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The rotational behavior model: asymmetry in the effects of unilateral 6-OHDA lesions of the substantia nigra in rats

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A basic assumption of the 'rotational behavior model' is that amphetamine (AMPH) produces ipsiversive rotational behavior in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal dopamine (DA) system. However, we report here that if the normally 'dominant' striatum is partially depleted of DA the majority of rats turn contraversive when given AMPH, i.e. in the opposite direction predicted by the model.

After unilateral damage to nigrostriatal neurons animals show lateral preferences in sensorimotor function often characterized by rotational (circling) behavior[2,3,24,25,26,27]. Although spontaneous circling gradually diminishes after the lesion, vigorous rotational behavior can be elicited by drugs that increase brain dopamine (DA) activity[5,25,27,28]. The rotational behavior model has been widely used to screen new drugs for dopaminergic activity (e.g. ref. 6), and to further our understanding of basal ganglia function[8,18,19]. A basic assumption of the model is that after a unilateral lesion of the nigrostriatal DA system with the neurotoxin 6-hydroxydopamine (6-OHDA) animals circle towards the side with the 6-OHDA lesion (ipsiversive) when injected with amphetamine[19,25,27]. However, there may be an endogenous asymmetry in the nigrostriatal DA system[9,10,14,15,22], and therefore the side of the brain that is lesioned could be an important variable. Indeed, in the experiment reported here we found that DA depletion of the 'dominant' striatum has a strikingly different effect than DA depletion of the 'non-dominant' striatum.

To estimate which hemisphere was intrinsically 'dominant' for rotational behavior intact (no lesion) rats were tested for amphetamine (AMPH)-induced rotational behavior, as described previously[4,21]. Briefly, each rat was placed in an automated spherical rotometer for a 15 min habituation period, and then injected i.p. with 1.2 mg/kg of D-amphetamine sulfate (AMPH) dissolved in saline. AMPH-induced rotational behavior was recorded for 60 min on two different occasions, one week apart. One full rotation is defined as 4 consecutive 90° turns in the same direction (see ref. 21). Only rats that turned in the same direction during both screen tests were used in this experiment.

On the basis of the screening tests the hemisphere contralateral to an animal's preferred direction of rotation was operationally defined as being 'dominant' for rotational behavior, and the other hemisphere as 'non-dominant'. Glick and his colleagues[10,14] have shown that when intact rats are given AMPH they turn predominantly in one preferred direction. This preferred direction of rotation is contralateral to the striatum with higher dopamine (DA) content and greater metabolic activity[9,11]. The striatum contralateral to the dominant direction of rotation also shows significantly more AMPH-induced DA release in vitro than the ipsilateral striatum[20].

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Half the animals were then injected with 6-OHDA into the substantia nigra on the dominant side, and half into the substantia nigra on the non-dominant side. The 6-OHDA (5–6 μg 6-OHDA·HBr in 4 μl saline) was infused into the zona compacta of the rostral substantia nigra through a 30-gauge cannula 30 min after pretreatment with 25 mg/kg of desmethylimipramine. After 5 weeks recovery the animals were again tested for AMPH-induced rotational behavior, first with a low dose, and then a week later with a higher dose of AMPH. Both male and female rats (Holtzman) were used in the experiment. Because of sex differences in the uptake of AMPH into the brain[4] it was necessary to use a different systemic dose of AMPH in males and females to insure an equivalent brain concentration of AMPH. Females received 0.65 (low dose) or 2.6 mg/kg (high dose), and males 1.0 or 3.0 mg/kg. We know from previous studies[4] these systemic doses result in the same brain levels of AMPH in male and female rats. One week after behavioral testing was completed all rats were killed by decapitation. The left and right striatum were removed and later assayed for DA[21].

There were no differences between males and females on any of the measures reported in this paper. Females did show more vigorous rotational behavior than males, as reported previously[4,22], but this did not influence the percent of total rotations made in the contraversive or ipsiversive direction. Therefore, the data from males and females were pooled for the analysis reported here.

