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# Lack of an Effect of 6-Hydroxydopamine Lesions of the Nucleus Accumbens on Intravenous Morphine Self-Administration

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DWORKIN, S. I., G. F. GUERIN, C. CO, N. E. GOEDERS AND J. E. SMITH. *Lack of an effect of 6-hydroxydopamine lesions of the nucleus accumbens on intravenous morphine self-administration.* PHARMACOL BIOCHEM BEHAV **30**(4) 1051–1057, 1988.—The neurotoxin, 6-hydroxydopamine (6-OHDA), has been used to selectively destroy dopamine containing neurons in discrete brain regions. Lesions of the nucleus accumbens with this neurotoxin decrease or eliminate cocaine and amphetamine self-administration and either increase or do not affect opiate self-administration in rats with unrestricted access to food and water. This study reports the effects of 6-OHDA lesions of the nucleus accumbens on responding maintained by food, water or morphine (3.3 mg/infusion). Six male rats with continuous access to three response levers were trained on a concurrent chained, fixed-ratio 1, fixed-ratio 9 schedule of reinforcer presentation. After stable patterns of responding were maintained by the three reinforcers, dose-effect curves for morphine were determined by substituting other doses of morphine or vehicle for 24-hour periods. Bilateral sham vehicle or 6-OHDA lesions of the nucleus accumbens were then completed and the effects of the lesion on food, water and morphine intake determined. Dose-effect evaluations were repeated after the lesion. The 6-OHDA lesions did not significantly affect responding maintained by food, water or morphine. The absence of an effect is most likely not the result of an insensitive baseline since other neurotoxin lesions produce long-term and selective decrements in morphine self-administration without affecting food and water responding. Like so many other manipulations, the magnitude of the effect that a neurotoxin lesion can exert on behavior may depend on the specific procedures that are used to maintain responding.

Neurotoxin lesions 6-Hydroxydopamine lesions Nucleus accumbens
Intravenous morphine self-administration Opiate reinforcement Food reinforcement
Water reinforcement Dopamine Neurotransmitter content

NEUROTOXIN lesion procedures have been used to assess the involvement of specific neurotransmitter systems in the neurobiological processes involved in drug reinforcement. 6-Hydroxydopamine (6-OHDA) lesions of the nucleus accumbens [14, 18, 19] and ventral tegmental area [20] decrease intravenous stimulant self-administration. On the other hand, increased intravenous morphine self-administration has been reported after 6-OHDA lesions of the nucleus accumbens with a corresponding shift to the right in the dose-response curves [24]. Thus, dopaminergic lesions appear to have a qualitatively different effect on the self-administration of stimulants and opiates. Additional qualitative differences between cocaine and opiates have been observed in conditioned place preference and intracranial self-administration studies. Heroin and amphetamine conditioned place preference is attenuated by 6-OHDA lesions of the nucleus accumbens [21,23] while cocaine conditioned place preference is not [22]. Intracranial injections of morphine [4], methionine enkephalin [10] and amphetamine [12], but not cocaine [11] into the nucleus accumbens maintain self-administration. These studies provide an indication of the role of dopaminergic innervations of the nucleus accumbens in central reinforcement mechanisms and suggest that some degree of specificity is associated with this system. In a more definitive study of the pharmacological specificity associated with this dopaminergic system, 6-OHDA lesions of the nucleus accumbens attenuated cocaine but not heroin self-administration in animals self-administering both drugs on alternative days [17]. The investigation was initiated to further assess the role of dopaminergic innervations of the nucleus accumbens in the processes maintaining intravenous opiate self-administration. The effects of 6-OHDA lesions of the nucleus accumbens on responding concurrently maintained by food, water

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and morphine was assessed in order to determine the behavioral specificity of this lesion. The data collected from this study were compared to the results from a previous study investigating the effects of 6-OHDA lesions of the nucleus accumbens on morphine self-administration [24]. In the previous study rats were given unrestricted access to food and water.

## METHOD

### *Subjects*

Six adult male Fisher-344 rats between 90 and 120 days old at the beginning of the study were used. The subjects had continuous access to food and water containing tetracycline (0.01%) until they were used in the study.

