of amphetamine resulted in greater contralateral rotation than did injections of the saline vehicle ($t = 3.32, p < 0.01$). Furthermore, this increase in contralateral rotation occurred with no concomitant change in total full turns ($p > 0.05$). A correlation analysis was undertaken to examine whether amphetamine treatments simply enhanced preexisting rotation biases of individual rats. The turning ratios of animals receiving initial saline treatments and 20-μg amphetamine treatments were not significantly correlated ($r = 0.312, p > 0.05, n = 23$).

To evaluate the role of dopamine receptor subtypes in amphetamine-induced rotation, an experiment was performed in which amphetamine was coinjected with a selective D1 (SCH 23390) or D2 (eticlopride) antagonist. In addition, injections of the antagonists alone were made to observe their affect on baseline rotation and activity. The rotation caused by amphetamine was significantly reversed by SCH 23390 but not by eticlopride at doses that failed to affect behavior when injected alone. The ANOVA comparing all treatment conditions revealed a significant main effect on rotation [$F(5, 50) = 2.91$, $p < 0.05$, Fig. 3b] but no effect on total full turns ($p > 0.05$). The contralateral rotation caused by 20 μg amphetamine was replicated when compared with the no-injection mean value ($t = 3.35, p < 0.01$). Whereas coinjection of 0.5 μg (3.1 mM) SCH 23390 with 20 μg amphetamine caused significantly less contralateral rotation when compared with amphetamine alone ($t = 2.98, p < 0.05$), coinjection of 1 μg (5.3 mM) eticlopride was not significantly different than amphetamine alone. Neither 0.5 μg SCH 23390 nor 1 μg eticlopride caused a significant rotational bias when injected alone ($p > 0.05$).

The effects of increasing doses of the D2 antagonist eticlopride on amphetamine-induced rotation were investigated.

