Pharmacology Biochemistry & Behavior, Vol. 12, pp. 781–787. Printed in the U.S.A.

Extinction and Recovery of Cocaine Self-Administration Following 6-Hydroxydopamine Lesions of the Nucleus Accumbens

D. C. S. ROBERTS[1] AND G. F. KOOB

A. V. Davis Center for Behavioral Neurobiology, The Salk Institute, La Jolla, CA 92037

AND

P. KLONOFF AND H. C. FIBIGER

Division of Neurological Sciences, Department of Psychiatry, University of British Columbia, Vancouver, Canada

Received 11 September 1979

ROBERTS, D. C. S., G. F. KOOB, P. KLONOFF AND H. C. FIBIGER. *Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens.* PHARMAC. BIOCHEM. BEHAV. 12(5) 781–787, 1980.—The effect of 6-OHDA injections into the nucleus accumbens was examined on cocaine self-administration behaviour. Rats were given access to cocaine (0.75 mg/kg/inj.) for three hours/day on a continuous reinforcement schedule. After daily intake of cocaine had stabilized, rats were injected with 6-OHDA (8 μg/2 μl). When tested the day following the 6-OHDA injection most rats failed to self-administer cocaine, however this disruption did not resemble extinction. After several days self-administration recovered in many animals to near preoperative levels, and the rate of this recovery correlated ($r = +0.75$) with the levels of dopamine remaining in the nucleus accumbens. The animals with the greatest depletion of dopamine did not recover cocaine intake. In a separate experiment, animals were pretreated with desmethylimipramine and/or pargyline to achieve a more extensive and selective lesion. When tested five days after the lesion all animals in these 6-OHDA groups showed a significant decline in cocaine intake compared to vehicle injected control animals. Several 6-OHDA treated animals displayed a pattern of behaviour resembling extinction, where a high rate of lever pressing was followed by cessation of responding. Some animals were also tested for apomorphine self-administration and this was found not to be affected by the 6-OHDA treatment. These data support the hypothesis that non-striatal dopamine may subserve cocaine reward.

Cocaine Self-administration 6-Hydroxydopamine Nucleus accumbens Dopamine

ANIMALS will perform various responses to obtain intravenous injections of psychomotor stimulant drugs (e.g. amphetamine, cocaine) [8, 10, 17]. The rate of this self-administration behaviour is, in part, a function of the injection dose, such that a decrease in dose produces a compensatory increase in injection rate [13]. Analogous increases in self-administration rate have been observed after pharmacological manipulations of dopaminergic systems [9,16], and these increases have therefore been interpreted as evidence of dopamine (DA) involvement in psychostimulant reward [18]. For example, low doses of the dopamine receptor antagonist pimozide, increase stimulant self-administration rate; high doses of pimozide causes extinction of self-administration for cocaine and amphetamine [3,19]. Inhibition of catecholamine synthesis also produces an apparent blockade of amphetamine reward [9].

Pretreatment with drugs that block noradrenergic receptors do not produce extinction of stimulant self-administration suggesting that dopamine may be the primary catecholamine involved [3,19].

In an effort to define the neural circuitry involved in the reinforcing effects of cocaine, we have examined the effect of 6-hydroxydopamine (6-OHDA) induced lesions of specific catecholamine pathways and terminal areas on cocaine self-administration. In an earlier report [11] it was demonstrated that lesions to ascending NA pathways did not affect this behaviour. In contrast, bilateral injections of 6-OHDA into the nucleus accumbens produced a marked disruption of cocaine self-administration. When tested the day following these lesions, animals typically pressed for one or two injections at the beginning of the session and then abruptly stopped. The pattern of responding did not resemble extinction behaviour however, thus making any conclusion as to reinforcement mechanisms somewhat tenuous. We now re-

[1]Present address: Department of Psychology, Carleton University, Ottawa, Canada, K1S 5B6.

port that extinction-like responding is observed when animals are not given access to the cocaine until five days after the 6-OHDA lesion of the nucleus accumbens.

We also report that unless the loss of DA reaches a critical level, many animals recover cocaine self-administration behaviour. These results constitute clear evidence for mesolimbic dopamine involvement in cocaine reinforcement.

