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Abnormal Pattern of Amphetamine Locomotion after 6-OHDA Lesion of Anteromedial Caudate[1]

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FINK, J. S. AND G. P. SMITH. *Abnormal pattern of amphetamine locomotion after 6-OHDA lesions of anteromedial caudate.* PHARMAC. BIOCHEM. BEHAV. **11**(1) 23–30, 1979.—6-Hydroxydopamine (6-OHDA) injections into the anteromedial caudate nucleus (AMCN) produced severe loss of dopamine (DA) fibers in this region of the caudate. After a low dose of d-amphetamine (1.5 mg/kg), AMCN 6-OHDA rats made fewer traverses of the length of the activity cage than control rats. In contrast, AMCN 6-OHDA rats interrupted a photocell beam that passed across the middle of the long axis of the activity cage as often as control rats. 6-OHDA injections into the nucleus accumbens (NAc) produced severe loss of DA fibers in NAc without significantly damaging the adjacent anteromedial caudate or olfactory tubercle. After d-amphetamine (1.5 mg/kg), NAc 6-OHDA rats interrupted the photocell beam and traversed the length of the activity cage as frequently as control rats. We conclude that the DA innervation to the anteromedial caudate, but not to the nucleus accumbens, is necessary for that part of the normal locomotor response to a low dose of d-amphetamine that is required for the performance of long traverses of an activity cage.

d-Amphetamine Nucleus accumbens 6-OHDA Activity Locomotion Dopamine Caudate nucleus

LOCOMOTION produced by low doses of d-amphetamine is dependent on the integrity of forebrain dopamine (DA) neurons. Destruction of DA neurons by intracerebral injections of the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA) into the ventricles, substantia nigra, mesolimbic DA terminal fields or along the fibers of the medial forebrain bundle abolishes or attenuates the locomotor response to amphetamine [4, 5, 6, 7, 10, 11, 20]. Release of DA in the nucleus accumbens or olfactory tubercle may be particularly important to amphetamine-induced locomotion because blockade of DA receptors by local infusion of haloperidol or destruction of DA terminals produced by local infusion of 6-OHDA attenuates the locomotor response to d-amphetamine [10, 11, 18]. However, these 6-OHDA lesions of the DA terminals in the nucleus accumbens produce variable depletions of DA in the caudate [10,11], suggesting that destruction of the DA innervation to the adjacent caudate may contribute to deficits in amphetamine induced locomotion observed after 6-OHDA injections into the nucleus accumbens. On the other hand, considerable evidence suggests that denervation of the DA terminals in the caudate has no effect on the locomotor response to amphetamine [1, 3, 14, 15].

Because these studies have employed biochemical assays of DA in regional dissections of brain as the measure of DA neuron destruction after 6-OHDA, the anatomical limits of the critical area of DA terminal loss required to produce deficits in amphetamine locomotion have not been delineated precisely. Furthermore, the measure of locomotion in these studies has usually been the interruption of a photoelectric beam passing through one or several areas of the activity cage, or mechano-electric detection devices. Unfortunately, these methods provide little information about the pattern of locomotion and, unless concurrent behavioral observations are made, may not index locomotion at all [19].

In this paper we report the effects of destruction of DA terminals in the nucleus accumbens or in the adjacent anteromedial caudate on the locomotor response to a low dose of d-amphetamine. We have determined the pattern of DA terminal loss histochemically and have analyzed the pattern of locomotion after d-amphetamine by using a closed circuit videotaping system. We find that destruction of DA termi-

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nals in the anteromedial caudate changes the normal pattern of locomotion after amphetamine, but destruction of DA terminals in the nucleus accumbens does not.

METHOD

Surgery

Male Sprague-Dawley rats (Hormone Assay, Chicago, Illinois) were housed individually at a temperature of about 24°C and with 12 hr of light (0700–1900 hr). At the time of surgery each rat weighed 200–250 g (mean, 228 g). Stereotaxic microinjections were made in animals anesthetized with barbiturate and chloral hydrate (Equithesin, Jensen Salsbery Laboratories, Kansas City, MO, or Chloropent, Fort Dodge, IA, 2.0 ml/kg, IP) and supplemented with inhalation of methoxyflurane (Metofane, Pitman-Moore, Inc., Washington Crossing, NJ) as needed. Injection solutions were mixed just prior to use and chilled until loaded into a Hamilton syringe (50 μl) equipped with an automatic Hamilton dispenser which was connected to a 30 ga stainless steel cannula by polyethylene tubing (PE 10). Control animals received injections of vehicle. During microinjections, the movement of a bubble through the tubing was measured to minimize variability of injected volumes [21]. To protect noradrenergic neurons from the toxic effects of 6-OHDA [20], rats were pretreated with desmethylimipramine (DMI, 25 mg/kg, IP: USV Pharmaceutical Corp., Tuckahoe, NY) 30 min prior to the acute infusion of 6-OHDA (Regis Chemical Co., Chicago, IL) or vehicle. The concentration of vehicle was 1 μg/μl ascorbic acid in 0.9% NaCl and 6-OHDA was 4 μg/μl base in vehicle. The infusion rate was 1 μl/min.

