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On the Role of Ascending Catecholaminergic Systems in Intravenous Self-Administration of Cocaine

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ROBERTS, D. C. S., M. E. CORCORAN AND H. C. FIBIGER. *On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine.* PHARMAC. BIOCHEM. BEHAV. 6(6) 615–620, 1977. – The role of ascending noradrenergic (NA) and dopaminergic (DA) systems in intravenous self-administration of cocaine in rats was investigated by examining the effects of 6-hydroxydopamine-induced lesions of these systems on responding for the drug on a FR-1 schedule of reinforcement. Lesions of the dorsal and ventral NA bundles that reduced hippocampal-cortical NA by 96% and hypothalamic NA by 72% failed to have any effects on responding for cocaine. Lesions of the nucleus accumbens that reduced the DA content of this nucleus by 90% resulted in a significant and long-lasting (15 days) reduction in self-administration of cocaine. Apomorphine self-administration was not affected in the same animals. Identical lesions of the n accumbens had only transient (2–3 days) effects on food-reinforced operant responding, suggesting that the prolonged disruption of cocaine self-administration was not the result of motor deficits. The results are discussed with reference to the possibility that DA terminals in the n accumbens may mediate some of the positive reinforcing properties of cocaine.

Self-administration Cocaine Dopamine Catecholamines Apomorphine Noradrenaline

THERE IS evidence to suggest that self-administration of psychomotor stimulants is reinforced by their central catecholaminergic agonist properties. For example, rats will leverpress to produce intravenous injections of apomorphine [3], a drug believed to act selectively as a direct dopaminergic agonist at dosages that are self-administered [1]. Other self-administered stimulants such as d-amphetamine, l-amphetamine, and cocaine are thought to act indirectly [16] by releasing and blocking the reuptake of central catecholamines [2,32]. More direct evidence for a catecholaminergic mediation of the self-administration of psychomotor stimulants can be found in the observation that alpha-methyl-para-tyrosine, which inhibits the synthesis of catecholamines, attenuates the reinforcing effects of stimulants [12, 19, 26].

Although it seems clear that central catecholamines are involved in the self-administration of stimulants, there is some disagreement about whether the reinforcing effects are mediated by dopamine (DA), noradrenaline (NA), or both of these amines. Davis and his colleagues have favored the view that both NA and DA are involved in the reinforcing effects of d-amphetamine in rats. They found that either inhibition of NA synthesis [14] or blockade of receptors for DA [13] resulted in a reduction of the reinforcing effects of d-amphetamine, as measured by the strength of the secondary reinforcing properties of a stimulus repeatedly paired with injections of the drug. Yokel and Wise [42,43], on the other hand, have provided data to suggest that the reinforcing properties of d-amphetamine depend on DA but not NA. They found that low dosages of the DA-receptor blockers pimozide [42] and butaclamol [43] increased the rate of responding for d-amphetamine; because a reduction of the dosage obtained per injection is known to result in increased rates of responding [25,41], Yokel and Wise [42,43] suggested that partial blockade of DA receptors produced a partial blockade of the reinforcing effects of d-amphetamine. They failed to observe any similar effects when the rats were given drugs that block central NA receptors.

Although the above experiments have implicated both NA and DA in mediating at least some of the reinforcing properties of d-amphetamine and cocaine, they cannot, of course, provide any information concerning which of the numerous dopaminergic and noradrenergic systems in the brain may be the neural substrates for these effects [22,36]. The present experiments were designed to evaluate the role of the two major ascending NA projections, the dorsal and the ventral bundles, in intravenous self-administration of cocaine in rats. Previous experiments using electrical self-stimulation of the brain have implicated both of these systems in central reinforcement mechanisms [4, 11, 29, 35], although more recent work has questioned their importance [6, 7, 8]. With regard to dopaminergic systems, the role of the mesolimbic DA projection, which

originates in the ventral tegmental area and has a major but not exclusive termination in the nucleus accumbens [22,36], was investigated. On the basis of previous work using electrical stimulation of the brain this DA system has also been implicated in central reward processes [11,24]. The present experiments attempted to clarify the role of these NA and DA projections in cocaine self-administration by examining the effects of selective lesions of these systems produced by stereotaxic injections of 6-hydroxydopamine (6–OHDA).