### *Behavioral Procedures*

The subjects were trained in standard operant conditioning chambers (24.5×23.5×21.0 cm) containing three retractable levers and three stimulus lights mounted directly above the levers. The chambers were enclosed in sound-attenuating boxes containing a house light, tone source, pellet dispenser and water dipper. A motor driven syringe pump was located on top of this external chamber. The rats were initially trained to lever press on two separate retractable levers. Food and water presentations were scheduled under a concurrent schedule of reinforcement. Under this schedule, one response on either the food or water lever resulted in the delivery of food or water, respectively. After stable responding was observed, the schedule was then changed to a concurrent chained (conc chain) schedule [1]. Under this schedule, the first response on the food or water lever resulted in the retraction of the other lever (FR1 initial link). A fixed number of responses, which was gradually increased from 1 to 9, was then required on the extended lever (terminal link). Food presentations consisted of the delivery of one 45 mg pellet. Water reinforcers were 20 sec access to a 0.1 ml dipper of tap water containing tetracycline (0.01%). Following completion of the schedule requirement, both levers retracted for 30 sec (time out or TO). A limited hold 100 sec contingency (from the first response) was also used. Elapse of the limited hold without completion of the terminal ratio resulted in the scheduling of a time out without reinforcer presentation. Following TO presentation, the levers were extended and the schedule contingencies were reset. The stimulus lights located above each lever were illumitated only when the levers were extended. The animals were contained in these chambers under a 12-hour light cycle (1700 to 500 hours and dark, 500 to 1700 hours) with continuous access to the food and water levers. After stable performance was observed under the conc chain FR1 FR9 schedule, the animals were surgically prepared as described below.

### *Surgical Procedures*

The rats were implanted with jugular catheters using previously described procedures [24]. The catheter (0.76 mm o.d. × 0.25 mm i.d., tigon tubing) was inserted into the right posterior facial vein and pushed down into the jugular vein until it terminated just outside the right atrium. The catheter was anchored to tissue in the area and continued subcutaneously to the back where it exited just posterior to the scapulae through a plastic shoulder harness that was implanted under the skin for attachment of a leash. Bilateral 23-gauge stainless steel injection guide cannulae were then stereotaxically implanted into the nucleus accumbens (9.5 mm anterior to lambda; 1.2 mm from the midline; and 5.1 mm below the surface of the brain [13] using previously described procedures [15]. The guide cannulae were permanently cemented to the skull with dental cement and contained 30-gauge stainless steel stylets which extended 0.75 mm below the tip. A stainless steel needle-tubing spring leash was then attached to the subcutaneous harness to protect the jugular catheter which was connected to a fluid swivel [5]. The swivel was suspended and counterbalanced above the self-administration cage permitting almost complete freedom of movement. The surgery was followed by 48 hours of hourly infusions of 0.2 ml of heparinized saline.

### *Morphine*

The rats were placed in one lever operant conditioning chambers and made physically dependent on morphine over a 12-day period by delivering hourly infusions of increasing doses of morphine. Morphine sulfate was dissolved in a bacteriostatic 0.9% sodium chloride solution containing 0.83 USP units/ml of sodium heparin. The dosage began at 0.83 mg/infusion and was increased every third day to a final dosage of 3.3 mg/infusion. Levers were then added and the rats were trained to respond under an FR1 schedule, which was gradually increased to an FR4. They were then placed back into the original multiple lever conditioning chamber. A morphine reinforcer option was added to the concurrent food and water schedule and all three levers were extended into the chamber under the described schedule contingencies. Subsequent responding was maintained under a conc chain FR1 FR9 schedule of food, water and morphine (3.3 mg/infusion) presentation. Morphine infusions, 0.2 ml delivered over a 5.5 sec period were paired with a 30 sec tone presentation.

### *Food Extinction*

Food extinction was investigated with each animal by removing food pellet presentation for a 24-hr period beginning at the start of the dark cycle (5:00 a.m.). All other aspects of the schedule remained the same during extinction including the extension and retraction of the food lever. At least two food extinction probes were completed for each animal. This manipulation was included in order to evaluate the effects of the lesion on the increased drug intake previously observed during food extinction [8].