METHOD

Male Wistar rats (Woodlyn Farms, Guelph, Canada) weighing 300–350 g at the start of the experiment were handled and housed as previously described [11]. Each rat was implanted with a chronic silastic jugular cannula which passed subcutaneously to a polyethylene assembly mounted on the animal's back. The technique used to construct and implant the cannula was an adaption of that of Weeks [15]. The cannula was permanently connected to a harness and swivel system which was in turn connected to a syringe pump.

One or two days after cannula implantation, the rats were given access to a lever mounted on the front wall of the cage for 3 or 4 hr/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 turned on at the onset of the infusion and stayed on for 20 sec. During this period the lever was inactive. The dosage of cocaine was 0.75 mg/kg/injection. Some animals were also given access to apomorphine at a dose of 0.06 mg/kg/injection. Animals that showed stable cocaine intake for four consecutive days were prepared for intracerebral infusions of 6-OHDA.

All rats were deprived of cocaine for 1 day prior to injection of 6-OHDA. Anesthesia was induced with ether and maintained by halothane. The animals head was positioned in a Kopf stereotaxic instrument. In the first experiment, one group of animals (N=15) received bilateral injections of 6-OHDA (8 μg/2 μl, dosage expressed as the free base) in saline containing ascorbic acid (0.2 mg/ml). Injections were made through a 30 ga needle at a rate of 1 μl/2 min. The needle was left in place for 6 min following the infusion. The injection site as located histologically corresponds to the following coordinates of König and Klippel [5]: A+8920; L $\pm$ 1.2; D−1.0. These animals were given access to cocaine the day following the lesion. Some animals in this group were given access to apomorphine after the lesion as previously described [11].

In a separate experiment, three groups of animals were prepared. One group (N=5) received pargyline (50 mg/kg/IP) 30 min prior to the 6-OHDA infusions as described above. A second group (N=8) received desmethylimipramine HCl (DMI, 25 mg/kg/IP) in addition to pargyline 30 min prior to the 6-OHDA treatment. A control group (N=6) received both pargyline HCl and DMI treatments prior to intracerebral infusions of the ascorbate-saline vehicle. These groups were not tested for self-administration of cocaine until the fifth post-lesion day, to allow for any long term effects of the pretreatments to dissipate and for degeneration of DA terminals to occur.

Several animals which showed disruptions of cocaine self-administration behaviour were selected for apomorphine testing. These animals were given access to apomorphine at 0.06 mg/kg/injection. In some cases cocaine was substituted during an apomorphine self-administration session, without any external cue to the animal that a change in drug solution had occurred.

At the end of the experiment the rats were killed by cervical fracture, and the brain was quickly removed. The brain was placed on a freezing microtome and sectioned. The nucleus accumbens and striatum were dissected from 1 mm thick sections. A sample of frontal cortex was also taken in some animals. Dopamine and noradrenaline (NA) were assayed as previously described [12].

In order to determine the pattern of catecholamine depletion, the lesion was examined histochemically in a separate group of rats. Eight naive rats received unilateral injections of 6-OHDA into the nucleus accumbens as described above. One week following the lesion, these animals were prepared for fluorescence histochemistry according to the method of Bloom and Battenberg [1]. Serial sections (20 μM) were taken through the lesioned area, reacted with glyoxylic acid, and the relative intensity of dopamine fluorescence compared between the lesioned and non-lesioned sides of the brain.

RESULTS

Injections of 6-OHDA into the n. accumbens produced an abrupt cessation of cocaine self-administration in all animals that were tested the day following the lesion. An example of the response pattern is shown for one animal in Fig. 1A. On the days following the lesion, these animals would typically make only 2–3 responses and failed to show regularly spaced patterns of responding. Figure 1B shows an example of recovery of cocaine self-administration after a period of marked disruption. Recovery was characterized by a slow regular response pattern which gradually increased in rate to pre-operative levels.

The effect of bilateral 6-OHDA injections on the dopamine content of the accumbens and striatum is given in Table 1. A variable degree of DA depletion was observed in the accumbens ranging from a reduction of 95% to 33% of control values. In order to correlate depletion of accumbens DA levels with recovery of self-administration, an index of recovery was determined for each rat. This was defined as the first day after the lesion on which cocaine intake was at least 50% of the preoperative levels. Animals that did not reinitiate self-administration were given a maximum score of 18. This index of recovery was found to correlate significantly with the DA content in the accumbens ($r=0.75$, $p<0.05$) but not with the DA content in the striatum ($r=0.48$, n.s.). To illustrate this recovery, the rats were divided into two groups according to whether each had above or below 20% dopamine remaining in the nucleus accumbens. Figure 2 shows that the group with the least depletion (43% DA remaining) displayed the faster recovery of self-administration. Also shown is the response rate of a control group (N=5) which were given saline following a baseline period of cocaine self-administration. This group showed a higher rate of responding on the first day of extinction than either of the 6-OHDA groups showed on the first day after the lesion.