METHOD

Fifteen male Wistar rats, weighing 300–350 g at the start of the experiment, were used. For the duration of the experiment the rats lived in individual operant-conditioning cages housed in sound-attenuating isolation chambers. Before the experiment began the rats were deprived of food and trained to press a lever to obtain food on various schedules of intermittent reinforcement. After training and for the rest of the experiment food and water were freely available. The rats received implantation of a chronic silastic cannula into the jugular vein under pentobarbital anaesthesia; the technique used to construct and implant the cannula was an adaptation of that of Weeks [38]. The cannula passed subcutaneously to a polyethylene assembly mounted on the animal's back, and flexible tubing connected the cannula to a fluid swivel, which was in turn connected to a syringe pump.

One or two days after the operation the rats were given access to a lever mounted on the front wall of the cage for 4 hr each day. Every depression of the lever produced an intravenous infusion of 0.2 ml of cocaine lasting for 4 sec. A signal light mounted above the lever was activated at the onset of the infusion and continued for 16 sec postinfusion, for a total of 20 sec. Most rats were given access to cocaine hydrochloride dissolved in 0.9% saline at a dosage of 0.75 mg/kg/injection, although some rats were given cocaine at a dosage of 0.5 mg/kg/injection. After self-injection of cocaine had stabilized, the rats that later received lesions of the nucleus accumbens (see below) were given the opportunity to self-inject apomorphine, dissolved in 0.9% saline containing ascorbic acid. The conditions of self-injection of apomorphine were the same as those for cocaine, and apomorphine was available at a dosage of 0.06 mg/kg/injection. After self-injection of apomorphine had stabilized, the rats were again given access to cocaine. The baseline pattern of self-injection of cocaine was determined for all rats, and they were then prepared for lesioning with 6–OHDA.

All rats were deprived of cocaine for 1 day prior to injection of 6–OHDA. Each animal received one of two types of lesion. One group (N = 4) received two stereotaxically placed bilateral injections of 6–OHDA hydrobromide (4 μg/2 μl, dosage expressed as the free base, in saline containing 0.2 mg/ml ascorbic acid) aimed at the dorsal and ventral NA bundles [36]. The injection coordinates from stereotaxic zero were: A + 2.5 mm; L ± 1.1 mm; DV + 3.7 mm; and A − 1.4 mm; L ± 1.3 mm; DV + 0.7 mm. The rat's head was held in the plane used in the atlas of König and Klippel [20]. Another group of animals (N = 11) received bilateral injections of 6–OHDA (8 μg/4 μl) into the n acumbens. Coordinates were: A + 11.7 mm; L ± 1.5 mm; DV + 2.7 mm. The injection rate in each case was 2 μl/5 min. Anaesthesia was induced with ether and maintained by halothane.

Cocaine was available to the rats for self-injection on the day after the injections of 6–OHDA. Self-injection of cocaine was monitored in all rats for 2–3 weeks postlesion; in addition, the rats in the accumbens-lesioned group were in some sessions given the opportunity to self-inject apomorphine instead of cocaine. At the end of the experiment the rats were killed by cervical fracture, and regional samples of fresh brain were obtained for biochemical analysis. Using a spectro-photofluorometric assay [23] levels of NA in the hippocampus, cortex, and hypothalamus were measured in the NA-lesioned rats. In the accumbens-lesioned rats, levels of DA were measured separately in the nucleus accumbens and in the caudate-putamen, obtained by manual dissection from sections of fresh brain rapidly frozen on a microtome.

RESULTS

The main results of these experiments are shown in Fig. 1. Lesions of the ascending NA projections did not significantly influence the rate or pattern of cocaine self-administration, despite the fact that these lesions reduced hippocampal-cortical NA by 96% and hypothalamic NA by 72% (Table 1). The effect of pimozide pretreatment (0.25 mg/kg, IP 30 min before the self-administration session) on responding for cocaine was tested on several animals with lesions of the ascending NA projections. Yokel and Wise [42,43] have previously demonstrated a marked increase in the rate of responding for intravenous d-amphetamine after such treatment. All animals showed essentially the same effect, and the results from one of these animals are shown in Fig. 2. Pimozide pretreatment was found to significantly increase the rate of responding for cocaine (1.25 mg/ml; 0.2 ml/injection). Interestingly, a nearly identical increase in the rate of responding was observed when the concentration of cocaine was reduced to 0.625 mg/ml. These results demonstrate that the NA-lesioned animals are similar to intact animals in that they are capable of modifying their behaviour in response to variables such as changes in dosage and drug pretreatment.