The direction of rotational behavior observed after the 6-OHDA lesion depended on at least 3 factors: (1) whether the dominant or non-dominant substantia nigra was lesioned, (2) the extent of the striatal DA depletion, and (3) the dose of AMPH used to elicit rotational behavior. It is readily apparent from Fig. 1A that after the low dose of AMPH all the rats (22/22) with non-dominant-sided lesions turned ipsiversive. They made only 4.8% of their total rotations in the contraversive direction (i.e. they made 95.2% ipsiversive rotations). In striking contrast, the majority of rats (15/22) with dominant-sided lesions turned predominantly contraversive,

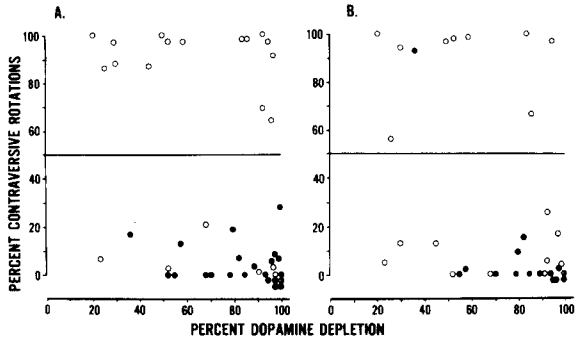

Fig. 1. The percent of total rotations (360° turns) made contralateral to the hemisphere with a 6-OHDA lesion (contraversive), plotted as a function of the percent difference in striatal DA content between the depleted and non-depleted side. Those symbols above the 50% contraversive rotations line represent individual rats that turned predominantly contraversive, whereas those below the line turned predominantly ipsiversive. ○, rats with dominant-sided 6-OHDA lesions; ●, rats with non-dominant-sided lesions (see text). A: after a low (0.65–1.0 mg/kg) dose of AMPH. B: after a higher (2.6–3.0 mg/kg) dose of AMPH (see text).

which is in the opposite direction predicted by the rotational behavior model[25,27]. The rats with lesions on the dominant side made 63.8% of their total rotations in the contraversive direction (Table IA, $P < 0.00001$). The difference between rats with dominant or non-dominant-

TABLE I

Direction of AMPH-induced rotational behavior in rats with a 6-OHDA lesion of the substantia nigra on the 'dominant' or 'non-dominant' side, after a low (0.65–1.0 mg/kg) or high (2.6–3.0 mg/kg) dose of AMPH

Lesion group	*n*	*Number of ipsiversive turners (%)*	*% Contraversive rotations*
(A) Low dose			
(1) 'Non-dominant'	22	22 (100)	4.8 ± 1.7
(2) 'Dominant'	22	7 (32)	63.8 ± 9.0*
(B) High dose			
(1) 'Non-dominant'	17	16 (94)	7.2 ± 5.5
(2) 'Dominant'	22	13 (59)	40.3 ± 9.3*,**

* Differs from group with 'non-dominant'-sided lesions; for low dose $t = 6.4$, $P < 0.00001$; for high dose $t = 2.8$, $P < 0.008$.

** Animals with 'dominant'-sided lesions differ when given a low vs high dose of AMPH ($t = 3.4$, $P < 0.003$, paired t-test).

sided lesions in percent contraversive rotations was less exaggerated when the animals were tested with the higher dose of AMPH, although rats with dominant lesions continued to make significantly more contraversive rotations (40.3%) than did rats with non-dominant lesions (7.2%, Fig. 1B, Table IB, $P < 0.008$).

The difference between the effects of the low and high dose of AMPH is not due to an order effect. We have obtained the same results as reported here in an independent replication of this study in which 3 different doses of AMPH were randomly administered. Also, Fig. 1 shows that one rat with a non-dominant lesion turned contraversive after the high dose of AMPH. This rat turned ipsiversive after the low dose. Of all the rats tested in this experiment, and an additional 45 rats with non-dominant lesions tested in an independent study, this is the only one with a non-dominant lesion we have ever observed to turn contraversive. The only explanation we can offer is that this rat may not have been very lateralized. During the screening tests it showed very few net rotations relative to the other animals.

In Fig. 2 we attempt to illustrate the present results schematically by integrating our knowledge of the neural systems underlying rotational behavior[8,10,19], and Glick's suggestion that there is an endogenous asymmetry in the nigrostriatal DA system[10]. Fig. 2A represents a normal intact rat in which the right nigrostriatal DA system is dominant for rotational behavior. If such a rat were injected with AMPH it would turn predominantly to the left. If this rat were treated with 6-OHDA on the non-dominant side (Fig. 2B) the intrinsic asymmetry would simply be enhanced, and the rat would turn even more vigorously to the left (ipsiversive) after AMPH. However, if the lesion was on the dominant side (Fig. 2C, D) the direction of AMPH-induced rotational behavior would depend to some extent on the magnitude of the DA depletion, and the dose of AMPH used. Fig. 2C illustrates that if some DA fibers remain on the damaged side (e.g. 10–20%), and the animal is given a low dose of AMPH, there is still more DA released on the side with the lesion (the dominant side) than on the intact side (non-dominant side), and the rat turns left (contraversive). However, after a higher dose of AMPH (Fig. 2D) the surviving neurons on the dominant side cannot increase their rate of DA release to the extent that the neurons on the intact side can, and the animal now turns to the right (ipsiversive). Of course, the dose of AMPH required to produce ipsiversive turning in a rat with a dominant-sided lesion, and the vigor of rotational behavior, will depend on the interaction of dose, magnitude of the DA depletion and the strength of the endogenous asymmetry. If the DA neurons on the dominant side are totally destroyed (Fig. 2E) the animal would turn right (ipsiversive), regardless of the dose of AMPH.