The anteromedial caudate nucleus (AMCN) was infused bilaterally with 1.5 μl of 6-OHDA (n=7) or vehicle (n=6) using the coordinates of Kelly *et al.*: A9.2, L1.7, V4.8 [11,16]. The nucleus accumbens (NAc) was infused bilaterally with 1.5 μl of vehicle (n=6) or 6-OHDA (n=7) using the following coordinates: A9.2, L1.7, V6.7 [16].

Behavioral Testing

6-Hydroxydopamine (6-OHDA) and vehicle-injected rats were tested for the locomotor response to d-amphetamine 2 weeks and 5 weeks after surgery. Rats were placed in an activity cage (see Ervin *et al.* [6] and Fig. 1 for a description of the apparatus) for 40 min and then injected intraperitoneally with d-amphetamine sulfate (1.5 mg/kg, Smith, Kline and French, Philadelphia, PA). Amphetamine was mixed in distilled water and injected in a volume of 2 ml/kg. Vehicle rats received injections of 2 ml/kg distilled water IP. Cumulative photocell counts were recorded every 10 min during the 40 min preinjection and 2 hr postinjection periods. At the end of each 10 min period, each rat was observed for 30 sec and received a behavioral score based on the following criteria: (0) no body or head movements, eyes closed: (1) awake, locomotion in one half of cage: (2) locomotion in both halves of cage: (3) discontinuous stereotypy (stereotyped behavior interrupted by other behaviors such as grooming or rearing during the 30 sec observation period): (4) continuous stereotypy (stereotyped behavior throughout the observation period). In addition, the form of the stereotyped behavior (sniffing, licking, gnawing or biting) was recorded when behavioral ratings of 3 or 4 were scored.

Traverses of the length of the activity cage were recorded using a closed circuit videotaping system. A camera (Hitachi No. FP71, Woodside, NY) mounted approximately 2.5 m from the activity cage, faced the long axis of the cage. A blue line on the Plexiglas cage marked the middle of the long axis of the cage (Fig. 1). Videotaping began at the beginning of the trial and was stored on a videotape recorder (TeleMation No. TVR1700, Nippon Electric Co., Tokyo, Japan). A clock in the field of the cage recorded elapsed time during the experiment. At a later time the tapes were replayed on a Sony black and white monitor and the number of traverses recorded by 2 observers. One traverse of the cage was scored if a rat was completely on one side of the center blue line and moved completely to the other side of the blue line (Fig. 1). Interrater reliability for this measurement was 0.97.

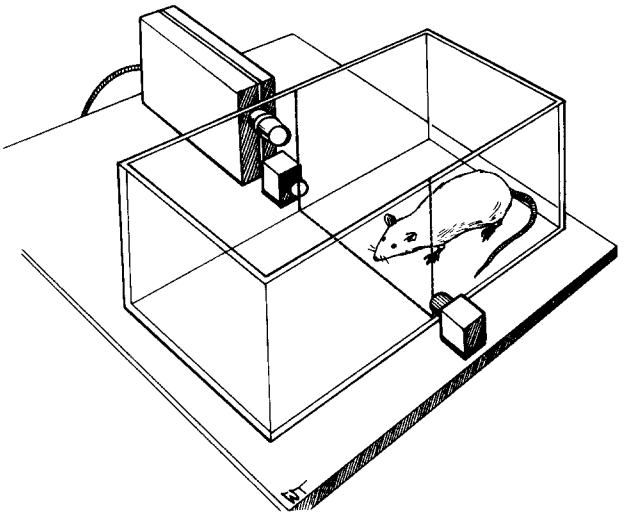

FIG. 1. Schematic representation of the activity cage including photocell and closed circuit videotaping system for the measurement of activity and traverses after d-amphetamine. A photocell beam (3.2 cm off the floor) passed through the center of the plastic cage (21×44×20 cm high) that had a wire mesh floor and was received on the opposite side by a photoelectric cell. The sensitivity of the photoelectric beam was adjusted so that it was interrupted by the rat's body, but not by its tail or limbs. A TV camera was mounted 2.5 m from the long axis of the cage and recorded movements in the cage during testing on a videotape recorder. A vertical line was marked on the cage halfway along its length. One traverse of the cage was recorded if the rat was initially on one side of the vertical line and moved its entire body or all of it except the tail to the other side of the line.