The daily self-administration rate of the groups which received pargyline or DMI treatment prior to intracerebral injections of 6-OHDA or vehicle is presented in Fig. 3. When tested five days after the lesion, the 6-OHDA treated animals showed a significant reduction in cocaine intake that declined to approximately 10% of baseline levels by 12 days after the lesion. The same result was obtained in the DMI pretreated group. All animals responded initially and all animals showed a decline in cocaine self-administration. In four of the eleven 6-OHDA treated animals extinction-like

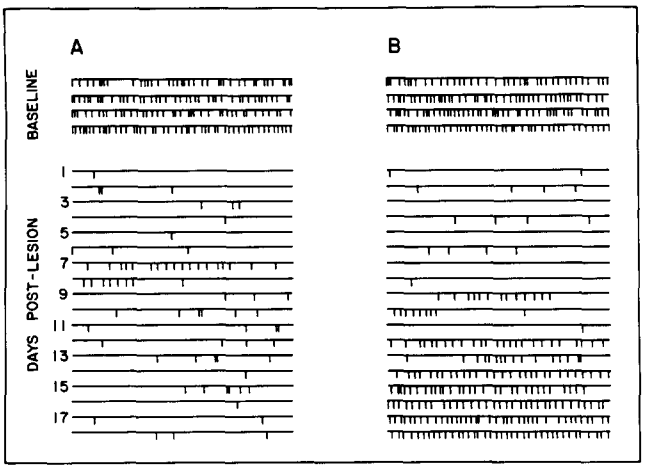

FIG. 1. Event records of cocaine self-administration in two rats before and after 6-OHDA infusions into the nucleus accumbens. Each line represents one daily three hour session. A. An example of one rat (No. 60) which did not resume cocaine self-administration. B. An example of a rat (No. 62) which gradually recovered baseline self-administration rate.

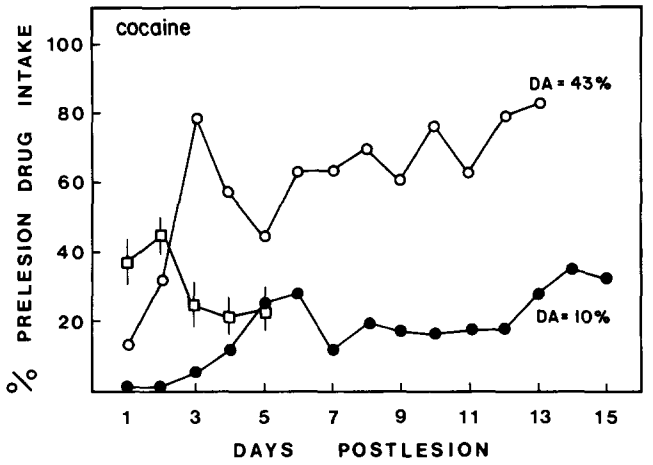

FIG. 2. Effect of bilateral injections of 6-OHDA into the nucleus accumbens on self-administration of cocaine. Each point represents the mean intake of cocaine per daily session expressed as a percent of each animal's prelesion intake. The animals were separated into two groups depending on whether DA was reduced to above or below 20% of control levels in the accumbens. The mean DA content of the accumbens of the animals in the top line was 43% (N=9). The animals in the bottom line had DA reduced to 10% (N=6). The open squares represent mean intake of saline during extinction in an unoperated group of rats (N=5).

behaviour was observed (Fig. 4A,B). This was characterized by irregular responding, sometimes in bursts, that eventually declined to very low levels. For comparison Fig. 4C is an example of a control animal showing extinction following substitution of saline for the cocaine solution.

The remaining animals displayed a more regular response pattern on the first day of access (post-lesion day 5) which steadily declined to very low levels.