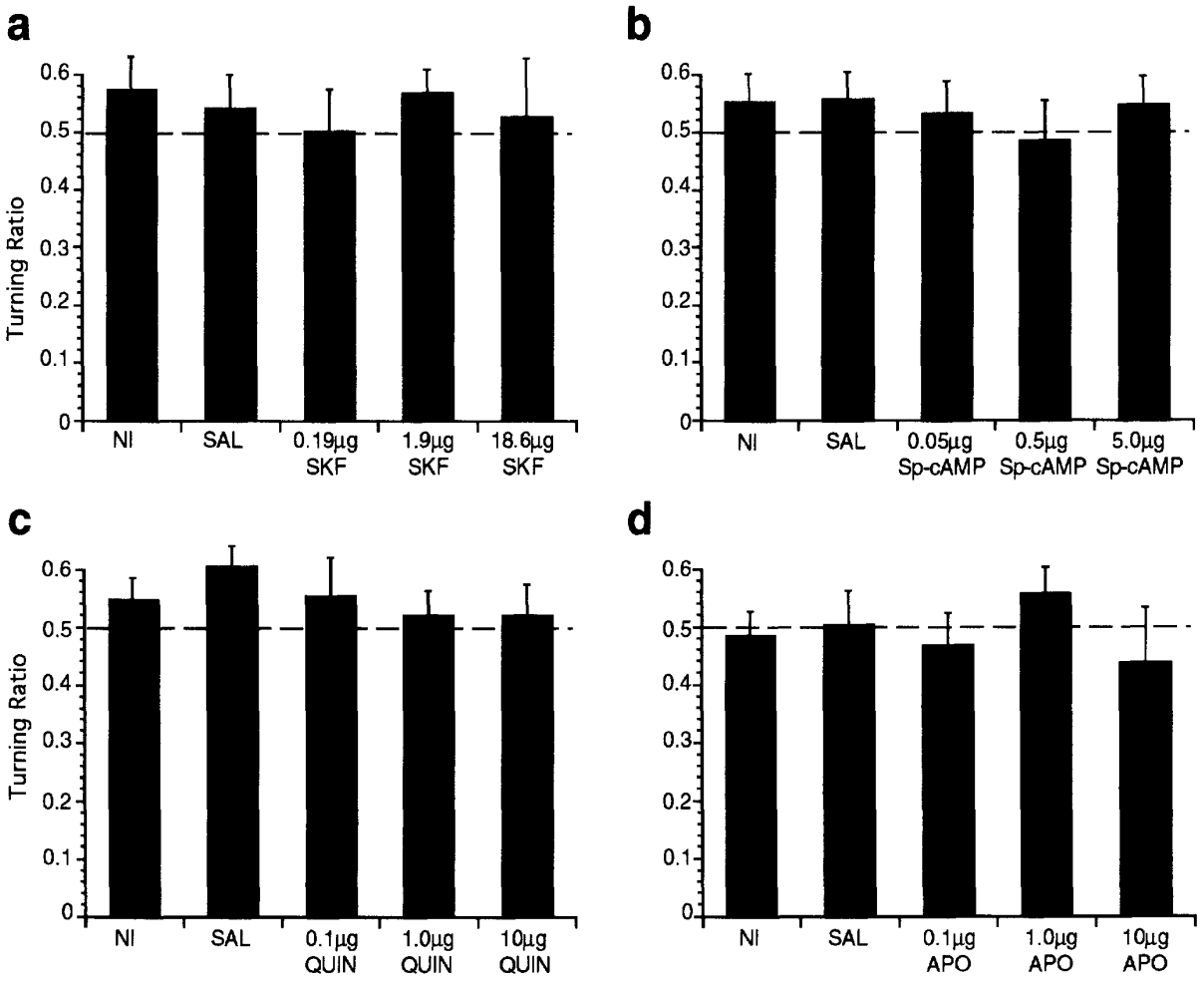

FIG. 2. Effects of direct dopamine agonists on rotation. No significant changes in mean ± SEM turning ratio were recorded following injections of the following compounds: (a) the D1 agonist SKF 81297, (b) the cyclic AMP analogue Sp-cAMP, (c) the D2 agonist quinpirole (QUIN) and (d) the mixed D1/D2 agonist apomorphine (APO). Dashed lines indicate an unbiased turning ratio of 0.5.

Eticlopride in 3 doses failed to significantly reverse contralateral rotation caused by amphetamine, although the coinjection of the highest dose of the antagonist with 20 μg amphetamine did not produce significant rotation. The overall effect of treatment on rotation was significant [$F(4, 44) = 2.74, p < 0.05$, Fig. 3c], whereas no significant effect on total full turns was observed ($p > 0.05$). Amphetamine injected alone and with 0.1 and 1.0 μg of eticlopride caused significant contralateral rotation when compared with the no-injection condition. None of the doses of eticlopride coinjected with amphetamine produced turning ratios that differed significantly from amphetamine injected alone.

A test of the dependency of amphetamine-induced rotation on glutamate receptor stimulation and on neuronal impulse flow was carried out by coinjecting the NMDA antagonist AP7, the AMPA/KA antagonist CNQX and the action potential blocker TTX with amphetamine. TTX [16 ng (100 μM)] completely reversed the rotation caused by amphetamine, whereas both AP7 [0.1 μg (0.9 mM)] and CNQX [29 ng (250 μM)] proved ineffective. There was a significant overall treatment effect [$F(4, 40) = 4.65, p < 0.01$, Fig. 3d], and amphetamine again caused more contralateral rotation than no injection ($t = 2.55, p < 0.05$). There was also significant contralateral rotation following amphetamine coinjected with CNQX ($t = 2.87, p < 0.05$) and with AP7 ($t = 2.76, p < 0.05$). TTX coinjected with amphetamine was significantly different than 20 μg amphetamine injected alone ($t = 2.65, p < 0.05$). An ANOVA on the total full turns for each session revealed no significant effect of the treatments [$F(4, 36) < 1, p > 0.05$].

