Pharmacology Biochemistry & Behavior, Vol. 36, pp. 217–223. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Unilateral Dopamine Depletion Causes Bilateral Deficits in Conditioned Rotation in Rats

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Received 21 December 1989

RICHARDS, J. B., K. E. SABOL AND C. R. FREED. *Unilateral dopamine depletion causes bilateral deficits in conditioned rotation in rats.* PHARMACOL BIOCHEM BEHAV **36**(2) 217–223, 1990.—Rats were trained to rotate for a water reward using a procedure which required each rat to turn in both the left and right directions. The rats were then lesioned with unilateral injections of 6-hydroxydopamine in the nigrostriatal bundle to produce unilateral dopamine depletion. Rats which had greater than 95% depletion had significant deficits in turning both ipsilateral and contralateral to the depleted side. Circling contralateral to the lesion was more impaired than circling ipsilateral to the lesion. All animals showed deficits in both the initiation of movement and in speed of turning. In addition, the rats displayed a chronic turning bias in the ipsilateral direction 16 weeks postlesion. These results indicate that unilateral dopamine depletion causes a variety of impairments in trained circling behavior. Although contralateral circling is most impaired, there is a significant decrease in ipsilateral performance. We conclude that normal conditioned circling behavior requires bilateral dopamine innervation.

Methamphetamine Trained circling 6-Hydroxydopamine Circling behavior Striatum Dopamine Brain lesion

BILATERAL injections of 6-hydroxydopamine (6-OHDA) into the ascending nigrostriatal dopamine system of rats depletes striatal dopamine (4). If the depletion caused by 6-OHDA injections is large enough, impairments analogous to those observed in human Parkinson's disease appear. Animals are akinetic, rigid, and show sensory neglect (16,17). In addition, rats with bilateral 6-OHDA lesions frequently fail to consume enough food and water to sustain themselves and must be tube fed (31). Rats given unilateral dopamine depleting lesions display sensorimotor impairments but only on the side contralateral to the lesion (14–16, 26). It is easier to study the behavioral effects of dopamine depletion in unilaterally dopamine-depleted animals because unilateral animals are not aphagic. In addition, contralateral performance can be directly compared with ipsilateral performance within the same rat.

A fundamental impairment observed in rats with unilateral dopamine lesions is failure to orient toward stimuli presented on the side contralateral to the lesion. This sensorimotor deficit has been ascribed to a variety of causes including sensory inattention (14,15), failure to initiate movement (5), and failure to disengage or switch motor programs (25).

Unilateral depletion of dopamine in the striatum also causes rats to spontaneously rotate in the direction ipsilateral to the lesion. Ipsilateral rotation can be greatly enhanced by giving rats methamphetamine (30,32). Methamphetamine acts by releasing dopamine and blocking its reuptake.

Rats can be readily conditioned to rotate for water reward (35). Furthermore, all rats can be trained to rotate in either the left or right direction independent of any endogenous behavioral or biochemical asymmetries (36). Previous researchers have reported that unilateral dopamine depletion causes impairment in the acquisition of conditioned circling contralateral to the lesioned side but not ipsilateral to the lesioned side (7). By contrast, in a preliminary study we found that unilateral dopamine depletion caused deficits in trained turning both contralateral and ipsilateral to the lesioned side in animals trained to circle in both directions (22).

The purpose of the present study was to resolve the question of whether unilateral dopamine depletion causes bilateral deficits in conditioned performance. We have also developed a more complete analysis of circling behavior. In this study, we used a novel discrimination procedure in which each rat was trained to turn in both the left and right directions for water reward (23). This training paradigm allowed the determination of both the ipsilateral and contralateral effects of unilateral dopamine depletion within a single rat. In addition, we describe the relationship between

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dopamine depletion in the striatum and both trained and drug-induced turning.

METHOD

Subjects

Thirty-six male Sprague-Dawley rats weighing 350 to 400 g at the time of surgery were used. They were housed 2–4 per cage under a 12:12 light-dark cycle with ad lib access to food. Rats were deprived of water for 23.5 hours during training and testing. Twenty-four of the rats received unilateral dopamine-depleting lesions on the right side and 12 rats served as unoperated controls. Five of the 24 lesioned rats died before testing was completed and their data were discarded from the study.

In addition to the trained rats described above, 11 rats were lesioned but not trained. These rats were tested only for drug-induced rotation.

Apparatus

Turning was monitored automatically with four identical rotometers connected to Commodore VIC 20 microcomputers (23). The rotometers consisted of a clear acrylic tube (diameter = 20 cm: height = 38 cm) placed upon a flat grid floor. A liquid dispenser (model 80201, Lafayette Instrument Company) was used to provide 0.05 ml water drops to the rats. Each rotometer was placed inside a sound-attenuating chamber equipped with a fan and a house light. The sound-attenuating chamber was made of 5 cm thick styrofoam.