TABLE 1

EFFECT OF BILATERAL INJECTIONS OF 6-OHDA INTO THE N. ACCUMBENS ON DA CONTENT IN THE N. ACCUMBENS AND STRIATUM AND LATENCY TO INITIATE SUSTAINED SELF-ADMINISTRATION AFTER THE LESION

	DA content (% of control)		Index of recovery of cocaine
Animal no.	Accumbens	Striatum	self-administration
25	67	95	2
28	38	84	4
29	17	88	18
32	8	73	6
33	58	63	4
34	5	77	14
37	15	78	18
38	8	64	18
40	46	82	3
42	36	97	2
43	44	92	5
54	40	108	1
60	21	62	18
61	40	77	2
62	12	54	12

The index of recovery was defined as the first day after the lesion on which total cocaine intake exceeded 50% of the mean daily preoperative intake. Control values for DA were 8.22 and 13.39 μg/g tissue for accumbens and striatum respectively.

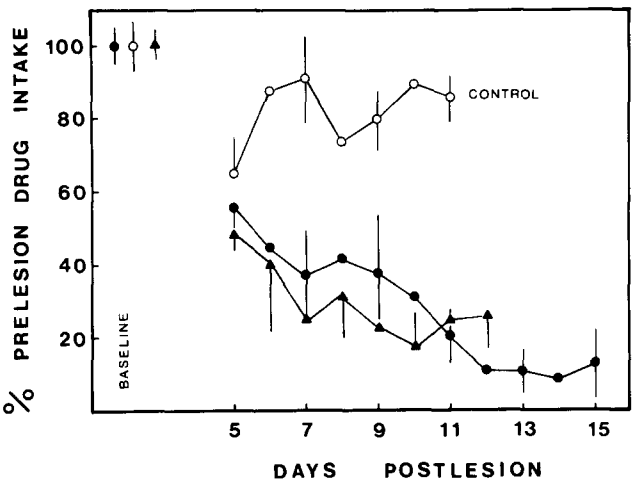

FIG. 3. Effect of 6-OHDA injections into the nucleus accumbens on cocaine self-administration. Points represent mean (±SEM) daily intake for each group. One group received pargyline (50 mg/kg) prior to 6-OHDA treatment (filled triangles). A second group received both pargyline and DMI (25 mg/kg) prior to 6-OHDA (filled circles). The control group received pargyline and DMI prior to vehicle infusions into the nucleus accumbens. Cocaine was not available for self-administration under day 5 post-lesion. Repeated measures ANOVA revealed a significant difference between the two lesion groups and the control group ($p<0.01$). No difference was observed between the 6-OHDA groups.

