Psychopharmacology (1984) 84:167 – 173

Psychopharmacology

Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats

Hugh O. Pettit[1], Aaron Ettenberg[2], Floyd E. Bloom[3], and George F. Koob[3]

[1] Department of Psychology, Texas Christian University, Fort Worth, TX, 76129, USA
[2] Department of Psychology, University of California, Santa Barbara, CA 93106, USA
[3] Division of Preclinical Neuroscience and Endocrinology, Scripps Clinic and Research Foundation, La Jolla, CA 92037, USA

Abstract. The hypothesis that separate neural systems mediate the reinforcing properties of opioid and psychomotor stimulant drugs was tested by examining the role of mesolimbic dopamine (DA) neurons in maintaining intravenous heroin and cocaine self-administration. After local destruction of the DA terminals in the nucleus accumbens (NAcc) with 6-hydroxydopamine (6-OHDA), rats trained to self-administer cocaine and heroin on alternate days were observed for changes in their drug-seeking behaviors. Postlesion responding for cocaine showed a time-dependent decrease or extinction, whereas heroin self-administration showed a time-dependent recovery. By the fifth trial postlesion, heroin self-administration had recovered to 76% of prelesion baseline levels, but cocaine self-administration had dropped to 30% of prelesion baseline rates. Thus, selective lesions of the DA terminals in the nucleus accumbens significantly attenuate cocaine but not heroin self-administration. These data support the hypothesis that independent neural subtrates are responsible for the reinforcing actions of these two drugs.

Key words: Cocaine – Heroin – Self-administration – Opiate – Psychomotor stimulant – Dopamine – Nucleus accumbens – 6-Hydroxydopamine – Reinforcement

Evidence suggests that operant responding for IV self-administration of psychomotor stimulant drugs is maintained by the reinforcing properties of these drugs (Pickens and Harris 1968; Woods and Schuster 1968; Deneau et al. 1969; Thompson and Pickens 1970; Yokel and Pickens 1973). Previous research has supported the theory of a catecholaminergic role in the reinforcing properties of psychomotor stimulants (Pickens et al. 1978). More specifically, the reinforcing properties of psychomotor stimulants have been linked to the activation of central DA neurons and their postsynaptic receptors. When the synthesis of catecholamines is inhibited by administering alpha-methyl-para-tyrosine, an attenuation of the reinforcing effects of psychomotor stimulants occurs (Pickens et al. 1968; Jonsson et al. 1971; Davis and Smith 1975). Furthermore, low doses of DA antagonists will increase response rates for IV injections of *d*-amphetamine (Yokel and Wise 1975, 1976). Yokel and Wise (1975, 1976) suggested that a partial blockade of DA receptors produced a partial blockade of the reinforcing effects of *d*-amphetamine, and the animals are thought to compensate for decreases in the magnitude of the reinforcer by increasing their self-administration behavior. The role of DA in the reinforcing properties of cocaine was extended by the observation that 6-hydroxydopamine lesions of the NAcc resulted in extinction-like responding and a significant and long-lasting reduction in self-administration of cocaine over days (Roberts et al. 1977, 1980; Lyness et al. 1979).

However, it is not clear if catecholaminergic neurons also mediate the reinforcing properties of opioids (Woods and Schuster 1968; Deneau et al. 1969; Thompson and Pickens 1970; Werner et al. 1976). In a place preference paradigm, the DA antagonist drugs (haloperidol and pimozide) were reported to block a conditioned place preference produced by the reinforcing properties of opioid agonists (Schwartz and Marchol 1974; Bozarth and Wise 1981a; Spyraki et al. 1983). However, a recent report from our laboratory has demonstrated that rats IV self-administering heroin also increase responding when pretreated with the opioid antagonist naltrexone, but do not exhibit a similar compensatory increase in responding when pretreated with the DA antagonist α-flupenthixol. Furthermore, pretreatment of these rats with naltrexone did not increase cocaine reinforced responding as did pretreatment with α-flupenthixol (Ettenberg et al. 1982). These results suggested that separate neural substrates are responsible for the reinforcing actions of heroin and cocaine.