The VIC microcomputers were programmed to monitor the rats' rotational behavior via a cable attached to the rat. The computers measured the frequency and direction of turning and provided water reward for turning. In addition, the computers measured movement and pause time components of the rats' trained turning behavior. Pause time was defined as the time it took the rats to rotate through 180 degrees in front of the spout. The pause time component included the time it took for the rats to consume the water reward for the preceding turn and to initiate the next turn. Movement time was defined as the amount of time it took the rat to rotate through 180 degrees opposite to the water spout. Movement time excluded the drinking and movement initiation and so provided a measure of how fast the rat turned. When trained to circle for drops of water, rats turned quickly through 360 degrees and then paused at the water spout. [For a complete description of the apparatus and training methods, see (23).]

Procedure

Trained rotation. On the first training day, rats were rewarded for turning in both the left and right directions. On all subsequent days, they were rewarded on alternate days for left turns or right turns. Two contrasting environments were used to condition left and right turning. Two of the four training chambers were always dark (the chamber light turned off) and two of the training chambers were always illuminated (the chamber light turned on). The darkened chambers did receive some light via a window in the chamber and by light transmission through the translucent styrofoam of the chamber. The rats were trained to turn either left or right depending upon whether they were placed in the darkened or the illuminated test chamber. This training procedure provided a direct comparison between left and right turning within a single rat. The rats were trained in this fashion for 10 sessions prior to being lesioned. Each session consisted of 100 rewarded turns or 60 minutes, whichever occurred first. When unlesioned, the rats usually completed the session in less than 20 minutes. Half of the animals were reinforced for turning left in the darkened chambers and right in the lighted chambers. The other half of the rats were reinforced for turning right in the dark chambers and left in the lighted chambers.

At eight weeks postlesion and again at 16 weeks postlesion the rats were tested for conditioned turning. During the testing periods, weeks 8–9 and 16–17 postlesion, the rats were water deprived as previously described; otherwise, the rats had continuous access to water in their home cages. At both the 8-week and 16-week postlesion evaluations, the rats were tested in both the left and right directions on alternate days for 10 days.

Surgery. Unilateral dopamine depleting lesions were made by injecting 6-OHDA into the nigrostriatal tract using the coordinates of Marshall and Ungerstedt (18) (AP: 4.4 mm posterior to bregma; L: 0.9 mm to the right of midline; V: 7.5 mm below dura; nose bar set at 2.3 mm below the interaural line). The rats were pretreated with the noradrenergic uptake blocker desipramine (15 mg/kg IP) and atropine sulfate (0.01 mg IP) and then anesthetized with 150 mg/kg chloral hydrate and 50 mg/kg ketamine. Twenty-four rats were infused with 8 μg (free base) of 6-OHDA in 4 μl of 0.2 mg/ml ascorbic acid/saline solution. The infusions were made through a 30-gauge stainless steel cannula over a six-minute period and then left in place for two minutes after injection.

Methamphetamine-induced rotation. Two weeks after lesion, the rats received 5.0 mg/kg methamphetamine IP and were placed in the test chamber for two hours. Drug testing was done using the same apparatus described above except that there were no water spouts mounted on the walls of the test cylinders. All of the chambers were equally illuminated. Half of the rats received drugs in the chamber in which they had previously been trained to turn right, and half of the rats received drugs in the chamber in which they had been trained to turn left. The rats were not water deprived. The computer automatically counted drug-induced rotations. Only rotations occurring between 30 and 120 min postinjection were used for analysis.

Biochemical assay. At the end of the experiment the rats in both the experimental and control groups were anesthetized with chloral hydrate and then decapitated. The brains were immediately removed and 1.5 mm thick coronal blocks were taken anterior to the optic chiasm (AP 0.3 mm posterior to bregma). The resulting slabs were frozen with dry ice. The striatum was then dissected bilaterally from these slabs. The tissue samples were weighed and stored at −70°C. In preparation for assay, the samples were homogenized in 0.1 M $HClO_4$ with 3,4-dihydroxybenzylamine (DHBA) as the internal standard. The homogenates were then centrifuged for 10 min. Supernatants were drawn off and kept on ice until ready for injection onto the HPLC column.

Chromatographic equipment consisted of a Model 6000 Waters pump, a model 7010 Rheodyne injection valve with 20 μl sample loop, a 100 × 2.1 mm reverse phase Hewlett Packard column with 5 μ C18 hypersil ODS packing, a BAS model LC-2A amperometric detector and a glassy carbon working electrode set at 0.70 V. The mobile phase was 0.05 M trichloroacetic acid (TCA), 0.2 M H_3PO_4, 0.2 mM octyl sodium sulfate, 0.1 mM EDTA, with pH = 3 as previously described (1, 9, 11). External standard injections were performed with 20 pmol dopamine, DOPAC, and DHBA.