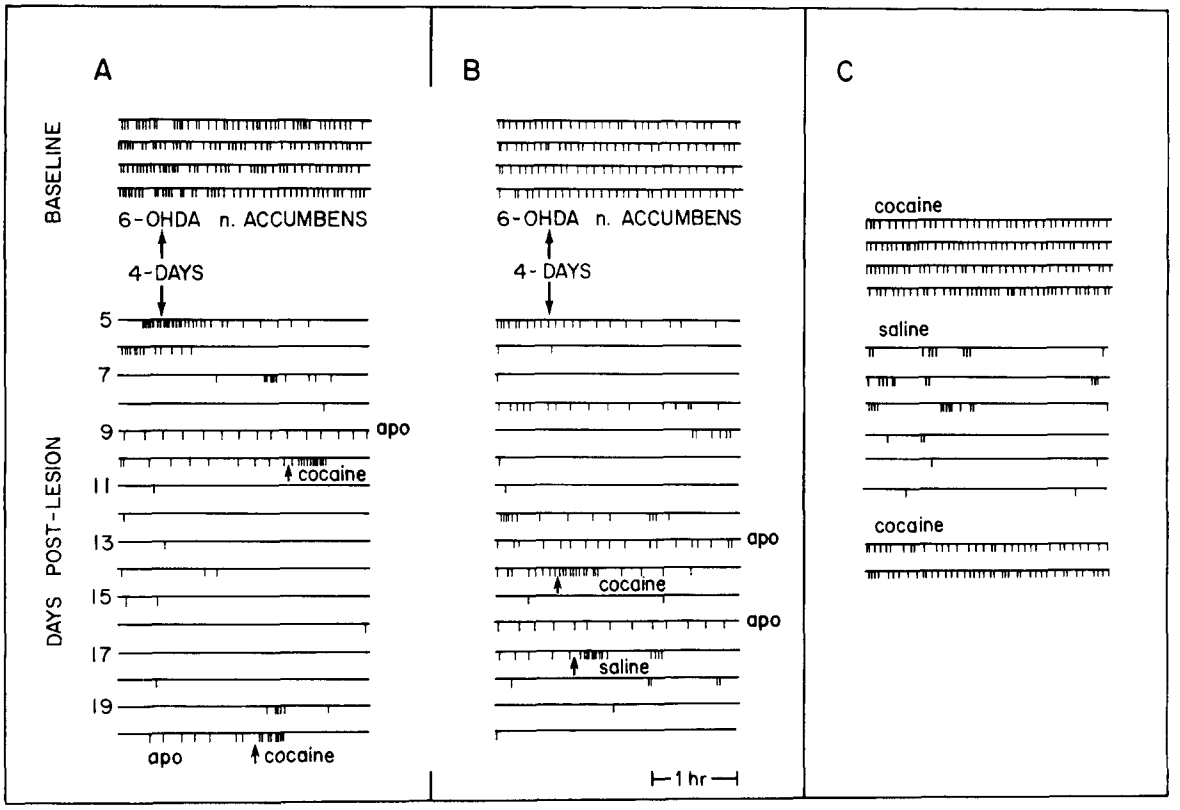

FIG. 4. Event records of cocaine self-administration after 6-OHDA infusions into the nucleus accumbens or saline substitution. Each line represents one daily three hour session. Downward pen deflections indicate drug injections. A. Example of cessation of responding for cocaine 5 days after 6-OHDA treatment. On post-lesion Day 9, regular responding is evident for apomorphine. On Day 10 and 20, cocaine was substituted for apomorphine, which produced an initial burst of responding followed by cessation. B. Another example of extinction of cocaine self-administration 5 days after 6-OHDA treatment. Apomorphine self-administration is shown on Days 13, 14, 16 and 17. Cocaine and saline were substituted for apomorphine on Days 14 and 17 respectively. C. An example of extinction of cocaine self-administration following saline substitution is shown for comparison. The first four and last two lines show responding for cocaine.

The effects of 6-OHDA on the dopamine content in the accumbens and striatum and noradrenaline content of cortex after pargyline or DMI pretreatment are presented in Table 2. The 6-OHDA treatment reduced DA in the accumbens to 20% of control values, and also resulted in significant decreases in striatal DA and cortical NA. DMI pretreatment significantly attenuated the reduction of cortical NA.

Two control and two experimental animals that received DMI died within a few days of the lesion, apparently from intestinal dysfunction. These animals displayed a grossly distended abdomen and reduced food and water intake. Several other animals showed milder symptoms of this reaction but recovered within 3–4 days. This reaction to DMI is similar to that reported by Saller and Stricker [13] and Koob *et al.* [18].

Histochemical analysis of the injection site showed a consistent pattern of fluorescence. The nucleus accumbens show a marked loss of fluorescence on the injected side. The olfactory tubercle also showed a near total loss of fluorescence in six of the eight animals. The striatum did not show a consistent loss of fluorescence, nor was a loss of fluorescence observed close to the cannula tract above the tip. Little variability was observed in the placement of the injection site which was always immediately medial to the anterior

TABLE 2

EFFECT OF 6-OHDA TREATMENTS ON CATECHOLAMINE CONTENT IN VARIOUS REGIONS OF THE RAT BRAIN

		NA	DA	
Group	N	Cortex	Striatum	Accumbens
6-OHDA (DMI + Parg)	6	82 ± 13	81 ± 6	20 ± 5
6-OHDA (Pargyline)	5	42 ± 8*	74 ± 7	11 ± 9

Values represent mean (± SEM) DA and NA content expressed as percent of control. Rats were injected with 6-OHDA (8 μg/2 μl) into the nucleus accumbens, after pargyline (50 mg/kg) or in addition to DMI (25 mg/kg). All values are significantly below control values ($p<0.05$). *=significantly different from 6-OHDA (DMI + Parg). DA control values are as indicated in Table 1. Control values for NA were 295 ± 18 μg/g.