In contrast to the lack of effect of lesions of the ascending NA neurons, 6 OHDA injections into the nucleus accumbens produced a significant alteration in both the rate and pattern of responding for cocaine. The 5 animals with the most extensive (>80%) depletions of accumbens DA are shown in Fig. 1. In this group, the 6–OHDA injections reduced DA in the accumbens by 90% of control levels, and striatal DA was also reduced by 24% (Table 2). The mean rate of self-injection declined precipitously on the day after the lesion, and then over the next 3–4 days gradually recovered to approximately 50% of prelesion values. During the subsequent 10 days the mean response rate of this group was maintained at levels ranging from 20 to 40 percent of the preoperative rates. Before the 6–OHDA-induced lesions of the accumbens, rats responded for cocaine at a steady hourly rate that was maintained throughout each 4-hr session. After the lesions, however, a different pattern was observed that was regular but at a lower rate than prelesion levels, and persisted for only 1 or 2 hr out of each 4-hr session. A representative example of the effects of the accumbens lesion upon the pattern of cocaine self-injection is shown in Fig. 3. In contrast to these results, injections of 6–OHDA that produced less than a 70% reduction of DA in the

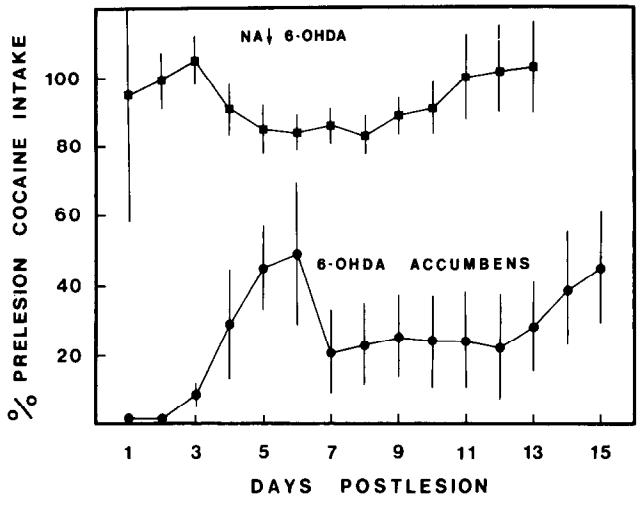

FIG. 1. Effect of 6-OHDA-induced lesions of the dorsal and ventral NA bundles (NA ↓ 6-OHDA) (N = 4) or nucleus accumbens (N = 5) on self-administration of cocaine. Each point represents the mean (±SEM) intake of cocaine per 4-hr session expressed as percent of each animal's prelesion intake.

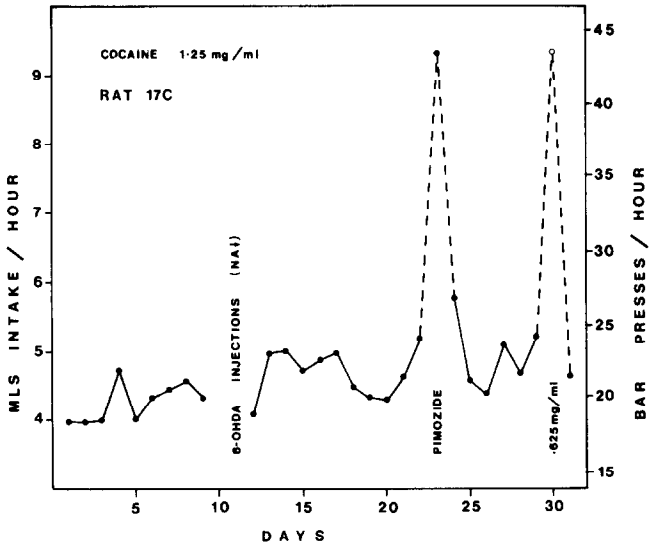

FIG. 2. An example of cocaine self-injection in one animal that received 6-OHDA-induced lesions of the dorsal and ventral NA bundles. On Day 23, pimozide (0.25 mg/kg) was administered 1/2 hr prior to the 4-hr session. On Day 30, the concentration of cocaine was reduced from 1.25 mg/ml to 0.625 mg/ml. Each bar press resulted in an intravenous injection of 0.21 ml.