Data analysis. As described above, the rats were trained for 11 days prelesion and were then retrained for 10 days at 8 and 16 weeks postlesion. Since the data from the 8- and 16-week postlesion retraining periods did not differ significantly, only data form the 16-week retraining period are reported. Since the rats were trained to turn left and right on alternate days, samples of performance both contralateral and ipsilateral to the lesioned side were obtained for each of the rats which completed the study (the last two days of the 16-week training period). Based on the results

TABLE 1

DOPAMINE CONCENTRATION IN THE STRIATUM CONTRALATERAL AND IPSILATERAL TO THE LESIONED SIDE

Group	N	Side	
		Contralateral	Ipsilateral
Control	12		
Mean ± s.e.m.		84.3 ± 2.1	82.2 ± 3.1
<95% depletion	9		
Mean ± s.e.m.		80.2 ± 4.1	9.8* ± 2.3
>95% depletion	8		
Mean ± s.e.m.		81.0 ± 3.7	1.4† ± 0.4

*Different from control ipsilateral ($p<0.05$).
†Different from <95% ipsilateral ($p<0.05$).
Values are nmole/g tissue.

of the biochemical assay, the lesion group was divided into two groups: rats with greater than 95% dopamine depletion (n = 8) and rats with less than 95% dopamine (n = 9) {dopamine depletion = 100 × [1 − (ipsi dopamine/contra dopamine)]}. Two rats which had less than 50% depletion were not included in the less than 95% depletion group.

The data from these two groups and the unoperated control group (n = 12) were analyzed using a mixed two-way analysis of variance with dopamine depletion as the between groups factor (control group, less than 95% depletion group, and greater than 95% depletion group) and lesion side as the within groups factor (contralateral performance and ipsilateral performance). If the two-way analysis of variance was significant, it was followed up by four between-group post hoc *t*-tests which compared performance of the lesion groups with the performance of the control group on the same side. Three additional paired *t*-tests were used to compare ipsilateral and contralateral performance within the three groups. The significance of the *t*-tests was adjusted using the Bonferroni inequality to take into account that seven *t*-tests were performed simultaneously (19). The significance level for the post hoc *t*-tests was set at $p<0.05$.

Four measures of performance were analyzed: turns/minute, movement time, pause time, and turns in the unrewarded direction. Data for analysis was taken from the last two days of the prelesion training period and the last two days of the 16-week postlesion training period.

RESULTS

Biochemistry Results

Table 1 shows the mean and standard error of the mean for dopamine levels in the two lesion groups and the unlesioned control group. The dopamine concentrations on the lesioned side in this study ranged from 0.4% to 88.3% of the intact side contralateral to the lesion. As described previously, the lesioned rats were divided into two groups based on depletion level: Animals with greater than 95% depletion and animals with less than 95% depletion. The data from the two rats which had less than 50% dopamine depletion were excluded from the less than 95% depletion group. As expected from the results of previous researchers (18), dopamine was depleted only on the side ipsilateral to the lesion. The side contralateral to the lesion had the same dopamine concentration as control animals.

Methamphetamine-Induced Rotation

Figure 1 shows the net number of ipsilateral turns induced by 5.0 mg/kg methamphetamine as a function of unilateral dopamine depletion for the 19 trained and lesioned rats used in this study. For comparative purposes, Fig. 1 also shows methamphetamine-induced turning for a group of 11 untrained rats. These rats received the same injections of 6-OHDA as the trained rats. Whether trained or untrained, only rats with greater than 95% depletion rotated faster than one turn/min. These data clearly show that methamphetamine-induced rotation distinguished between rats with greater than 95% depletion and rats with less than 95% depletion.

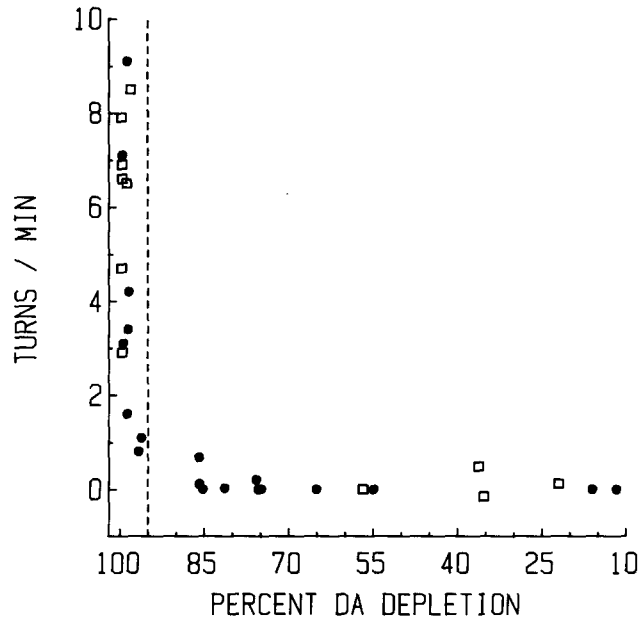

FIG. 1. Rotation ipsilateral to the lesioned side induced by 5.0 mg/kg methamphetamine IP as a function of dopamine depletion. Data points to the left of the dashed line indicate rats with greater than 95% depletion (% depletion = 100 × [1 − (ipsi DA/contra DA)]. Closed circles show methamphetamine-induced circling data from lesioned animals which were trained to circle. Open squares show circling in untrained lesioned rats. Only rats with >95% dopamine depletion circled with methamphetamine. No reward was given and trained and untrained animals showed the same circling profile for a given level of dopamine depletion.