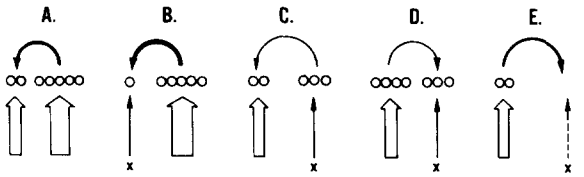

Fig. 2. Schematic illustration of proposed effects of dominant and non-dominant-sided 6-OHDA lesions of the substantia nigra on AMPH-induced rotational behavior. The vertical arrows represent the dopaminergic input into the striatum. The relative size of the input is characterized by the thickness of the arrows. The circles represent the relative amount of DA released from nigrostriatal neurons. The semi-circular arrows indicate the direction of AMPH-induced rotational behavior, and the thickness of these arrows the relative rate of rotation. The X marks the side with a 6-OHDA lesion. A: normal animal. The endogenous asymmetry favors the right nigrostriatal DA system. B: partial 6-OHDA lesion of the non-dominant substantia nigra. C: partial 6-OHDA lesion of the dominant substantia nigra. The rat is tested for rotational behavior with a low dose of AMPH. D: same as C, but tested with a higher dose of AMPH. E: total, or nearly total 6-OHDA lesion of the dominant substantia nigra. (See text for discussion of proposed effects.)

In the situation diagrammed in Fig. 2D the rat is turning against its intrinsic asymmetry, and therefore one might expect it to turn less vigorously. In support of this we found that male rats with a 20–90% DA depletion and a lesion on the dominant side made an average (S.E.M.) of 55.4 ± 18.5 net rotations, whereas rats with a similar DA depletion but a non-dominant lesion made an average of 172.1 ± 45.6 net rotations ($t = 2.37$, df = 12, $P < 0.035$, two-tailed t-test). Glick and his colleagues have reported a comparable

attenuation in rotational behavior after dominant-sided electrolytic lesions of the striatum[7,10].

Although the above scenario is reasonable, it is hard to believe that after the dominant side is depleted of 70–95% of its DA that the remaining 5–30% of the neurons can overcome the influence of all the neurons on the intact side, especially since the endogenous asymmetry is estimated to be only on the order of 15–20%[10]. Glick and Cox[7] previously suggested that the ability of the dominant striatum to overcome the effects of partial damage may be partly due to its intrinsic ability for a larger compensatory response[1,12] than the non-dominant striatum is capable of (Fig. 2C). We have collected some preliminary and tentative evidence to support this idea using the ratio of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) to DA as an index of DA release per neuron[1,12,16]. In rats with 60–90% DA depletions the ratio of DOPAC to DA in the lesioned striatum of rats with dominant-sided 6-OHDA lesions (n = 4) was significantly greater than the DOPAC/DA ratio in the lesioned striatum of rats with non-dominant lesions (n = 7; 0.164 ± 0.012 vs 0.130 ± 0.011, U = 3, $P <$ 0.042, two-tailed Mann–Whitney U-test). For rats with either dominant or non-dominant lesions the DOPAC to DA ratio on the lesioned side was significantly greater than that on the unlesioned side (paired t-tests, $P < 0.05$).

In conclusion, we find a robust asymmetry in the effects of 6-OHDA lesions of the nigrostriatal DA system[10]. The AMPH-induced rotational behavior of rats with DA depletions in the dominant striatum was in the opposite direction of that observed in rats with damage to the non-dominant striatum. We suggest that when using the '6-OHDA rotation model' the intrinsic asymmetry in the nigrostriatal DA system be considered in choosing the side of lesion placement, since different results may be obtained depending on the side of the lesion. This asymmetry in the effects of unilateral damage to nigrostriatal DA neurons may also have clinical relevance to the phenomenon of hemiparkinsonism[13,17,23], and to asymmetries in the dyskinesias produced by the chronic administration of neuroleptic drugs[29].

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