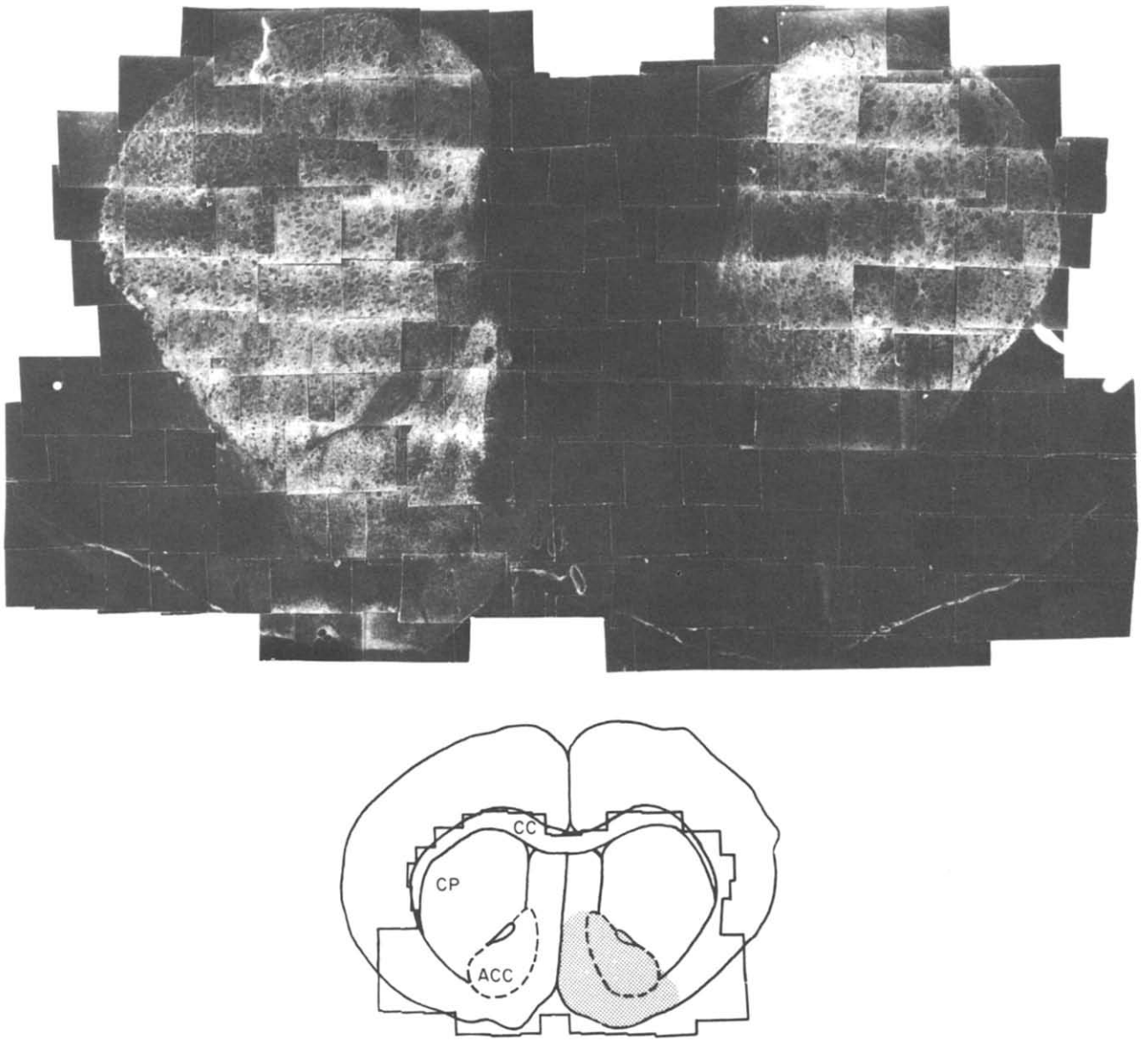

FIG. 5. Photomontage of a coronal brain section showing glyoxylic acid-induced catecholamine fluorescence. The section was taken from a rat which received a unilateral injection of 6-OHDA (8 μg/2 μl) into the nucleus accumbens (ACC). The line drawing shows the boundaries of the montage in relation of the total brain section. The stipled area shows the region of complete loss of fluorescence. (Abbreviation: CC=Corpus Callosum, CP=Caudate Putamen, Acc=nucleus accumbens.)

commissure. Figure 5 is a photomontage of a coronal brain section at the level of the injection site. Relatively little spread is observed into the striatum, however a total loss of fluorescence is observed in the olfactory tubercle.