Direct observation of rats rotating in response to 5.0 mg/kg methamphetamine in the present apparatus indicated that rats with less than 95% depletion became "trapped" against the vertical wall of the cylinder. That is, they contacted the wall of the cylinder by arching their bodies in the direction ipsilateral to the lesion. [The apparatus differed from that used by Ungerstedt (30) in that it had a flat rather than concave floor.] These rats displayed stereotyped sniffing and licking often directed at the wall. This stereotyped behavior appeared to disrupt circling behavior. Rats with greater than 95% depletion also came into contact with the wall of the cylinder. However, rats with the more extensive depletion displayed less stereotyped sniffing and licking and continued to rotate.

Circling for a Water Reward After Lesion

Results of circling for a water reward are shown in Fig. 2A. These data revealed that rats with greater than 95% dopamine depletion had profound deficits in their ability to turn contralateral to the lesioned side. These rats also displayed deficits in the rate of turning for a water reward in the ipsilateral direction although the

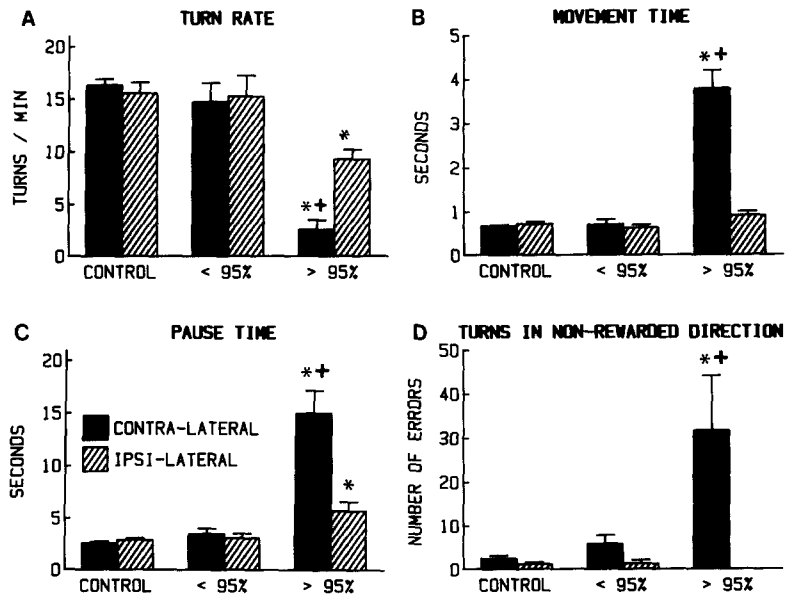

FIG. 2. Effects of unilateral dopamine depletion on water-reinforced circling behavior. Animals are grouped as unlesioned controls, and animals with less than 95% or greater than 95% dopamine depletion. Four measures of performance are given: (A) Rate of turning, (B) Movement time, (C) Pause time, and (D) Turns in the nonrewarded direction. Results are shown for both the contralateral and ipsilateral directions (solid bars and hatched bars, respectively). The data are presented as mean and s.e.m. (*significantly different from control group; +significantly different from opposite side, $p<0.05$). In all measures, only animals with >95% lesions had behavioral deficits. In these severely lesioned animals, contralateral circling showed deficits in overall rate, in movement and pause time and in the number of circles performed in the unrewarded direction. Ipsilateral circling was less impaired but there was a significant reduction in overall circling and a significant increase in pause time compared to controls.

ipsilateral deficit was smaller. Rats in the less than 95% depletion group did not have significant deficits in the rate of turning in either direction. The overall F test indicated a significance of both main effects [depletion, $F(2,26)=24.477, p<0.0001$]; side, $F(1,29)=5.595$, $p<0.05$, and the interaction, $F(2,26)=9.299$, $p<0.001$. Post hoc t-tests showed that compared to unlesioned controls the rate of turning was significantly decreased in both the ipsilateral and contralateral directions in the greater than 95% depletion group but not the less than 95% depletion group.