In the amphetamine test done two weeks postoperatively, photocell interruptions and behavioral ratings were recorded. In the amphetamine test done five weeks postoperatively, photocell interruptions and the videotaping method were used simultaneously.

Both the photocell interruption and the traverse measured by the videotaping method indexed locomotor behaviors. However, the pattern of locomotion that these measures scored were different: Interruption of the photocell beam measured both long traverses of the length of the activity cage as well as shorter locomotor excursions whereas the videotaping system scored only long traverses of the activity cage. To record a traverse, the rat had to move almost the entire length of the cage. To record a photocell interruption, the rat had to move half the length of the cage or less. Thus, a

TABLE 1

PHOTOCELL BEAM INTERRUPTIONS AND DISTRIBUTION OF BEHAVIORAL RATINGS PRODUCED BY d-AMPHETAMINE (1.5 MG/KG) TWO WEEKS AFTER 6-OHDA INJECTIONS INTO THE ANTEROMEDIAL CAUDATE OR NUCLEUS ACCUMBENS

Behavioral Rating:	Mean Percentage of Total Ratings 0	1	2	3	4	Photocell Counts
Anteromedial Caudate						
6-OHDA (n=7)	6	72*	22†	0	0	541 ± 61
Vehicle (n=6)	0	27	63	0	0	592 ± 74
Nucleus Accumbens						
6-OHDA (n=7)	0	34	66	0	0	626 ± 124
Vehicle (n=6)	0	30	70	0	0	642 ± 76

*$p=0.015$, †$p=0.02$ compared with Anteromedial Caudate Vehicle group (Mann-Whitney *U* Test).

The behavioral ratings and the photocell counts are shown for the postinjection period (120 min).

Photocell counts are mean ± SE.

rat could move half the length of the cage or less and interrupt the photocell beam, but still remain on the same side of the blue line that bissected the long axis of the cage. This pattern of locomotion would register a photocell interruption, but it would not be scored as a traverse.

Histochemistry

After drug testing was completed and 6–7 weeks after surgery, all rats were processed for visualization of CA neurons using the glyoxylic acid-paraformaldehyde method on cryostat sections [2]. In this procedure, animals were pretreated with nialamide (300 mg/kg, IP, 1–3 hr prior to sacrifice), anesthetized, immersed in an ice bath (−3° to 0°C), and perfused transcardially with 400 ml of cold 2% glyoxylic acid monohydrate and 0.5% paraformaldehyde in phosphate buffered mammalian Ringer's (pH 7.4). The brain was rapidly dissected from the cranium, the desired regions cut into 2 mm blocks, frozen onto cryostat chucks on dry ice and sectioned in the coronal plane at 16–24 μm at −12°C. sections were thawed onto chilled glass slides, immersed in glyoxylic acid (2% in phosphate buffered Ringer's) for 11 min, dried under a warm air stress (45°C) for 7 min and heated for 6 or 10 min in a closed glass container. Because we have observed variability in the development of CA fluorescence in different brain areas with this method, adjacent sections were heated for 6 to 10 min at 100°C. Usually, one of these heating times produced optimal CA fluorescence from every brain area. Sections were cut in the coronal plane every 240 μm from optic chiasm to frontal pole and mounted in paraffin oil.

Sections were viewed by transmitted darkfield microscopy on a Zeiss fluorescence microscope equipped with a Schott BG12 or BG3 primary lamp filter, and Zeiss 41 and 47 barrier filters. Regions of CA denervation were sketched onto plates of a rat brain atlas [12] according to the following criteria: +—little or no detectable CA fiber loss, 2 +—moderate CA fiber loss, 3 +—severe CA fiber loss with few or no CA fibers remaining.

Statistics

Data were analyzed by Student's *t*-test (comparison between independent means). Nominal and ordinal data were analyzed by the Mann-Whitney U Test.