DISCUSSION

The present results demonstrate that rats will show extinction of cocaine self-administration behaviour when tested five days following 6-OHDA lesion of the nucleus accumbens. All the animals responded initially, however the response rate eventually declined to near operant levels. Four animals showed an increase in response rate prior to response cessation which was similar to saline substitution. By contrast, when tested the day following the 6-OHDA lesions, the animals typically self-injected one or two infusions of cocaine and then abruptly ceased responding. This suggests that cocaine has different stimulus properties depending on the time of post-lesion testing. The day following the 6-OHDA lesion of the nucleus accumbens the animals appear to detect the cocaine, however this dose may be considered punishing in that it decreases the probability of the response. By five days after the lesion, the injection of cocaine may not be punishing, but we may conclude that it is no longer reinforcing, and no longer capable of supporting self-administration behaviour.

6-Hydroxydopamine infusions into the n. accumbens [4] or DA cell bodies [2,12] abolish the locomotor stimulant ac-

tions of cocaine and amphetamine. These results parallel the present findings in several important aspects. First, the blockade is not apparent until several days post-lesion. Stimulants can elicit vigorous and bizarre behaviours immediately following the 6-OHDA injections [2]. It may be that these effects are aversive and account for the suppression of self-administration observed the day following the lesion. Second, unless a severe depletion of DA is achieved with 6-OHDA injections, no blockade of the drug induced locomotor response is observed (Joyce and Roberts, unpublished observations). Thirdly, the blockade of the locomotor response is not permanent but recovers in many animals just as does the self-administration behaviour [5].

The mechanism which allows cocaine self-administration behaviour to recover is not clear. It is possible that the mesolimbic DA system functionally recovers even though the DA levels do not return to normal. In support of this hypothesis increases in turnover in remaining DA terminals have been reported several days following 6-OHDA lesions [20]. Changes in DA receptor sensitivity might also be involved in this recovery process [14]. The greater the depletion of DA, the longer it would be expected for these compensatory mechanisms to occur. The present results suggest that this compensation accounts for the observed correlation between DA depletion and recovery of cocaine self-administration. It is noteworthy that the animals which showed the greatest depletion of DA did not recover cocaine self-administration behaviours within the time frame of the present experiments. These data therefore support the hypothesis that the DA innervation of the nucleus accumbens is critically involved in cocaine self-administration behaviour.

In the first group of animals reported here, the 6-OHDA injections also caused destruction of ascending noradrenergic fibers which course through the accumbens and innervate the telencephalon. To minimize the damage to these fibers, one group of rats was pretreated with DMI which is known to protect NA systems from the neurotoxic effects of 6-OHDA [4,12]. In this group the mean forebrain NA reduction was only 18%, and in three rats no depletion of NA was observed. In spite of this sparing of NA, this group showed essentially the same disruption of cocaine self-administration as did the animals that did not receive DMI pretreatment. This indicates that the observed results were not due to a loss of telencephalic NA. In a previous experiment [11] another test of the involvement of NA in cocaine self-administration was performed through selective lesions of the ascending systems in the midbrain. Near total depletion of hippocampal, cortical and hypothalamic NA had no observable effect on the rate and pattern of cocaine self-administration. These data cast serious doubt on any hypothesis that noradrenergic mechanisms underlie stimulant based reinforcement.

Many of the animals studied here were also tested for apomorphine self-administration. In no case was the rate or pattern of apomorphine self-administration altered by the lesion. This suggests a pharmacologically specific deficit and that the disruption of cocaine self-administration is not attributable to a general non-specific debilitation. How this disruption generalizes to other classes of self-administered drugs remains to be determined.

The 6-OHDA injections into the nucleus accumbens were found to spread ventrally into the olfactory tubercle and cause a depletion of dopamine fluorescence in this area. These lesions also deplete cortical and septal dopamine (data not shown). The degree to which the dopamine depletion in these areas contribute to the present results will require further investigation.

The lesions also caused damage to the striatal DA innervation as was evidenced by the 20–25% mean reduction of DA from this structure in the two pargyline treated groups. Histochemical examination of the lesion showed that this depletion was probably due to spread of the 6-OHDA along the ventral surface of the striatum rather than up the cannula tract. The effect of specific lesions to the striatum is currently under investigation.

The reason for the large variability in the DA depletion from the nucleus accumbens which was observed in the first series of animals is not readily apparent. It is possible that the high intake levels of cocaine prior to the 6-OHDA injections may have contributed to this variability. Nevertheless, pargyline pretreatment produced a more consistent depletion from the 6-OHDA in the second series of experiments and also produced less variability in the behavioural data.