Movement and Pause Time Analysis

The effect of lesioning on the rapid component of circling, the movement time, is shown in Fig. 2B. Contralateral movement time was significantly prolonged in the greater than 95% depletion group compared to the control. Ipsilateral movement time was not significantly increased. The overall F test indicated a significant effect of both depletion, $F(2,28)=55.375$, $p<0.0001$, and side, $F(1,29)=59.330$, $p<0.0001$. The interaction was also significant, $F(2,26)=77.160$, $p<0.0001$. Within group comparisons showed that the greater than 95% depletion group had longer movement times in the contralateral direction when compared to the ipsilateral direction. There were no significant effects of depletion on movement time in the less than 95% depleted rats.

The effect of lesioning on the slow component of circling, the pause time, are shown in Fig. 2C. Statistical values for these effects of lesion on pause time were: depletion, $F(2,28)=33.759$, $p<0.0001$; side, $F(1,29)=15.975$, $p<0.0001$; interaction, $F(2,26)=35.294$, $p<0.0001$. There was a significant effect of unilateral dopamine depletion only for the greater than 95% depletion group. Rats in the greater than 95% depletion group had longer pause times than unlesioned control rats. In contrast to the movement times noted above in which only contralateral movements were slowed, pause times were prolonged for animals circling both contralateral and ipsilateral to the lesion. Pause times in the contralateral direction were more prolonged than in the ipsilateral direction but both were greater than unlesioned controls.

Ipsilateral Turn Bias

Figure 2D shows the mean number of errors (turns in the nonrewarded direction) the rats made in both the contralateral and ipsilateral directions. Unilateral dopamine depletion had significant effects on this measure of performance: depletion, $F(2,28)=6.153$, $p<0.01$; side, $F(1,29)=9.614$, $p<0.01$; interaction, $F(2,26)=7.189$, $p<0.01$. Post hoc t-tests showed that when rewarded for turning in the contralateral direction, the >95% depletion group made significantly more errors (turns in the ipsilateral direction) than the control group. This result indicates that rats with >95% dopamine depletion had an ipsilateral turning bias even when contralateral turning was being rewarded. The ipsilateral turn bias was also readily apparent when handling the rats. When rewarded for turning ipsilateral, the >95% depletion rats made no errors (no contralateral turns).

Figure 3 shows the effects of dopamine depletion on the distribution of contralateral and ipsilateral movement and pause times for a representative rat in the greater than 95% depletion group both pre- and postlesion. Shown is a histogram of 100 turn

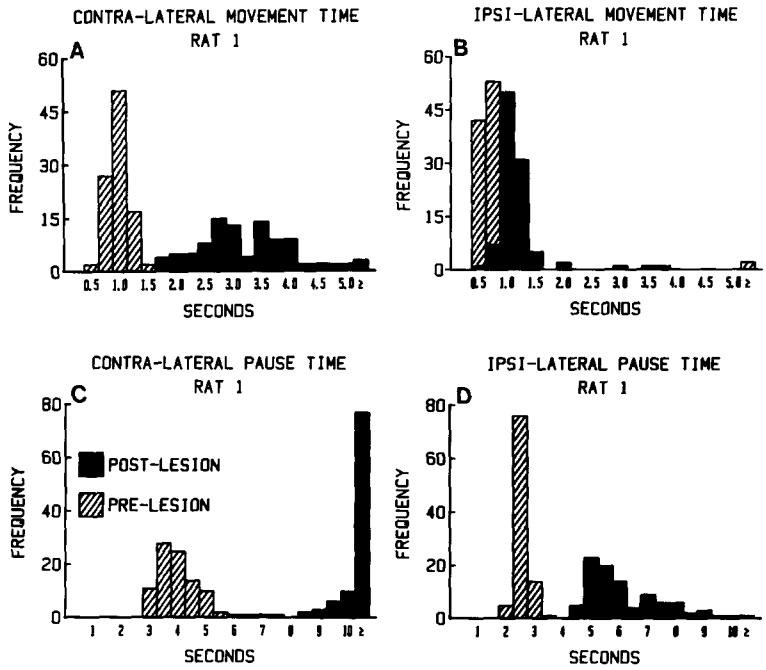

FIG. 3. Time interval histograms for a representative rat from the >95% depletion group showing the distribution of movement and pause times. The bars with diagonal lines indicate prelesion performance and the bars with solid lines indicate postlesion performance. After lesioning, movement times and pause times were prolonged with a broader distribution of times as responses were more variable. Effects on performance contralateral to the lesion were greater than ipsilateral.

times before and after lesioning. The movement time distribution is shown in Fig. 3A and B and the pause time distribution in Fig. 3C and D. Before lesioning, the pause and movement components were executed in relatively narrow time windows. Postlesion performance of both portions of the circling task was slowed and there was a broader distribution of the times indicating more variability in task performance. This shift in the temporal distribution occurred in both the contralateral and ipsilateral directions although the contralateral shift was greater.

During turning in the contralateral direction, the >95% depleted rats often executed turns by following the wall of the cylinder instead of pivoting on their hindlimbs as did nonlesioned rats. After earning a drop, these rats spent an inordinate amount of time licking the spout (or doing nothing) before initiating another turn. With turning in the ipsilateral direction, these deficits were not so obvious.