The amphetamine-induced rotation was consistent within animals across different measurement sessions. Turning ratios following initial and final amphetamine injections sessions in the glutamate antagonist and dopamine antagonist experiments were significantly correlated ($r = 0.46, p < 0.01, n = 33$). There was also a significant correlation between full contralateral turns ($r = 0.74, p < 0.01, n = 33$).

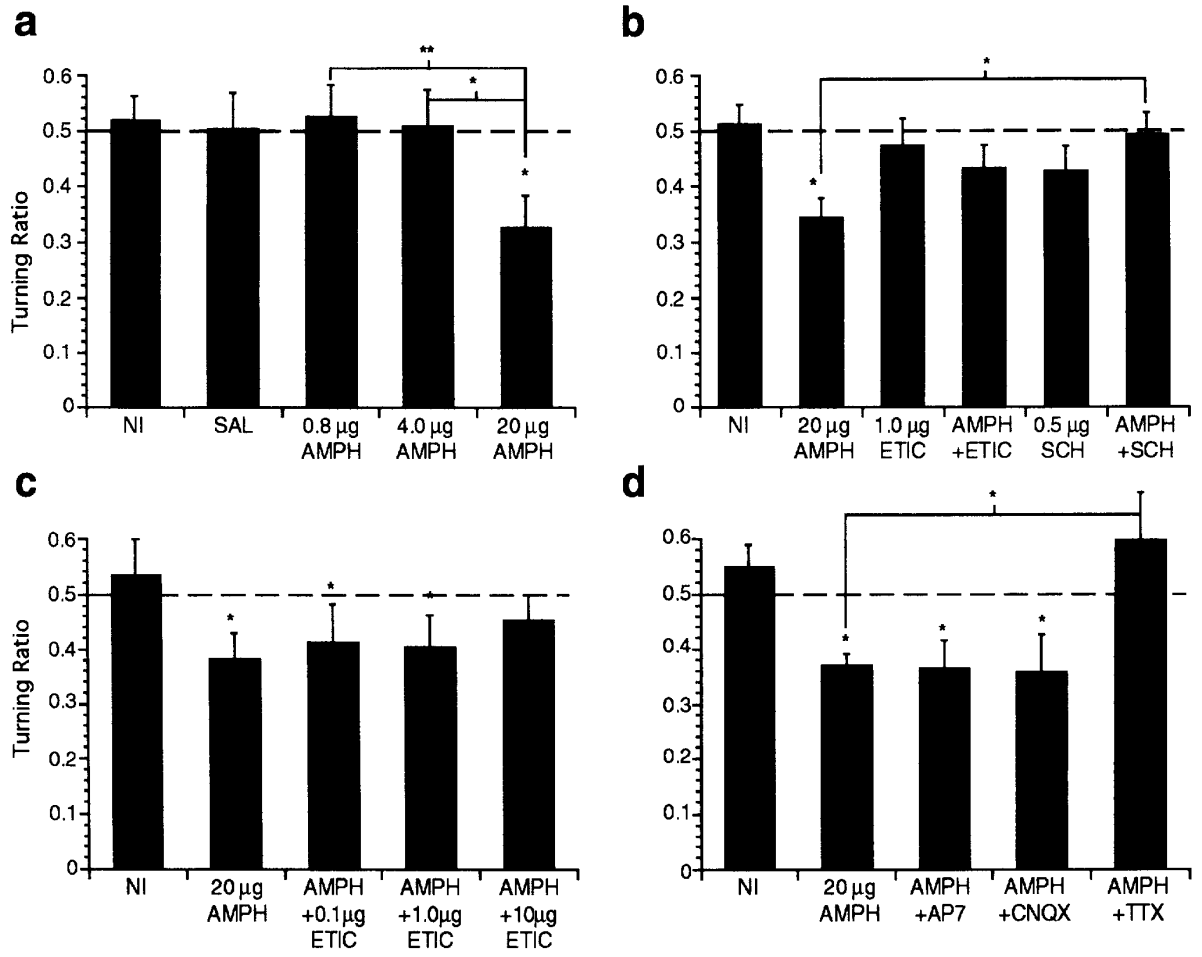

FIG. 3. Effects of amphetamine and coinjections of amphetamine with glutamate and dopamine antagonists on rotation. a: Intrastriatal amphetamine injections caused contralateral rotation. b: The contralateral rotation caused by 20 µg amphetamine is reversed by coinjection of 0.5 µg SCH 23390 (SCH) but not by 1.0 µg eticlopride (ETIC). c: Coinjection of three doses of eticlopride failed to significantly alter the effects of 20 µg amphetamine. d: Amphetamine-induced rotation was not blocked by coinjection of the NMDA antagonist AP7 or the kainate/AMPA antagonist CNQX but was significantly reversed by the action potential blocker TTX. Dashed lines indicate an unbiased turning ratio of 0.5. $^{*}p < 0.05$, $^{*}p < 0.01$.

Drug Effects on Contralateral and Total Full Turns

A parallel analysis of each experiment was undertaken using contralateral full turns as a dependent measure. Table 2 shows that, with the exception of apomorphine, the drug effects observed in the turning ratio analyses also were evident for contralateral rotations. All of the direct dopamine agonists except quinpirole failed to affect contralateral full turns. Quinpirole (10 µg) caused a decrease in contralateral turns. Amphetamine caused significant contralateral rotation at the highest dose (20 µg). This effect was replicated in all of the antagonist coinjection studies. SCH 23390 blocked the amphetamine-induced increase in contralateral rotation, whereas eticlopride at 3 doses failed to significantly reduce the effect. The glutamate antagonists APV and CNQX also failed to block the amphetamine effect. TTX, however, did reverse the increase in contralateral full turns.

The time course of change in rotation following amphetamine, apomorphine and quinpirole injections is illustrated in Fig. 4. Rats were typically most active when first placed in the experimental chamber. During this time, some rats were observed visually. Their overt behavior included normal exploration of the experimental chamber and grooming activity. In animals that exhibited a rotation bias, there was no evidence of unusual motor activity such as seizure-related clonus or the stereotyped nose-to-tail rotation and postural asymmetry reported in rats with unilateral lesions of the dopamine system (30). The behavior of drug-treated animals was to a large extent indistinguishable from that of no-injection sessions, apart from reliable rotational biases as described above. The mean number of full turns differed little among experiments over all treatments, with a grand mean ± SEM of 15.64 ± 2.02 full turns per 20-min session (Table 2).