In the present study, we sought to clarify further the role of mesolimbic DA neurons in drug reinforcement by examining the effects of DA denervation of the NAcc on heroin and cocaine self-administration. Given that the mesolimbic dopamine system appears to be critical for psychomotor stimulant reinforcement (Roberts et al. 1977, 1980; Lyness et al. 1979) any hypotheses regarding a role for dopamine in opioid reinforcement would likely focus on this same mesolimbic system. This is particularly relevant since rats will maintain self-administration of morphine applied directly into the brain region containing the mesolimbic DA cell bodies, the ventral tegmental area (Phillips and LePaine 1980; Bozarth and Wise 1981b). The present study was therefore directed at determining whether there was a critical role for the mesolimbic DA system in opioid reinforcement.

Materials and methods

Subjects and apparatus

Male Wistar rats ($N = 13$, Charles River, Kingston NY, USA) weighing 200 – 225 g at the start of the experiment

Offprint requests to: G. F. Koob, Division of Preclinical Neuroscience and Endocrinology, Scripps Clinic and Research Fdn., 10666 North Torrey Pines Road, La Jolla, CA 92037, USA

served as subjects. To aid initial self-administration acquisition, the association of an operant response with delivery of a positive reinforcement was made by training each animal to lever press for food reinforcement on a continuous reinforcement schedule. After 2 days of consistent responding, animals were surgically implanted with a chronic silastic jugular vein catheter under 50 mg/kg sodium pentobarbital anesthesia. The techniques used to construct and implant the catheter were an adaptation of that of Weeks (1972). The catheter passed SC to a piece of marlex mesh secured SC on the animal's back. The catheter was permanently connected to a swivel system through a metal spring, which was in turn connected to a infusion pump as described by Roberts et al. (1977, 1980). Animals were housed individually inside Plexiglas operant-conditioning cages enclosed in sound-attenuated chambers. The subjects were provided with ad lib access to food and water and maintained on a 12-h shifted light-dark cycle (lights off from 11:00 AM to 11:00 PM).

Procedure

Four days after implantation, each subject was allowed access for 3 h (commencing 2 h after lights out) to one of two levers mounted on either the left or right side of the front wall of the cage. A lever press delivered a 0.1-ml intravenous infusion of either cocaine (0.75 mg/kg injection) or heroin (0.06 mg/kg injection) into the right external jugular vein of the rat. These doses were chosen because they were approximately equi-effective ED50 doses for each drug for numbers of infusions self-administered over a given session (for cocaine, see Thompson and Pickens 1970; for heroin, see deWit and Stewart 1983). In addition, this dose ratio of 12.5:1.0 cocaine/heroin, is similar to that reported by others using an alternative measure of reinforcement, place preference conditioning (Spyraki et al. 1982, 1983). In this place conditioning study, the respective dose of cocaine and heroin needed to produce a robust place preference (an approximate doubling of preconditioning preference) are 5.0 and 0.5 mg/kg or a ratio of 10:1.

Both drugs were randomly assigned so that one-half of the animals had initial experience with heroin and one-half had cocaine as the first drug. The drugs were dissolved in 0.9% physiologic saline and were infused over a period of 4 s. The following day, the rats were given access to the lever not used on the preceding day. This lever when depressed delivered an infusion of the drug not administered on the previous day. This alternating drug self-administration procedure was continued until stable intake and titration on both drugs had occurred. For each rat, each drug was delivered via a given lever (left or right), and a colored light (red or yellow) was used as a constant discriminative stimulus that was turned on at the onset of the infusion and remained on for 20 s. During the drug infusion periods, the lever was inactive to prevent the possibility of continuous infusion and overdose. Visual cues for drugs and levers for drugs were randomly paired.