TABLE 1

EFFECT OF 6-OHDA-INDUCED LESIONS OF THE DORSAL AND VENTRAL NA BUNDLES ON THE MEAN (± SEM) CONTENT OF NA IN THE HIPPOCAMPUS, CORTEX AND HYPOTHALAMUS

	NA (μg/g)	
	Hippocampus and cortex	Hypothalamus
Control	0.392 ± 0.04	2.260 ± 0.21
NA ↓ 6-OHDA (N = 4)	0.015 ± 0.01	0.632 ± 0.18

TABLE 2

EFFECT OF 6-OHDA INJECTIONS INTO THE N ACCUMBENS ON MEAN (±SEM) CONTENT OF DA IN THE ACCUMBENS AND STRIATUM

	DA (μg/g)	
	Striatum	Accumbens
Control	12.13 ± 1.10	8.82 ± 0.50
6-OHDA Accumbens (N = 5)	9.22 ± 0.72	0.87 ± 0.52

accumbens (N = 6) had only transient effects on responding for cocaine. In each case the rate and pattern of self-injection of cocaine returned to preoperative levels within 3 days postlesion.

In contrast to the self-injection of cocaine, self-injection of apomorphine was not significantly affected by the 6-OHDA-induced lesions of the nucleus accumbens. As shown in Fig. 4, periodic testing with apomorphine indicated that the rate and pattern of apomorphine self-injection did not vary after the lesions, even though the same rats displayed marked alterations in responding for cocaine. This difference was especially dramatic in the case of one rat that virtually ceased to self-inject cocaine after the lesions, but continued to display unchanged levels of self-injection of apomorphine.

Inasmuch as the integrity of central dopaminergic neurons is known to be important in the motor aspect of operant responding [6,15] an experiment was conducted to examine the possibility that the reduced responding for cocaine may have been due to motor deficits rather than to changes in the reinforcing properties of the drug. The failure of accumbens lesions to affect self-administration of apomorphine does not necessarily control for this possibility, because the DA-agonist properties of apomorphine may have produced a pharmacological reversal of any motor deficits [45]. Therefore, to provide a more adequate control for any general disruption of operant responding produced by 6-OHDA-induced lesions of the nucleus accumbens, an additional group of rats (N = 3) was trained to leverpress for food on a variable-ratio 2.5 schedule of reinforcement. After their responding stabilized, these rats received 6-OHDA-induced lesions of the nucleus accumbens identical to those described above. As shown in Fig. 5, operant responding for food was depressed for the first three days after the lesions but recovered completely by the

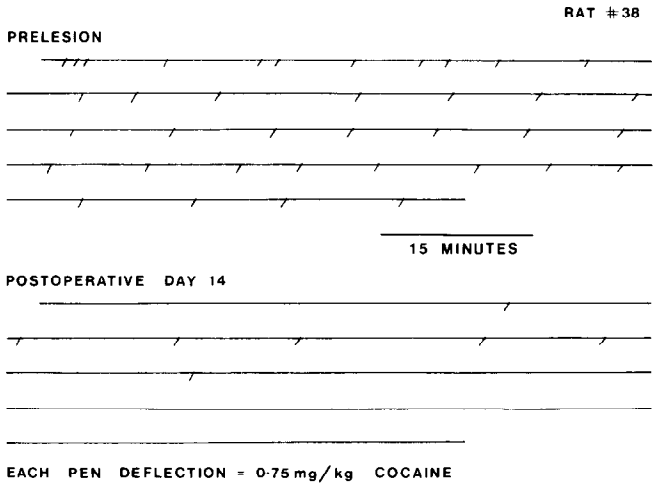

FIG. 3. An example the effect of 6–OHDA injections into the n accumbens on intravenous self-administration of cocaine (0.75 mg/kg/injection). Event records are shown from two 4-hr sessions. The top portion represents baseline responding showing evenly spaced self-injections. The bottom record represents the pattern of self-injections 14 days postoperatively. Note regular responding at a slower than baseline rate, which was not maintained throughout the session.