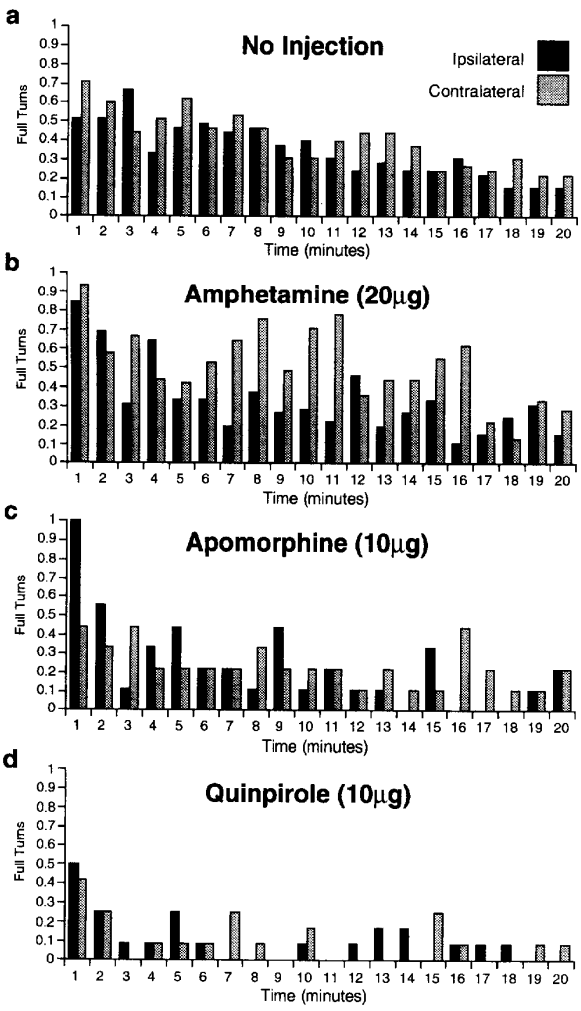

FIG. 4. Effects of intrastriatal dopamine agonists on contralateral and ipsilateral rotation over time. a: Average number of full turns per minute following no intrastriatal injections. No rotation bias was observed as indicated by approximately equal contralateral and ipsilateral full turns (n = 42). Activity was highest when the animal was first placed in the rotometer chamber and decreased over the 20-min recording session. b: Dorsal striatum injections of 20 μg amphetamine in 0.5 μl produced a significant contralateral bias, with no change in overall activity. Contralateral rotation increases while ipsilateral rotation decreases (n = 42). c,d: Injections of 10 μg apomorphine (n = 9) and 10 μg quinpirole (n = 12) caused a decrease in total full turns, with no accompanying rotation bias.

DISCUSSION

In the present report, we show that injections of dopaminergic drugs unilaterally into the dorsal striatum of intact rats have different behavioral effects depending on the pharmacological mechanism of action. The D1 agonist SKF 81297 and the activator of the D1-linked enzyme cascade Sp-cAMPS failed to affect behavior significantly. The D2 agonist quinpirole and the mixed D1/D2 agonist apomorphine caused a dose-dependent decrease in locomotion. None of these treatments caused locomotor asymmetry. In contrast, the dopamine releaser and uptake blocker amphetamine induced contralateral rotation that was consistent across repeated measurements and different experimental groups. This effect was blocked by a D1 antagonist but not by a D2 antagonist at several doses. In addition, both NMDA and AMPA/KA antagonists failed to reverse amphetamine-induced rotation, whereas the action potential blocker TTX blocked the effect.

Amphetamine may have caused a motor asymmetry due to spread of the drug to the contralateral striatum, but this is unlikely because this effect was blocked by coinjections of a low dose of TTX and moderate doses of a D1 antagonist and, in prior experiments, the broad-spectrum dopamine antagonist cis-flupenthixol (35). Intact rats will often exhibit a directional motor bias in response to systemic amphetamine injections that is resistant to the effects of unilateral dopamine depletion (40). Thus, intrastriatal amphetamine injections may have simply enhanced an endogenous asymmetry in animals that received injections contralateral to their biased side. This possibility is unlikely given that a correlation analysis showed that amphetamine caused contralateral rotation that is independent of motor asymmetry measured at a no-injecion baseline.

The decrease in locomotor activity following apomorphine and quinpirole injections was accompanied by mild orofacial stereotypy. Single-unit recordings in behaving rats suggest that more ventral and lateral regions of the striatum are involved in orofacial behavior such as licking and vibrissa movement (9). Quinpirole injections into the ventrolateral striatum produce head-down sniffing and mouth movements such as the ones reported in the present study, whereas D1 receptor stimulation produce a different pattern of behavior that includes intense self-biting (19). Thus, the mild stereotypy described in the present study may have resulted from high doses of quinpirole and apomorphine acting on D2 receptors after diffusing to nearby striatal regions.

Investigations of intrastriatal dopaminergic drugs and rotation in intact rats have yielded conflicting results. Most have found no rotation with high doses of dopamine agonists including dopamine (16,26), apomorphine (50), the D2 agonist lisuride, the D1 agonist SKF 38393 (20) and a mixture of SKF 38393 and quinpirole (43). Some studies, however, have reported a dopamine-induced contralateral bias after long delays (6,27). A recent study of this issue was carried out by McKenzie et al. (32) who failed to find any effects with dopamine, apomorphine or amphetamine injections. The present results corroborate these findings to some extent, in that the direct dopamine agonists apomorphine, SKF 81297 and quinpirole did not elicit a rotational bias. These results further support a reevaluation of the view derived from lesion studies that a simple imbalance in striatal dopamine receptor tone will lead to motor asymmetry. The maximal doses of direct dopamine agonists used in the present study were also high, exceeding those of other studies using intrastriatal injections (32,42,50). Rotation may have been observed at higher doses, although the use of higher doses of selective and potent agonists such as quinpirole and SKF 81297 would further complicate the interpretation of the results due to an increased likelihood of drug diffusion to sites distal to the injection.