RESULTS

Behavioral Tests

Two weeks after surgery the locomotor respone to amphetamine in AMCN 6-OHDA rats was characterized by a normal increase in photocell activity, but by an abnormal distribution of behavioral ratings (more 2 and fewer 1 ratings, Table 1). This suggested that AMCN 6-OHDA rats failed to traverse the length of the test cage as often as vehicle rats. Five weeks after surgery AMCN 6-OHDA rats were tested again. This time their pattern of locomotion was recorded on videotape. Prior to injection AMCN 6-OHDA rats made as many traverses as controls (Table 2 and Fig. 2, top panel), but after amphetamine they made only 54% as many traverses of the length of the activity cage as controls (Table 2).

When the tapes were reviewed, both groups of rats showed increased activity after the amphetamine injection. This activity consisted of locomotion and sniffing about all areas of the activity cage. The most striking qualitative difference between AMCN 6-OHDA and vehicle groups was in the long runs of the length of the activity cage. These long runs occurred frequently in both vehicle groups after amphetamine: A rat would locomote from one end of the cage to the other end, sniff at the end of the cage and return to the other end of the cage. This sequence of behaviors was scored as a traverse (see Method). In the AMCN 6-OHDA rats the long runs of the cage were truncated compared with those of the vehicle rats. The AMCN 6-OHDA rats would locomote from one end of the cage toward the other end, but before reaching the far end of the cage they would stop, sniff and return toward the other end of the cage. Frequently, during this shortened run, the AMCN 6-OHDA rats did not move completely from one side of the blue halfway line to the other. Thus, a traverse was not scored. Fewer traverses after amphetamine in AMCN 6-OHDA rats was not due to inhibition of traverses by stereotyped behavior because review of the tapes of AMCN 6-OHDA rats did not show stereotyped behavior.

TABLE 2

TRAVERSES AND PHOTOCELL BEAM INTERUPTIONS PRODUCED BY d-AMPHETAMINE (1.5 MG/KG) FIVE WEEKS AFTER 6-OHDA INJECTIONS INTO THE ANTEROMEDIAL CAUDATE OR NUCLEUS ACCUMBENS

		Traverses		Photocell Counts	
	n	Preinjection	Postinjection	Preinjection	Postinjection
Anteromedial Caudate					
6-OHDA	7	35 ± 6	125 ± 28*	134 ± 16	767 ± 104
Vehicle	6	40 ± 6	232 ± 32	158 ± 28	783 ± 50
Nucleus Accumbens					
6-OHDA	7	47 ± 3†	188 ± 41	185 ± 27	770 ± 99
Vehicle	6	38 ± 6	217 ± 32	152 ± 26	776 ± 52

*$p<0.025$, †$p<0.05$, compared with Vehicle group (Student's t-test).

Traverses are the number of excursions of the length of the activity cage measured by a videotape-recording system described in Methods.

The preinjection period was 40 min and the postinjection period was 120 min.

Data is mean ± SE.

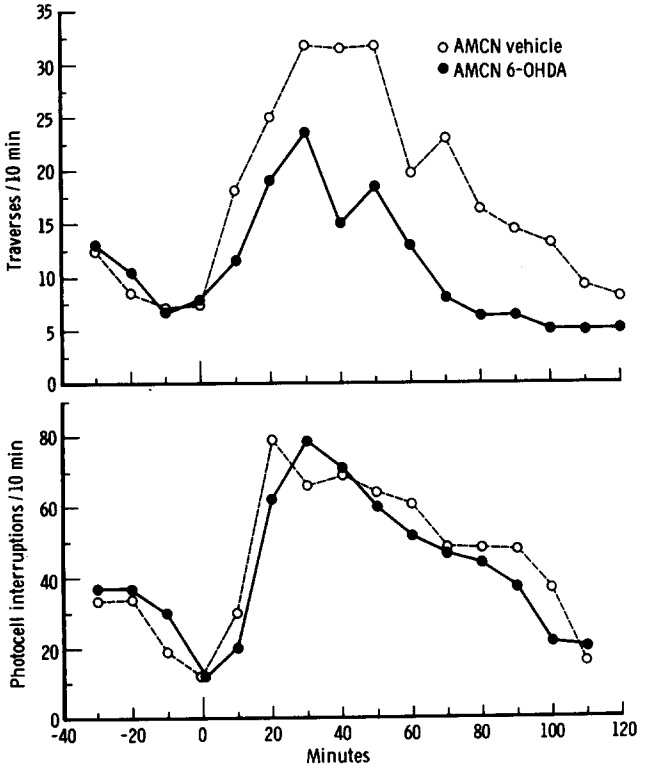

FIG. 2. Mean traverses (top panel) and photocell beam interruptions (lower panel) per 10 min prior to and 120 min after 1.5 mg/kg d-amphetamine in rats 5 weeks after 6-OHDA or vehicle injections in the anteromedial caudate. Traverses were measured using a closed circuit videotaping system described in Fig. 1 and Method.