In summary, unilateral dopamine depletion had significant effects on movement and pause times only in animals with >95% dopamine depletion. These severely depleted animals had deficits in movement time and pause time in both the contralateral and ipsilateral directions. The deficits in the contralateral performance were greater than the deficits in ipsilateral performance.

DISCUSSION

Drug-Induced Rotation

In this study, the rate of turning induced by 5.0 mg/kg methamphetamine in rats with >95% dopamine depletion was slower than reported by others (3,27). Rotation rates of greater than 7 turns/min in response to 5.0 mg/kg methamphetamine have typically been used to identify rats with >95% depletion. A similar cut off in this study would have eliminated most of the >95% depleted rats. The probable explanation for the slower rates of turning in the present study is a difference in apparatus. Following the technique of Ungerstedt and Arbuthnott (32), most researchers have used a hemispherical bowl to test rats for rotation. By contrast, the rats in our study were tested in a cylinder with a flat floor which Ungerstedt and Arbuthnott (32) have shown leads to decreased rotation rate.

Our results show that rotation on a flat surface is still a reliable indicator of dopamine depletion. The rats in this experiment demonstrated a marked increase in drug induced turning when dopamine depletion reached >95% levels. In our cylindrical apparatus, rotation rates of greater than 2 turns/min predicted a lesion of >95% dopamine depletion.

Effect of Unilateral Dopamine Depletion on Trained Turning

Unilateral dopamine lesions which caused greater than 95% depletion resulted in long-term deficits (16 weeks postlesion) in the ability of rats to execute trained turning responses. The rate of trained turning was impaired both contralateral and ipsilateral to the lesioned side. Contralateral turning was more impaired than ipsilateral turning. The ipsilateral deficits observed in this study were not due to depletion of dopamine on the contralateral side since the biochemical assay data show no contralateral depletion.

In previous reports of trained turning in rats with unilateral dopamine lesions, deficits in ipsilateral turning were not reported (6,7). There are a number of differences between these studies and our report which could account for this discrepancy. First, we trained each rat to turn in both the left and right directions and animals were trained before rather than after lesioning. Second,

the baseline rates of turning were much higher in our study, i.e., 15 turns/min versus 6 to 9 turns/min. The higher rate of turning obtained could have made the present study more sensitive to deficits in ipsilateral turning. Third, there were differences in apparatus. While the present study used a computer to measure rotational behavior and to provide reinforcement, the Dunnett and Bjorklund (7) study evidently used a manual procedure. In addition, they trained animals using a 30 cm diameter concave bowl while our study confined the rats on a flat surface with a 20 cm diameter cylinder.

Other investigators have found ipsilateral deficits following unilateral dopamine lesions. Whishaw *et al.* (33), Dunnett *et al.* (8) and Spirduso *et al.* (28) saw ipsilateral deficits in unilateral forelimb use. Whishaw and Tomie (34) reported large ipsilateral deficits using a neuroethological test in which unilaterally dopamine-depleted rats lost their ability to perform a species typical dodging response in order to avoid having food stolen from them. There is substantial evidence then, that unilateral dopamine depletion causes ipsilateral as well as contralateral impairments. The detection of ipsilateral impairments depends upon the nature and sensitivity of the behavioral test.

Unlesioned rats performed the turning response by rapidly pivoting 360 degrees on their hindlimbs and then pausing to consume the water drop before beginning another turn. Each turn could be broken down into two components: a rapidly executed movement time component (pivoting) which took about 0.5 sec to complete and a pause time component (made up of consuming the drop and initiating the next turn) which lasted approximately 2–3 sec. If unilateral dopamine lesions caused a selective deficit in the ability of rats to initiate movement, the rats should show increased pause times but not increased movement times. In contrast, a motor execution impairment or a combination of motor execution and movement initiation deficits would predict increase in both pause time and movement time.

We found that rats with unilateral dopamine depletion were impaired in both the initiation of contralateral turns (indicated by longer pause times) and in the execution of contralateral turns (indicated by longer movement times). In the ipsilateral direction, circling slowed as a result of an increase in pause time. Other researchers (5,7) have focussed on initiation of movement but not execution of movement as the primary impairment caused by unilateral dopamine depletion. The changes in movement time that we have observed reflected changes in the topography of the trained turning response in the contralateral direction. Direct observation of lesioned rats turning in the contralateral direction indicated that these rats turned in wide arcs while sniffing along the side of the cylinder wall. By contrast, ipsilateral turns appeared to be normally executed.

Changes in response topography caused by unilateral dopamine depletion have been observed in other behavioral paradigms as well. Schallert and Hall (25) found that under certain circumstances after recovery from a lesion their rats responded to contralateral stimulation as quickly as controls but the nature of the orientation response was changed. Whishaw *et al.* (33) and Sabol *et al.* (24) reported changes in the way unilaterally dopamine-lesioned rats executed skilled reaching movements.