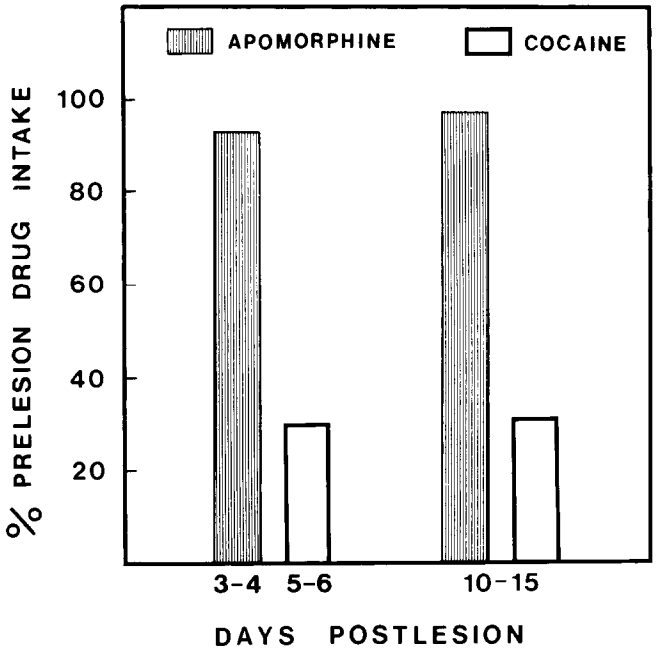

FIG. 4. Self-injection of cocaine and apomorphine in rats whose accumbens DA was depleted to a mean of 10% of control levels by injections of 6–OHDA (N = 5). Bars indicate mean total intake of each drug during 4-hr sessions as a percent of prelesion intake. The bars on the left represent the data of 2 rats that received apomorphine on Days 3 and 4 and cocaine on Days 5 and 6. The bars to the right represent the mean drug intake of all five rats 10–15 days postoperatively; for each animal, cocaine and apomorphine were available on different days during this interval.

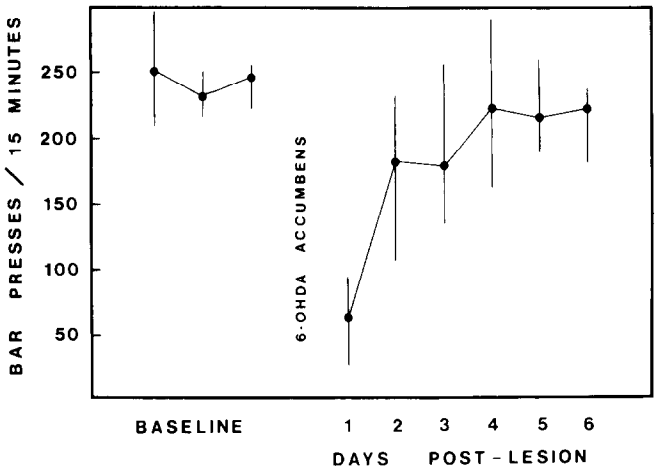

FIG. 5. Effect of 6–OHDA injections into the n accumbens on food-reinforced operant responding. Each point represents the mean (±range) for three animals responding on a VR 2.5 schedule during one 15-min session each day.

fourth day postlesion. We therefore conclude that the prolonged reduction in the rate of cocaine self-injection of the accumbens-lesioned rats was not due to a lesion-induced motor deficit, although such a deficit could have contributed to the reduction in self-injection observed during the first two or three days postlesion.

DISCUSSION

The results reported here have direct implications for the hypothesis that self-administration of psychomotor stimulants such as cocaine, amphetamine, and methylphenidate depends upon the catecholaminergic agonist properties of these drugs [12, 42, 43]. The stability of cocaine self-administration after extensive lesions of the ascending NA projections is consistent with pharmacological data [42,43] that suggest that noradrenergic mechanisms are not critically involved in self-injection of these agents. In this regard, it is of interest that recent experiments have also failed to demonstrate any essential contribution of central noradrenergic neurons to the reinforcing properties of intracranial self-stimulation [7, 8, 21]. Those and the present experiments therefore cast serious doubt on the hypothesis that central noradrenergic neurons have a primary function in the mediation of either pharmacologically or electrically induced reinforcement or reward [35]. It could be argued of course that because the lesions of the ascending NA systems were not complete, the remaining NA terminals together with the development of postjunctional supersensitivity [44] may have been sufficient to maintain the reinforcing properties of cocaine. We view this as unlikely because there is no evidence that behavioural compensation occurs after lesions of a central NA system. In fact, recent data showing that lesions of ascending NA neurons, similar to those used in the present experiments, profoundly influence several pharmacological properties of morphine argue against such a compensatory mechanism [28,31].