In conclusion, the present data offer further support to the hypothesis that cocaine interacts with dopaminergic neuronal mechanisms to produce reinforcement and maintain self-administration behaviour.

ACKNOWLEDGEMENTS

The support of the Medical Research Council is gratefully acknowledged. D.C.S.R. is an M.R.C. Fellow. We thank Dr. Michael E. Corcoran, Dr. L. Koda, Betty Richter, Robert Strecker and Nancy Callahan for valuable assistance.

REFERENCES

1. Bloom, F. E. and E. L. F. Battenberg. A rapid and sensitive method for the demonstration of central catecholamine neurons and axons by glyoxylic acid-induced fluorescence. II. A detailed description of methodology. *J. Histochem. Cytochem.* **24:** 561–571, 1976.
2. Creese, I. and S. D. Iversen. The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res.* **83:** 409–436, 1975.
3. deWit, H. and R. A. Wise. Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine and phenoxybenzamine. *Can. J. Psychol.* **31:** 195–203, 1977.
4. Kelly, P. H. and S. D. Iversen. Selective 6-OHDA-induced destruction of mesolimbic dopamine neurons: abolition of psychostimulant induced locomotor activity in rats. *Eur. J. Pharmac.* **40:** 45–56, 1976.
5. Kelly, P. H., P. W. Saviour and S. D. Iversen. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res.* **94:** 507–522, 1975.
6. König, J. F. R. and R. A. Klippel. *The Rat Brain, A Stereotaxic Atlas of the Forebrain and Lower Parts of the Brain Stem.* Huntington: Krieger Publishing, 1970.
7. Koob, G. F., S. S. Riley, S. C. Smith and T. W. Robbins. Effect of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity and amphetamine anorexia in the rat. *J. comp. physio. Psychol.* **92:** 917–927, 1978.
8. Pickens, R. and W. C. Harris. Self-administration of d-amphetamine by rats. *Psychopharmacologia* **12:** 158–163, 1968.

9. Pickens, R., R. A. Meisch and J. A. Dougherty. Chemical interactions in methamphetamine reinforcement. *Psychol. Rep.* **23:** 1267–1270, 1968.
10. Pickens, R. and T. Thompson. Cocaine reinforced behavior in rats: Effects of reinforcement magnitude and fixed ratio size. *J. Pharmac. exp. Ther.* **161:** 122–129, 1968.
11. Roberts, D. C. S., M. E. Corcoran and H. C. Fibiger. On the role of ascending catecholamine systems in intravenous self-administration of cocaine. *Pharmac. Biochem. Behav.* **6:** 615–620, 1977.
12. Roberts, D. C. S., A. P. Zis and H. C. Fibiger. Ascending catecholamine pathways and amphetamine induced locomotor activity: importance of dopamine and apparent non-involvement of norepinephrine. *Brain Res.* **93:** 441–454, 1975.
13. Saller, C. F. and E. M. Stricker. Hyperphagia and increased growth in rats after intraventricular injection of 5,7-dihydroxytryptamine. *Science* **192:** 385–387, 1976.
14. Ungerstedt, U. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta. physiol. scand.* **83:** suppl. 367, 69–93, 1971.
15. Weeks, J. R. Long-term intravenous infusion. In: *Methods in Psychobiology, Vol. 2,* edited by R. D. Myers. London: Academic Press, 1972, pp. 155–168.
16. Wilson, M. C. and C. R. Schuster. The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. *Psychopharmacologia* **26:** 115–126, 1972.
17. Yanagita, Y., G. A. Deneau and M. H. Seevers. Evaluation of pharmacological agents in the monkey by long term intravenous self or programmed administration. *Excerpta Medica Int. Cong. Serv.* **87:** 453–457, 1969.
18. Yokel, R. A. and R. A. Wise. Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. *Science* **187:** 547–549, 1975.
19. Yokel, R. A. and R. A. Wise. Alteration of intravenous amphetamine reinforcement by central dopamine blockade in rats. *Psychopharmacology* **48:** 311–318, 1976.
20. Zigmond, M. J. and E. M. Stricker. Adaptive neurochemical changes following destruction of central dopamine-containing terminals. In: *Catecholamines: Basic and Clinical Frontiers, Vol. 2,* edited by E. Usdin, I. J. Kopin and J. Barchas. New York: Pergamon Press, 1979, pp. 1399–1401.