Another factor which contributed to the contralateral turning deficit (but not the ipsilateral turning deficit) was that rats with >95% depletion made unrewarded ipsilateral turns when contralateral turns were being rewarded. This impairment reflected a chronic bias in severely lesioned rats to rotate ipsilateral to the lesioned side. It is informative to note that despite this ipsilateral bias, these rats still demonstrated ipsilateral impairments in trained turning. This indicates that factors independent of the ipsilateral bias were responsible for the impairment in ipsilateral trained circling. Since the deficit was in the pause time rather than the movement time, the ipsilateral lesion likely influences drinking performance or movement initiation.

In agreement with previous reports (13,15), only rats with greater than 95% dopamine depletion showed deficits in conditioned circling. This result is in accord with autopsy studies of Parkinson's disease patients which indicate that the clinical signs of Parkinson's disease appear only after 80% depletion of dopamine (2,12). Furthermore, Kish *et al.* (12) showed that dopamine concentration in the putamen of Parkinson patients was less than 5% of control brain in exact parallel with the rat observations. In rats, less severe dopamine depletion has been reported to cause sensorimotor impairments when depletion is localized to the lateral striatum (10,24). Since the lateral striatum of the rat is thought to be homologous to the primate putamen (20, 21, 24, 29) it is possible that the sensorimotor deficit in the rat is a model for putamen deficits in primates.

In summary, we have found that unilateral dopamine depletion resulted in deficits in trained turning both contralateral and ipsilateral to the side of the lesion. Performance contralateral to the lesion was the more severely affected. Impairments were observed only when lesions produced greater than 95% dopamine depletion. Deficits in both the initiation of circling and speed of movement were observed in the contralateral direction while deficits only in initiation or drinking were seen in the ipsilateral direction.

ACKNOWLEDGEMENTS

This work was supported by U.S. Public Health Service Grants NS 18639, NS09199, and HL30722.

REFERENCES

1. Asmus, P.; Freed, C. R. Reversed-phase high-performance liquid chromatography of catecholamines and their congeners with simple acids as ion-pairing reagents. J. Chromatogr. 169:303–311; 1979.
2. Bernheimer, H.; Birkmayer, W.; Hornykiewicz, O.; Jellinger, K.; Seitelberger, F. Brain dopamine and the syndromes of Parkinson and Huntington: Clinical, morphological and neurochemical correlations. J. Neurol. Sci. 20:415–455; 1973.
3. Bjorklund, A.; Dunnett, S. B.; Stenevi, U.; Lewis, M. E.; Iversen, S. D. Reinnervation of the denervated striatum by substantia nigra transplants: functional consequences as revealed by pharmacological and sensorimotor testing. Brain Res. 199:307–333; 1980.
4. Breese, G. R.; Traylor, T. D. Effect of 6-hydroxydopamine on brain norepinephrine and dopamine: Evidence for selective degeneration of catecholamine neurons. J. Pharmacol. Exp. Ther. 174:413–420; 1970.
5. Carli, M.; Evenden, J. L.; Robbins, T. W. Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. Nature 313:679–682; 1985.
6. Dunnett, S. B.; Whishaw, I. Q.; Jones, G. H.; Isacson, O. Effects of dopamine-rich grafts on conditioned rotation in rats with unilateral 6-hydroxydopamine lesions. Neurosci. Lett. 68:127–133; 1986.
7. Dunnett, S. B.; Bjorklund, A. Conditioned turning in rats: Dopaminergic involvement in the initiation of movement rather than the movement itself. Neurosci. Lett. 41:173–178; 1983.
8. Dunnett, S. B.; Whishaw, I. Q.; Rogers, D. C.; Graham, H. J. Dopamine-rich grafts ameliorate whole body motor asymmetry and sensory neglect but not independent limb use in rats with 6-hydroxydopamine lesions. Brain Res. 415:63–78; 1987.
9. Echizen, H.; Freed, C. R. Long-term infusion of L-5-hydroxytryptophan increases brain serotonin turnover and decreases blood pressure in normotensive rats. J. Pharmacol. Exp. Ther. 220:579–584; 1982.
10. Fairly, P.; Marshall, J. Dopamine in the lateral caudate-putamen of