Despite making fewer traverses after amphetamine, AMCN 6-OHDA rats had the same total photocell counts as vehicle rats (Table 2). The time course of the photocell count response to amphetamine was also very similar in AMCN 6-OHDA and vehicle rats, although AMCN 6-OHDA rats tended to have a lower peak response and a shorter duration of action (Fig. 2, top panel).

In contrast to the effects of 6-OHDA injections into the AMCN, 6-OHDA into the NAc had no effect on the locomotor response to amphetamine (Tables 1 and 2). In the preinjection period, NAc 6-OHDA rats scored more traverses in the test 5 weeks after surgery (Table 2) and more photocell counts 2 weeks after surgery (data not shown) than NAc vehicle rats. The reason for this is not known.

Total photocell counts after amphetamine were slightly higher for all 4 groups in the second test (5 weeks postoperatively; compare Tables 1 and 2). We do not know the reason for this difference, but it could be due to nonspecific postoperative depression in the 2 week test or prior experience with the testing procedure in the 5 week test.

Histochemistry

6-Hydroxydopamine (6-OHDA) injections into the anteromedial caudate and nucleus accumbens produced a marked loss of fluorescent CA fibers (Figs. 3 and 4). There was an area of severe (3+) and partial (2+) denervation which was common to all animals in each lesion group (Fig. 5). AMCN 6-OHDA injections produced severe denervation of DA fibers in the anterior juxtaventricular caudate at the level of the nucleus accumbens and a larger area of partial DA fiber loss (Fig. 5a). The area of severe and partial DA fiber loss in the AMCN 6-OHDA rats did not include the nucleus accumbens except in 2 cases where the dorsal aspect of this nucleus was partially denervated (2+) unilaterally. The AMCN 6-OHDA injection also produced varying damage to the lateral septal nucleus in all six brains: There was severe (3+) bilateral denervation in three rats, moderate (2+) bilateral denervation in one rat and severe (3+) unilateral denervation in two rats.

Catecholamine fibers were present in apparently normal density in the parietal neocortex in the AMCN 6-OHDA rats. Because this area has a predominantly noradrenergic innervation [13], pretreatment with DMI probably protected most passing noradrenergic fibers from the toxic effects of 6-OHDA. There were no areas of DA fiber loss in rats after