### *Morphine Dose-Effect Study*

Dose-effect determinations were completed in each animal. A range of doses from 0.0–13.2 mg/infusion were investigated. The 0.0 dose served as a morphine extinction probe and was used to evaluate the effect of the lesion on the increase in responding on the drug lever and decrease in water intake previously observed during this manipulation [8]. Dose-effect curve determinations were made by replacing the daily morphine dose (3.3 mg/infusion) with another dose of morphine or saline for 24 hr. Drug substitutions were always made at the start of the dark cycle (5 a.m.). At least two determinations of each dose or vehicle were evaluated.

### *Lesions*

When food extinction and dose-effect probes were completed (6–8 weeks) the animals received either a bilateral 6-OHDA lesion (N=4) or sham-vehicle treatment (N=2).

The rats were pretreated with desmethylimipramine (30 mg/kg, IP) 30 min prior to anesthetization with methohexital (1 mg/kg, IV) and the stylets removed. Forty-five minutes after desmethylimipramine either 0.5 μl of the vehicle (isotonic saline-0.02% ascorbic acid) or 6-OHDA (4 μg in isotonic saline 0.02% ascorbic acid) was bilaterally injected over 6 min into the medial central nucleus accumbens through 30-gauge injection cannulae extending 0.5 mm below the guide cannulae. The injection cannulae were left in place an additional 10 min, removed and the stylets replaced. The animals were placed in a small housing cage and received response-independent morphine infusions for 48 hours, since the 6-OHDA lesions are debilitating and could disrupt physical dependence resulting in an artificial change in self-administration. The response-independent infusions were delivered at equal intervals with the total number per day being equal to the average intake for each rat during the five days prior to lesion. The rats were then returned to the three lever condition chamber and were again allowed to self-administer morphine, food and water. When stable responding was again obtained (6–10 days), food extinction and dose-effect probes were completed as outlined above.

*Sacrifice and Histological Procedures*

The rats were sacrificed by total immersion for 5 minutes in liquid nitrogen, the brains removed at −18°C and stored at −70°C.

The location of the guide cannulae and histological assessment of the lesions were determined in each animal. The brains were warmed to −18°C in a cryostat and a coronal cut made at the point of entry along the tract of the guide cannulae. Four 16 μm frozen sections of the cannulae site were taken and then the total nucleus accumbens and adjacent anterior caudate nucleus-putamen and pyriform cortex dissected at −18°C for assessment of biogenic monoamine content.

*Biogenic Monoamine Content*

The content of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid, serotonin (5-HT), 5-hydroxyindoleacetic acid and norepinephrine (NE) were concurrently measured in extracts of the nucleus accumbens, anterior caudate nucleus-putamen and pyriform cortex by high pressure liquid chromatography with electrochemical detection using a previously reported procedure [6].

## RESULTS

*Prelesion*

*Dose-effect.* The patterns of responding maintained by this schedule contingency have been described in greater detail [8,9]. Responding on the food lever occurred at a higher rate than responding on the water lever, whereas morphine infusions maintained the lowest rate of responding. Figure 1 shows the effects of increasing the dose of morphine available for self-administration on food, water and morphine intake. Changes in the morphine dose did not affect responding maintained by food presentations. The dose-effect curve for water intake indicates a modest dose-related increase in responding on the water lever. Increasing the dose of morphine available during a 24-hour period resulted in an increase in the number of ratios completed on the water lever. The morphine dose-effect curve shows a dose related decrease in the number of infusions self-administered as the morphine dose was increased.

*Food and morphine extinction.* The behavioral effects of removing food deliveries for 24-hour periods on responding on the three levers are also shown in Fig. 1. The 3.3 mg/infusion dose was always available during these food extinction probes. Food extinction decreased responding on the food lever from a mean of 317±75 to 109±85. Furthermore, food extinction probes had variable effects of responding maintained by water. The number of ratios completed on the water lever ranged from 5 to 296 during food extinction. The most consequential effect of food extinction was the considerable increase in morphine self-administration. Morphine intake increased from a mean of 16±6 to 30±6 infusions during a 24-hour period. This represents a large increase in the daily intake of drug from a mean of 52.8 to 99 mg/day.