In contrast to direct agonists, injections of amphetamine did cause rotation, as has been reported previously from this laboratory (35). The discrepancy between our results showing amphetamine-induced contralateral rotation and the negative results reported by others may be due to methodoligical differences in measuring rotational behavior. In prior studies, a ratio measure permited reliable quantitation in a repeated-measures design using animals with low levels of overall activity.

We employed both a ratio measure and an absolute dependent measure and found similar results with each analysis. In studies of dopamine-depleted animals with reduced terminal autoreceptor regulation of release, the number of rotations per minute is typically far more exaggerated (40,50,54). The sensitivity of our recording apparatus may have allowed for reliable measurement of a behaviour pattern at low levels of activity.

The difference in efficacy between direct dopamine agonists and amphetamine in producing rotation may be due to their modes of action. Other studies have demonstrated a difference in efficacy between indirect and direct dopamine agonists in increasing the expression of the immediate-early gene product Fos, a process implicated in metabolic activation. Paul et al. (38) reported that systemic treatment with a direct D1 or D2 agonist or with a combination of both does not alter Fos levels in the normosensitive striatum, whereas the indirect agonists amphetamine and cocaine cause a robust increase in striatal Fos (3). Receptor stimulation by selective direct agonists may occur at a much higher level than is normally encountered by the affected tissue. In contrast, the release of endogenous stores of dopamine by an indirect agonist may result in postsynaptic effects that are more similar to normal physiological conditions. Several reports have suggested a concentration-dependent postsynaptic effect of dopamine receptor stimulation in the striatum. In vivo experiments in rats have shown that low levels of dopamine receptor stimulation cause an increase in spontaneous or evoked striatal cell firing rate, whereas higher doses cause inhibition (13,24,46,52,55).

Drugs that cause contralateral rotation when injected into the striatum also increase striatal cell firing rate. Examples include GABA-A receptor antagonism (7,32,47), cholinergic muscarinic receptor activation (32,33) and glutamate receptor stimulation at NMDA (5,23,53) and kainate/AMPA (7,37,47) and metabotropic receptors (5,8,42,48). It is also likely that motor asymmetry following amphetamine injections resulted from a unilateral increase in striatal neural activity. Rotation was blocked by TTX coinjections, and amphetamine enhanced the firing of motor-related neurons in the striatum (22).

Rotation in intact rats following striatal drug injections also appears to be dependent on intact dopamine neurotransmission. The rotation caused by caffeine (25), neuropeptide Y (35) and glutamate receptor agonists (42,46,53) can be reversed by coinjection of a dopamine antagonist. These findings reveal a permissive role of endogenous dopamine in producing motor asymmetry and suggest that these treatments may have resulted in the release of dopamine from terminals in the striatum, as has been demonstrated with exogenous neuropeptide Y and glutamate agonists (2,14,34).

Amphetamine-induced rotation was reversed by the D1 antagonist SCH 23390 injections at a dose that did not affect rotation alone. In contrast, the D2 antagonist eticlopride was relatively ineffective in blocking amphetamine-induced rotation, suggesting that this effect is mediated primarily by D1 receptor stimulation. Autoradiography studies have shown that there is a higher density of D1 receptors in the dorsal striatum than in other basal ganglia regions (4). In addition, D1 receptors may mediate the changes in striatal physiology caused by psychomotor stimulants. Systemic treatment with amphetamine or cocaine causes an increase in the expression of striatal Fos in D1-associated neurons but not in D2-associated cells, and this effect is blocked by SCH 23390 (3,15). However, eticlopride also blocks Fos induction in striatonigral neurons following systemic amphetamine treatment (41), suggesting that cooperativity between D1 and D2 receptors may be required for this effect in some striatal cells.