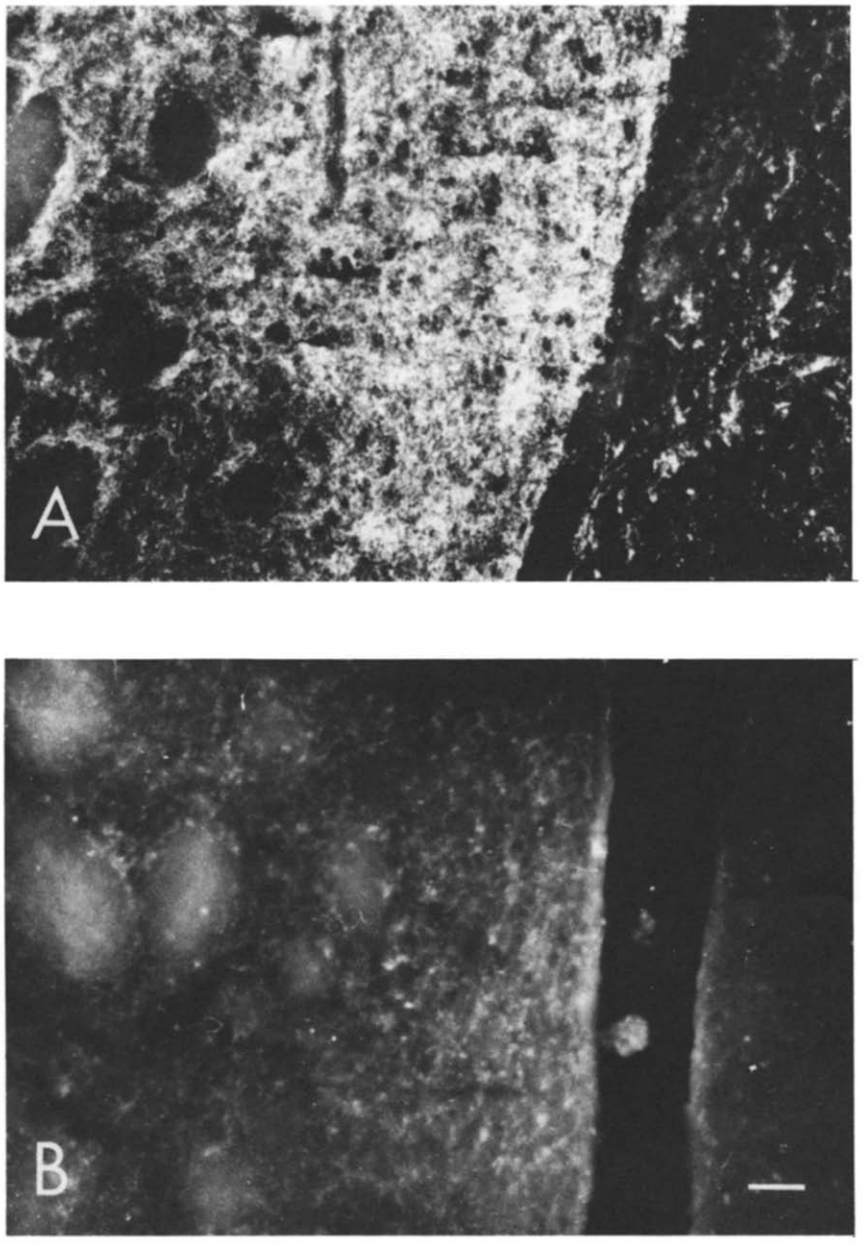

FIG. 3. Fluorescence photomicrographs of the anteromedial caudate nucleus, lateral ventricle and adjacent lateral septum 6 weeks after vehicle (A) or 6-OHDA (B) injections into the anteromedial caudate. In A the dense plexus of dopamine fibers in the caudate surrounds the fiber bundles of the internal capsule and in the septum the catecholamine fibers appear as islands of fluorescent fibers. The severity of denervation in the caudate in A is rated +. In B there is a complete loss of fluorescent dopamine fibers in the anteromedial caudate and septum. The severity of denervation in B is rated 3+. Glyoxylic acid-paraformaldehyde method on 16 μm cryostat sections. Calibration bar=20 μm.

vehicle injections into the AMCN. Nonspecific damage at the cannula tip appeared equal in 6-OHDA and vehicle-injected rats and was always less than 120 μm in diameter.

NAc 6-OHDA injections produced a common area of severe DA fiber loss that included most of the NAc medial to the anterior limb of the anterior commissure and a larger area of partial (2+) fiber loss (Fig. 5b). The common area of severe DA fiber loss did not include the DA terminal fields in the anteromedial caudate, lateral septal nucleus or dorsal nucleus interstitialis stria terminalis. However, the lateral septal nucleus was severely denervated bilaterally in 5 of 7 NAc 6-OHDA rats. There were areas of severe DA fiber loss in the olfactory tubercle, anteromedial caudate and anteroventral caudate in individual NAc 6-OHDA rats, but we could not distinguish these animals behaviorally from animals with severe DA fiber loss restricted to the NAc. In NAc