The elimination of morphine from the infusions resulted in a slight decrease in responding on the food lever. The number of delivered food pellets decreased from a mean of 317±75 to 205±73. There was a considerable decrement in responding on the water lever during the 24-hour morphine extinction period. The number of water deliveries decreased from a mean of 83±27 to 15±18. Responding on the morphine lever increased from a mean of 16±6 to 59±25 throughout the morphine extinction period.

*Postlesion*

The 6-OHDA lesion of the nucleus accumbens did not alter responding on any of the levers. The lesions did not result in any significant changes in morphine, food or water intake. The dose-effect curves for the effects of morphine on responding maintained by the three levers were also unchanged. Further, the effects of the extinction probes were also unchanged by the lesion. The behavioral data collected from the rats given the saline lesion were not significantly different from the rats exposed to the neurotoxin, either before or after the lesion. The data collected from an earlier study investigating the effects of a similar lesion on responding maintained by intravenous morphine self-administration are presented in Fig. 2. In this previous study [24], the 6-OHDA lesion of the nucleus accumbens increased morphine self-administration.

Histological assessments indicated that the guide cannulae in all rats were placed in the medial central nucleus accumbens. No significant gliosis was observed in the medial prefrontal cortices, medial septum, hippocampus, amygdala, substantia nigra or ventral tegmental area. The 6-OHDA lesion resulted in a significant decrease in the content of DA (−17%) and DOPAC (−30%) and HVA (−29%) in the total nucleus accumbens (Table 1). Although the 6-OHDA lesion resulted in a relatively small decrease of dopamine content in the nucleus accumbens even smaller decreases have altered morphine self-administration (Table 2).

## DISCUSSION

The results from this study are in disagreement with a number of studies demonstrating the effects of 6-OHDA lesions of the nucleus accumbens on drug self-administration. Lesions of the nucleus accumbens with this neurotoxin decreased the self-administration of cocaine [18,19] and amphetamine [14] and increased morphine self-administration [24]. In this study the lesion had no apparent effect on either morphine self-administration or food and water intake. There were several differences in the present experiment