In contrast to the failure of lesions of the ascending NA systems to significantly influence cocaine self-

administration, 6-OHDA-induced lesions of the nucleus accumbens resulted in large and long-lasting decreases in responding for the drug. Several factors may have been responsible for this observation. First, inasmuch as some ascending DA systems are known to be critically involved in operant behaviour, it is possible that the 6-OHDA-induced lesions of the accumbens produced motor deficits that interfered with the leverpress response [6,15]. This is unlikely, however, because identical lesions had only transient effects in animals responding for food (Fig. 5). Second, it is possible that the reduced rate of responding after the lesions resulted from some nonspecific effects of the surgical procedure. This also appears unlikely, however, because not only did the responding of the NA-lesioned rats fail to be influenced by the surgery, but also animals in which the 6-OHDA injections produced less than a 70 percent reduction in accumbens DA levels did not show the reduced responding for cocaine. Third, our findings may be related to the hypothesis that the rate and pattern of cocaine self-injection are partially controlled by the nonreinforcing suppressant effects cocaine is thought to exert upon operant behaviour [27,39]. According to this view, the decreased rate of self-injection produced by the accumbens lesions may have been due to a lesion-induced potentiation of the general disruptive effects of cocaine. If the lesions were affecting responding for cocaine primarily via modulation of the nonreinforcing disruptive effects of the drug, however, the rate and pattern of self-injection should have been sustained, although in altered form, throughout each 4-hr session. Because the lesions did not merely lengthen postreinforcement pauses (Fig. 3), as would be demanded by this hypothesis, we conclude that the observed changes in self-administration were not due to alterations in the general disruptive effects of cocaine. It could also be argued that the reduced intake of cocaine may have been due to a potentiation of the reinforcing effects of the drug by the lesion. However, at present we feel that this is unlikely, again because of the failure of lesioned animals to maintain responding for the drug throughout each session.

A fourth alternative is that destruction of the DA terminals in the accumbens altered the balance between the rewarding and punishing properties of cocaine, thus resulting in the reduced rate of responding for the drug. It is known that many psychoactive drugs have both rewarding and punishing properties [5, 9, 10, 37, 40], and furthermore recent experiments suggest both of these effects of psychomotor stimulants may be mediated via dopaminergic mechanisms (Grupp, personal communication, [30,31]. The present results could be incorporated within the context of previous observations if it is assumed that different groups of DA terminals (or neurons) mediate the positive-reinforcing and punishing properties of cocaine. More specifically, we hypothesize that the DA terminals in the accumbens mediate some of the reinforcing but not the punishing properties of cocaine. Lesions of these DA terminals in the accumbens would then have the overall effect of reducing the rate of self-administration because the positive-reinforcing properties of the drug would be reduced relative to its unimpaired aversive effects. In this regard, it is noteworthy that although the effects of punishment have not been studied extensively, the reported suppression of self-injection produced by the introduction of a punishing stimulus [17,33] is not inconsistent with the present observations on accumbens-lesioned animals. At first glance, our hypothesis appears to be at variance with well-documented data that show that a reduction in the reinforcing value of the drug, either by decreasing the amount of drug per injection or by pretreating the animals with DA-receptor blocking agents, increases the rate of responding for the drug [25, 41, 42, 43]. However, by blocking receptors for DA throughout the brain, peripherally administered neuroleptics would reduce the reinforcing and punishing properties of cocaine equally, and hence would not shift the balance between these two effects of the drug. Partial blockade of DA receptors by neuroleptics would therefore be expected to result in a compensatory increased rate of self-administration of cocaine (Fig. 2). Although the above formulation is admittedly speculative, it does reconcile the apparently discrepant effects of lesions of DA terminals in the accumbens and pharmacological blockade of central receptors for DA. Further experiments designed to test the validity of this hypothesis are currently being conducted.

Finally, the specificity of the 6-OHDA-induced lesions of the accumbens requires comment. In the amount used in the present experiments (8 μg/4 μl), it is known that some nonspecific damage is produced near the injection site [18,34]. Consistent with these reports was the observation that during the brain dissection some general necrosis was evident in the accumbens of the lesioned animals. To what extent this may have contributed to the reduced responding for cocaine cannot be determined with certainty from the present experiments. However, the amount of nonspecific damage varied between the lesioned animals and did not appear to correlate with the magnitude of the effect on cocaine self-administration. Furthermore, it is noteworthy that although the lesions significantly reduced responding for cocaine, in the same animals they did not affect apomorphine self-administration. If, therefore, some of the reinforcing properties of apomorphine are mediated via postsynaptic DA receptors in the nucleus accumbens, then these receptors apparently survived the 6-OHDA-induced lesions, again suggesting that the effects on self-injection of cocaine were mediated by specific actions of 6-OHDA on DA terminals and axons in the nucleus accumbens.

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