Two opposing output pathways may exist through which the striatum can affect behavior and separate neuronal populations within the striatum participate in each. The direct pathway involves a monosynaptic inhibitory projection to the output nuclei of the basal ganglia, the substantia nigra pars reticulata (SNZR) and the entopeduncular nucleus (EP). Activation of these striatal neurons would inhibit basal ganglia output neurons, serving to disinhibit SNZR/EP targets in pontine and thalamic regions, thus increasing excitation of brainstem and cortical motor areas. The indirect pathway is a multisynaptic route through the globus pallidus and subthalamic nucleus to the SNZR/EP, resulting in a net excitation of output neurons and thus an inhibition of motor activity (1). Investigations of the induction of immediate-early genes in the basal ganglia have shown that D1 agonists are associated primarily with the direct pathway (21) and may produce excitation of striatal neurons (1,21). In the present experiment, intrastriatal amphetamine might have caused contralateral rotation through an excitation in the D1-associated direct pathway and a resultant unilateral imbalance in SNZR/EP output. The observation that the GABA-A agonist muscimol injected into the SNZR (36) or the EP (44) causes contralateral rotation in consistent with this idea.

In the present study, the rotation caused by intrastriatal amphetamine was not dependent on intact glutamatergic neurotransmission. Neither the NMDA antagonist AP7 nor the AMPA/KA antagonist CNQX reversed amphetamine-induced rotation. The possibility that insufficient doses of these antagonists were used is unlikely given that the rotation caused by NMDA injections and by both AMPA and KA injections was reversed by AP7 and CNQX, respectively, injected in concentrations similar to those used in the present study. These concentrations of each antagonist failed to affected rotation when injected alone (47,52).

It is often suggested that dopamine in the striatum acts through modulating glutamatergic input from the cortex. Glutamate receptor-induced increases in firing can be augmented by coapplication of dopamine agonists (12,13,24), and the hyperlocomotion and conditioned place preference caused by amphetamine is antagonized by glutamate antagonists injected into the nucleus accumbens (28,29). Intact cortical input seems to be involved in the behavioral effects of dopamine agonists in the dopamine-depleted striatum. In the unilaterally 6-OHDA-lesioned rat, transecting cortical glutamate input reduces both the rotation and the increase in Fos expression following amphetamine and apomorphine treatments (11). If amphetamine caused an increase in striatal discharge that led to contralateral rotation, the mechanism through which this increase occurred remains to be determined. Dopaminergic influences on other neurotransmitter systems such as the cholinergic or GABAergic input to striatal cells may have contributed to this effect. In addition, the direct postsynaptic effects of dopamine could have caused a change in neuronal excitability through its actions on sodium and potassium channels in striatal cells (51).

The implications of these findings to the behavior of the animal can be approached by considering the possible effects of a global increase in inhibition of basal ganglia targets. Both locomotor and postural elements could have contributed to this rotation because there are basal ganglia projections to nuclei that serve various behavioral functions. Thalamic projections participate in the preparation for voluntary movement, superior colliculus projections modulate head, neck and eye orientation to environmental stimuli, and pedunculopontine tegmental nucleus projections likely mediate the overall

arousal level of the animal. The possible involvement of sensory or attentional factors could be addressed by further experiments that investigate the salience of stimuli in contralateral and ipsilateral sensory fields (10).

In summary, direct dopamine agonists injected into the dorsal striatum were ineffective in producing locomotor asymmetry, whereas the dopamine releaser caused dose-dependent contralateral rotation. This effect was mediated primarily by D1 receptors and possibly occurred through an increase in striatal activity in the direct projection to basal ganglia output nuclei. Rotation was independent of intact glutamate activity.

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