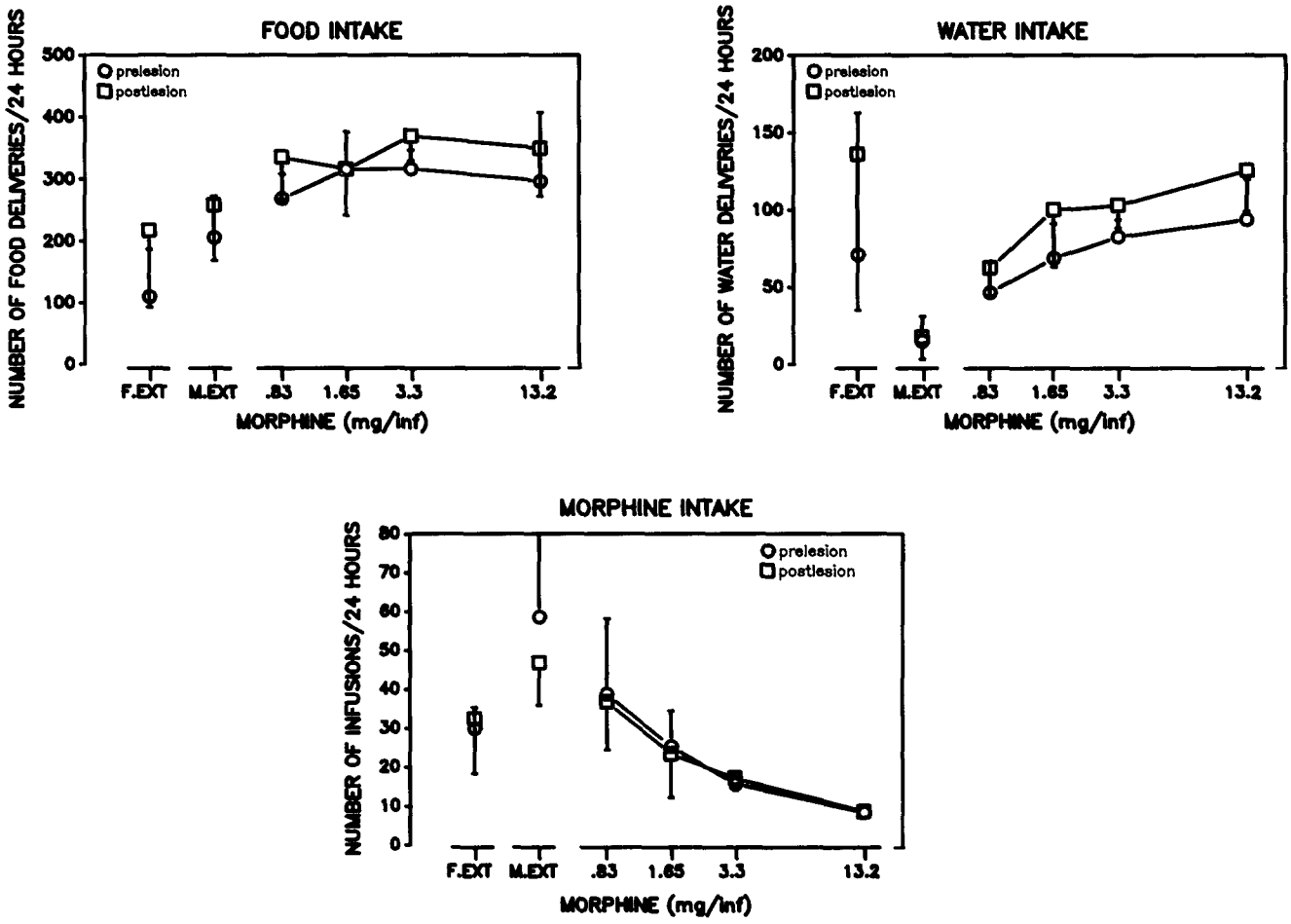


FIG. 1. The number of ratios completed on the food lever (top left), water lever (top right) and morphine lever (bottom center) during 24 hour continuous sessions. The open circles and squares depict data collected before and after the neurotoxin lesion, respectively. The points are means from 4 rats. The vertical lines above the circles and below the squares indicate 1 SD. Points displayed above "F.EXT" and "M.EXT" show data collected during 24 hour food and morphine extinction probes.

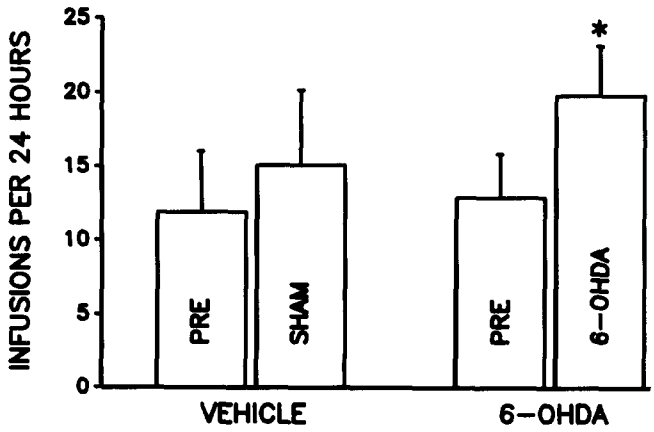


FIG. 2. Effects of sham-vehicle or bilateral 6-OHDA lesions of the nucleus accumbens on intravenous morphine self-administration. Values are means and error measures standard deviations for daily intake of intravenous morphine for 15 pairs of littermates before (pre) and after bilateral injection of either vehicle or 6-OHDA into the central medial nucleus accumbens. Pretreatment intake represents the five days just prior to the sham-vehicle or 6-OHDA lesion. The other two bars represent days 6–14 posttreatment significance of the difference between means determined with Student's $t$-tests were: $p<0.001$, Smith, *et al.* 1985. Reprinted with permission.