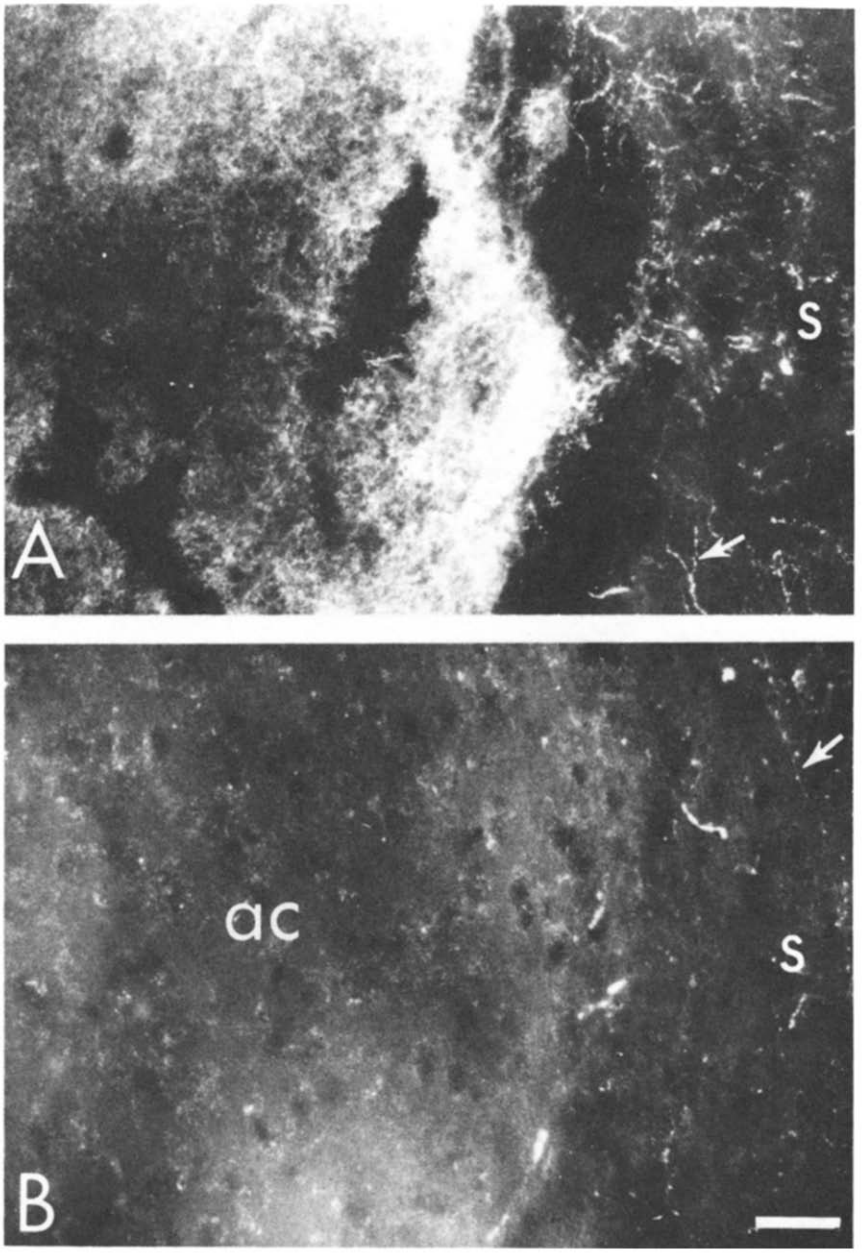

FIG. 4. Fluorescence photomicrographs of the nucleus accumbens (ac) and adjacent septum (s) 6 weeks after vehicle (A) or 6-OHDA (B) injections into the nucleus accumbens. After vehicle injections (B) there is a dense plexus of fine, small diameter dopamine fibers in the nucleus accumbens and a sparse innervation of the septum by large diameter fibers (arrow). After 6-OHDA injection (B) there is a complete loss of fluorescent fibers in the nucleus accumbens and a few fibers remain in the septum (arrow). The degree of denervation in A is rated + and in B is 3+. The areas within the nucleus accumbens in A that are devoid of fluorescent fibers represent artifacts of tissue preparation. Calibration bar=40 μm.

6-OHDA rats, CA fibers in the parietal neocortex were present in apparently normal density indicting that DMI pretreatment effectively protected noradrenergic neurons passing through the area from the toxic effects of 6-OHDA.

There was no apparent loss of DA fibers in rats with injections of vehicle into the nucleus accumbens. Nonspecific damage at the cannula tip at the time of sacrifice was apparently the same in NAc vehicle and 6-OHDA-injected rats and was always less than 250 μm in diameter.

DISCUSSION

These experiments demonstrate the locomotor response to a low dose of d-amphetamine is abnormal after denerva-

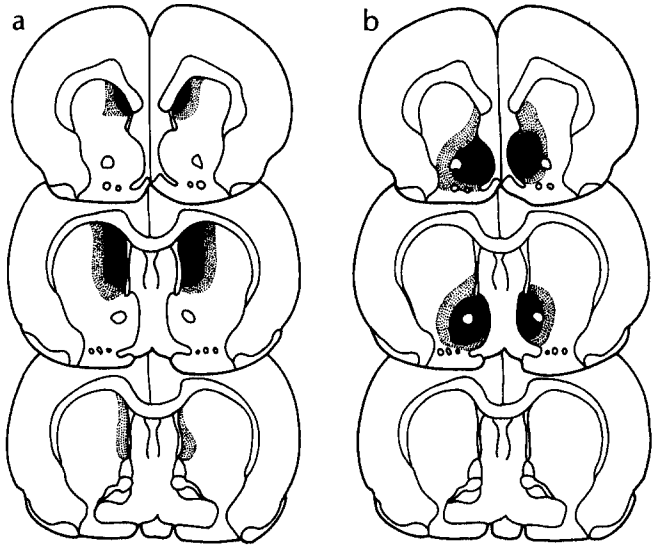

FIG. 5. Schematic representation of the areas of severe (3+, dark strippling) or moderate (2+, light stippling) loss of fluorescent dopamine fibers in the caudate and nucleus accumbens 6-7 weeks after 6-OHDA injections into the anteromedial caudate (a) or nucleus accumbens (b). The schematics depict the common areas of dopamine fiber loss in 7 AMCN 6-OHDA and 7 NAc 6-OHDA rats sketched onto plates of a rat brain atlas [12].