the rat is essential for somatosensory orientation. Behav. Neurosci. 100:652–663; 1986.
11. Freed, C. R.; Asmus, P. Brain tissue and plasma assay of L-dopa and alpha-methyldopa metabolites by high performance liquid chromatography with electrochemical detection. J. Neurochem. 32:163–168; 1979.
12. Kish, S. J.; Shannak, K.; Hornykiewicz, O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. N. Engl. J. Med. April 7:876–880; 1988.
13. Lees, G. J.; Kydd, R. R.; Wright, J. J. Relationship between sensorimotor neglect and the specificity, degree and locus of mesotelencephalic dopaminergic cell loss following 6-hydroxydopamine. Psychopharmacology (Berlin) 85(1):115–122; 1985.
14. Ljungberg, T.; Ungerstedt, U. Sensory inattention produced by 6-hydroxydopamine induced degeneration of ascending dopamine neurons in the brain. Exp. Neurol. 53:585–600; 1976.
15. Marshall, J. F. Somatosensory inattention after dopamine-depleting intracerebral 6-OHDA injections: Spontaneous recovery and pharmacological control. Brain Res. 177:311–324; 1979.
16. Marshall, J. F.; Richardson, J. S.; Teitelbaum, P. Nigrostriatal bundle damage and the lateral hypothalamic syndrome. J. Comp. Physiol. Psychol. 87:808–830; 1974.
17. Marshall, J. F.; Levitan, D.; Stricker, E. M. Activation-induced restoration of sensormotor functions in rats with dopamine-depleting brain lesions. J. Comp. Physiol. Psychol. 90:536–546; 1976.
18. Marshall, J. F.; Ungerstedt, U. Supersensitivity to apomorphine following destruction of the ascending dopamine neurons: Quantification using the rotational model. Eur. J. Pharmacol. 41:361–367; 1977.
19. Neter, J.; Wasserman, W. Applied linear statistical models. Homewood, IL: D. Irwin, Inc.; 1974.
20. Pisa, M.; Schranz, J. Dissociable motor roles of the rats striatum conform to a somatotopic model. Behav. Neurosci. 102:429–440; 1988.
21. Pisa, M. Motor somatotopy in the striatum of rat: Manipulation, biting and gait. Behav. Brain Res. 27:21–35; 1988.
22. Reite, M.; Richards, J. B.; Freed, C. R. Effects of unilateral dopamine lesions of substantia nigra on trained circling in the rat. Soc. Neurosci. Abstr. 12:875; 1986.
23. Richards, J. B.; Sabol, K. E.; Freed, C. R. Conditioned rotation: A behavioral analysis. Physiol. Behav. 47(6):in press; 1990.
24. Sabol, K. E.; Neill, D. B.; Wages, S. A.; Church, W. H.; Justice, J. B. Dopamine depletion in a striatal subregion disrupts performance of a skilled motor task in the rat. Brain Res. 335:33–43; 1985.
25. Schallert, T.; Hall, S. "Disengage" sensorimotor deficit following apparent recovery from unilateral dopamine depletion. Behav. Brain Res. 30:15–24; 1988.
26. Schallert, T.; Upchurch, M.; Lobaugh, N.; Farrar, S.; Spirduso, W. W.; Gilliam, P.; Vaughn, D.; Wilcox, R. E. Tactile extinction: Distinguishing between sensorimotor and motor asymmetries in rats with unilateral nigrostriatal damage. Pharmacol. Biochem. Behav. 16:455–462; 1982.
27. Schmidt, R. H.; Ingrar, M.; Lindvall, O.; Stenevi, U.; Bjorklund, A. Functional activity of substantia nigra grafts reinnervating the striatum: Neurotransmitter metabolism and (14c)-deoxy-D-glucose autoradiography. J. Neurochem. 38:737–748; 1982.
28. Spirduso, W. W.; Gilliam, P. E.; Schallert, T.; Upchurch, M.; Vaughn, D. M.; Wilcox, R. E. Reactive capacity: A sensitive behavioral marker of movement initiation and nigrostriatal dopamine function. Brain Res. 335:45–54; 1985.
29. Snyder, A.; Stricker, E.; Zigmond, M. Stress-induced neurological impairments in animal model of Parkinsonism. Ann. Neurol. 18: 544–551; 1985.
30. Ungerstedt, U. Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behavior. Acta Physiol. Scand. [Suppl.] 367:49–68; 1971.
31. Ungerstedt, U. Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiol. Scand. [Suppl.] 367:95–122; 1971.
32. Ungerstedt, U.; Arbuthnott, G. W. Quantitative recording of rotational behavior in rats after 6-hydroxydopamine lesions of the nigrostriatal dopamine system. Brain Res. 24:485–493; 1970.
33. Whishaw, I. Q.; O'Connor, W. T.; Dunnett, S. B. The contributions of motor cortex, nogrostriatal dopamine and caudate-putamen to skilled forelimb use in the rat. Brain 109:805–843; 1986.
34. Whishaw, I. Q.; Tomie, J. Food wrenching and dodging: A neuroethological test of cortical and dopaminergic contributions to sensorimotor behavior in the rat. Behav. Neurosci. 102:110–123; 1988.
35. Yamamoto, B. K.; Freed, C. R. The trained circling rat: A model for inducing unilateral caudate dopamine metabolism. Nature 298:467–468; 1982.
36. Yamamoto, B. K.; Freed, C. R. Reversal of amphetamine-induced circling preference in trained circling rats. Life Sci. 34:675–682; 1984.