TABLE 1

CONTENT OF BIOGENIC MONOAMINES AFTER 6-OHDA OR SHAM-VEHICLE LESIONS IN RATS ON THE MULTIPLE REINFORCEMENT PROCEDURE

| | Content (pmoles·mg protein$^{-1}$) | | | | | |
|---|---|---|---|---|---|---|
| Brain Region Treatment | DA | DOPAC | HVA | 5-HT | 5-HIAA | NE |
| Nucleus Accumbens | | | | | | |
| Sham-Vehicle Lesion | 619.6 ± 22.2 | 100.6 ± 16.1 | 44.1 ± 2.4 | 38.1 ± 2.9 | 26.2 ± 2.3 | 31.7 ± 6.4 |
| 6-OHDA Lesion | 517.1 ± 25.9* | 70.8 ± 6.1* | 31.5 ± 4.5* | 35.7 ± 3.1 | 20.0 ± 3.1 | 13.2 ± 3.7† |
| Anterior Ventral Caudate Putamen | | | | | | |
| Sham-Vehicle Lesion | 755.1 ± 100.3 | 74.5 ± 2.3 | 55.0 ± 3.4 | 33.5 ± 1.6 | 21.4 ± 4.0 | 7.6 ± 3.8 |
| 6-OHDA Lesion | 837.0 ± 52.7 | 69.2 ± 11.9 | 46.9 ± 7.1 | 32.0 ± 3.5 | 20.0 ± 2.4 | 6.4 ± 3.0 |
| Pyriform Cortex | | | | | | |
| Sham-Vehicle Lesion | 155.3 ± 20.7 | 22.4 ± 1.6 | 7.7 ± 0.9 | 29.0 ± 2.4 | 7.9 ± 0.2 | 9.3 ± 1.2 |
| 6-OHDA Lesion | 137.4 ± 31.1 | 21.5 ± 1.0 | 9.4 ± 0.2 | 29.7 ± 0.9 | 9.3 ± 1.3 | 11.9 ± 2.3 |

Values are means ± S.D., N=4 for 6-OHDA Lesion; N=2 for Sham-Vehicle Lesion.
The significance of the difference between means determined with Students' $t$-tests were: *$p<0.05$; †$p<0.01$.

TABLE 2

CONTENT OF DOPAMINE, DIHYDROXYPHENYLACETIC ACID, HOMOVANILLIC ACID, 5-HYDROXYTRYPTAMINE 5-HYDROXYLINDOLACETIC ACID AND NOREPINEPHRINE IN THE NUCLEUS ACCUMBENS, ANTERIOR CAUDATE NUCLEUS-PUTAMEN AND PYRIFORM CORTEX OF PAIRS OF INTRAVENOUS MORPHINE SELF-ADMINISTERING LITTERMATE RATS RECEIVING EITHER 6-OHDA OR SHAM-VEHICLE LESIONS OF THE NUCLEUS ACCUMBENS

| | Content (pmoles·mg protein$^{-1}$) | | | | | |
|---|---|---|---|---|---|---|
| Brain Region Treatment | DA | DOPAC | HVA | 5-HT | 5-HIAA | NE |
| Nucleus Accumbens | | | | | | |
| Sham-Vehicle Lesion | 669.6 ± 90.9 | 94.4 ± 15.6 | 45.6 ± 9.4 | 30.6 ± 3.2 | 23.1 ± 4.7 | 7.7 ± 4.9 |
| 6-OHDA Lesion | 574.6 ± 71.7* | 71.1 ± 15.4† | 40.2 ± 11.8 | 31.9 ± 5.4 | 27.6 ± 6.3 | 5.1 ± 1.7 |
| Anterior Caudate Putamen | | | | | | |
| Sham-Vehicle Lesion | 1129.5 ± 173.6 | 85.1 ± 16.7 | 73.5 ± 16.7 | 35.9 ± 9.1 | 34.2 ± 9.2 | 3.9 ± 2.2 |
| 6-OHDA Lesion | 979.4 ± 183.5 | 82.1 ± 17.7 | 63.2 ± 17.4 | 34.4 ± 4.3 | 30.6 ± 6.5 | 4.2 ± 1.8 |
| Pyriform Cortex | | | | | | |
| Sham-Vehicle Lesion | 238.1 ± 92.0 | 32.6 ± 13.6 | 17.3 ± 6.8 | 57.4 ± 8.8 | 21.1 ± 4.5 | 18.8 ± 2.7 |
| 6-OHDA Lesion | 223.7 ± 66.0 | 31.7 ± 10.9 | 15.7 ± 4.6 | 47.4 ± 7.5‡ | 18.6 ± 2.4 | 15.8 ± 5.2 |