tion of the DA fibers in the juxtaventricular area of the anteromedial caudate. The abnormality was a decreased rate of the long locomotor sequences that carried the rat from one end of the activity cage to the other. The lower rate of emitting these sequences was only present after amphetamine; AMCN 6-OHDA rats had a normal rate of these locomotor sequences in the preinjection period (Table 2). Since we used only one dose of amphetamine, it is not possible to decide if the decreased rate is the result of a decreased sensitivity or is a reduction in the maximal response to amphetamine. This description of the deficit suggests that the deficit is primarily one of motor organization, and the fact that the DA lesion is in the caudate is consistent with this interpretation.

An alternative view, emphasizing the perceptual function of the caudate, is also plausible. This would explain the decreased rate of traverses as a decrease in the ability of distal environmental stimuli (the far end of the activity cage) to control behavior. This view is consistent with the hypothesis of Van Rossum *et al.* [22] that the locomotor response to amphetamine should be interpreted as increased exploratory behavior due to a generalized enhancement of sensorimotor reactions to environmental stimuli. From this hypothesis one would predict that AMCN 6-OHDA rats might have a general deficit in exploratory behaviors, but their locomotor exploration of a novel open field and the investigation of a novel object were normal (mean squares traversed in a novel open field in 5 min: AMCN 6-OHDA (n=7)=234 ± 14, AMCN vehicle (n=6)=254 ± 20, $t(11)=0.52$, $p>0.05$: mean approaches to a novel object in a 3-min trial: AMCN 6-OHDA (n=7)=5.0 ± 1.2, AMCN vehicle (n=6)=5.5 ± 0.9, $t(11)=0.36$, $p>0.05$; see Fink and Smith [8] for methodology).

A third possibility, that the decreased rate of traverses is a decrease in arousal and is related to the extent of loss of DA terminals, is not likely because all behaviors after amphetamine were not decreased (total photocell counts were normal) and a similar loss of DA terminals in the nearby nucleus accumbens did not have a similar effect.

The failure of denervation of the nucleus accumbens to alter the pattern of magnitude of the locomotion after amphetamine is consistent with the results of Costall *et al.* [3], but not with those of Kelly *et al.* [10] and Kelly and Iversen [11]. The injection coordinates used in the present experiments were identical to those of Kelly *et al.* [10], but our injection volume was 0.5 μl smaller. This could mean that the extent of denervation of the nucleus accumbens may have been less in our animals, but the area of severe denervation involved almost all of the nucleus (Fig. 5b). It is difficult to compare the two measures of DA damage because Kelly *et al.* [10] and Kelly and Iversen [11] used biochemical assays of regional brain dissections while we used a histochemical method to assess DA neuron damage in complete brain sections. In situations such as this, where one is concerned with determining total or near total denervation within a specific brain area, the pattern of histochemical fiber loss may be more informative than biochemical assay because it is not subject to the imprecision of regional dissections, and it may disclose any uneven denervation within the brain area.

Although there is abundant experimental evidence that activation of DA receptors in the nucleus accumbens elicits locomotion [9,17], our results and the results of Costall *et al.* [3] and Wirtshafter *et al.* [23] demonstrate that most, if not all, of the DA terminals in the nucleus accumbens are not necessary for the normal locomotor response to a low dose of d-amphetamine. The DA innervation of other forebrain DA areas appears to be sufficient to produce normal locomotion to d-amphetamine after a chronic lesion of the nucleus accumbens, but apparently not after pharmacological blockade with haloperidol [18].

In summary, the dopaminergic innervation to the anteromedial caudate appears to be important for the elaboration of long traverses of the activity cage which are elicited by a low dose of d-amphetamine. Total or nearly total denervation of DA terminals in the nucleus accumbens had no such effect. These results suggest that the DA innervation of the caudate, particularly of its anteromedial region, may be more important for the locomotor response to amphetamine than has been evident from prior experiments and, conversely, the nucleus accumbens may be less so.

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