Values are means ± S.D. for nine pairs of littermates.
The significance of the difference between means determined with Student's $t$-tests were *$p<0.05$; †$p<0.01$; ‡$p<0.02$. Smith *et al.* [24]. Reprinted with permission.

that may have attenuated or eliminated the behavioral effects of the neurotoxin lesion. The studies probing the effects of this lesion on stimulant self-administration investigated the self-administration of only a single dose of the drug before and after the lesion. Thus the rats had no experience with other doses of the drug. Dose-effect curves for self-administration were determined in the present study after providing the rats with an extended history during which responding was maintained by several doses of the drug. Behavioral history is an important determinant of both the behavioral effects of environmental events and the behavioral effects of psychoactive drugs [3]. For example, historical determinants of the effects of amphetamine have been reported in squirrel monkeys [2]. Furthermore, exposure to several doses of morphine before a lesion of the nucleus accumbens with kainic acid, attenuated the effects of the lesion on drug intake [9]. Rats exposed to only one dose before or after the lesion had a significant increase in drug self-administration after the lesion while the lesion had less of an effect on drug intake in rats experienced with several doses of the drug [9]. A second factor that may have reduced the behavioral consequences of the 6-OHDA lesion of the nucleus accumbens was the concurrent schedule of food, water and drug self-administration investigated in the present study.

The neurochemical measures presented in this study did not provide an explanation for the lack of an effect on drug self-administration. The 6-OHDA lesion resulted in significant decreases in dopamine content. Moreover, a similar lesion of this region producing comparable changes in dopamine content, increased morphine self-administration in rats given unrestricted access to food and water [24]. Since the decrease in content was not correlated with a change in self-administration, content measures may not be sensitive

to behavioral factors which can dramatically alter the consequences of the lesion. The inability of 6-OHDA lesions to alter morphine self-administration was not the result of a behavioral induction after the lesion. That is, responding maintained by food and water did not recover first after the lesion. Responding maintained by all three reinforcers were equally unaffected by the lesion. Since there were no changes in either food, water or drug self-administration when the rats were initially placed back into the operant chambers after the lesion, the lack of an effect on drug self-administration was not the result of behavioral induction. The behavioral processes involved in dampening the effects of the lesion most likely occurred before the lesion. The results from this study indicate that when similar responses are maintained by different consequent events it is more difficult to disrupt the resulting behavior. In consideration of the concept of resistance to change being an indication of response strength [16] (i.e., behavior that is easily disrupted is occurring with low strength and responding not affected by various challenges is occurring at high strength) similar responses maintained by different reinforcers may result in stronger behavior.

The present study suggests that the immediate (context) and extended history of an organism may alter the behavioral effects of 6-OHDA lesions of the nucleus accumbens on drug self-administration. Two other studies have shown similar effects with both kainic acid [9] and 5,7-dihydroxytryptamine [7]. Morphine self-administration is increased after either kainic acid [25] or 5,7-DHT lesions [26] of the nucleus accumbens under conditions during which food and water deliveries are not contingent on a lever press response. However, morphine self-administration is only decreased when similar lesions are made in rats responding under the concurrent schedule of food, water and morphine self-administration used in this study.

A description of the neurochemical and behavioral effects of a neurotoxin lesion should include the specification of the precise conditions under which the behavior of interest occurred. It is not appropriate to assume that the effects of a lesion on either neurochemical or behavioral measures are not influenced by environmental or behavioral variables. In fact, behavioral factors are as important as pharmacological parameters (i.e., dose, rate of infusion, specificity of neurotoxin) in the modulation of the effects of neurotoxin lesions on behavior. Several behavioral factors including a subject's prior experience, characteristics of other behavior in the current repertoire, and other aspects of the total environmental situation in which the behavior occurs can potentially influence the behavioral and neurochemical effects of a neurotoxin lesion. Thus, the variables that have been shown to influence the effects of substances that activate neuronal systems also influence the effects of substances that selectively destroy these neuronal systems.

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