Animals that showed stable baselines over 3 days with each drug (i.e., those rats that varied less than 20% of the mean for any individual trial) were given an intracerebral injection of either 6-hydroxydopamine (6-OHDA) or vehicle into the NAcc. For this surgery the drug-trained animals were anesthetized with 50-mg/kg sodium pentobarbital injected IP. The animal's head was positioned in a Kopf stereotaxic instrument and given a bilateral injection of 6-OHDA (8 μg/2 μl, dosage expressed as the free base) in 0.9% physiologic saline containing a 0.1-mg/ml concentration of ascorbic acid as an antioxidant. The total injection volume was 2 μl on each side and was injected at a rate of 1 μl over 2 5 min. Injections were made from pump-driven, 10 μl Hamilton syringes, through a 30-gauge stainless steel cannula. The injector was left in place for 1 min to allow for dispersion of the 6-OHDA. Stereotaxic coordinates were with the tooth bar situated 5 mm above the interaural line: 3.0 mm anterior to bregma, 1.7 mm lateral to the midline, and 7.8 mm below the skull surface at the point of penetration. Nine rats were injected with 6-OHDA and four others were injected with the saline ascorbic vehicle.

Four days following lesion the subjects were allowed to resume the alternating schedule of administration described above. The "extinction-like" effect previously observed with NAcc 6-OHDA lesions is not evident on the day immediately after the lesion (Roberts et al. 1977, 1980); therefore, in the present study, the animals were tested after 4 days postlesion, similar to that employed in Roberts et al. 1980.

Data analysis

For each drug the untransformed data for the number of injections per session were subjected to a one-way analysis of variance with repeated measures on one factor. Individual means comparisons to the prelesion baseline were made with Dunnett's *t*-test. Individual animals' postlesion intake baselines of cocaine and heroin were also analyzed by calculating percent change from each of the individual baseline levels on the last drug trial preceding the lesion. These percent values were subjected to a two-way analysis of variance with repeated measures on both factors. Similar analyses were performed on ARC sin-transformed data to control for a possible skewed distribution of scores due to the percentage measure. However, the ARC sin-transformed *F* scores did not differ significantly from *F* scores of the raw data, thus suggesting that these samples were not drawn from such a skewed distribution. Here, paired *t*-tests were used for individual means comparisons.

Because of the length of time required to complete the experiment, animals did not always maintain stable postlesion self-administration (due to cannula leaks or blockages) and had to be dropped from the study. As a result only animals that completed at least five postsurgery trials on each drug (a minimum of 24 days of self-administration including baseline prelesion) were used in the data analysis, and five postsurgery trials on each drug were established arbitrarily as the termination point of the experiment. Suspected cannula leaks were tested by examining the animal's susceptibility to 10-mg sodium pentobarbital anesthesia applied through the cannula. Animals ($N = 24$) were initially trained and reached baseline criteria. Of those, 11 had cannula breaks before reaching five trials postsurgery on both drugs. Of the 13 rats that completed five trials (ten days) postlesion on each drug, three NAcc lesion rats were continued for five trials more on both drugs (20 days).

Dissection and biochemical assay

At the end of behavioral testing, lesion and sham rats were killed by decapitation and the brains dissected on ice. the olfactory tubercle was removed by a freehand horizontal cut along the lateral olfactory tract. The subsequent dissection

procedure involved taking three coronal cuts, using a wire brain slicer starting 3 mm from the tip of the frontal pole and including this as the first slice. The three coronal slices were 3 mm, 2 mm, and 4 mm in succession from anterior to posterior. Four pieces were dissected on ice from these coronal slices, frozen on dry ice, and subsequently stored at −40° C until thawed for the catecholamine determinations. The frontal cortex was dissected from the most anterior slice, and the nucleus accumbens and anterior striatum were removed from the second coronal slice (Konig and Klippel 1970). The posterior striatum was dissected from the dorsal part of the anterior surface of the third coronal cut. Dopamine and norepinephrine levels were determined using high pressue liquid chromatography with electrochemical detcetion (Felice et al. 1978). For each lesion animal, one unoperated, experimentally naive littermate was sacrificed at the same time for determination of control catecholamine levels. One lesion rat died of unknown causes while being held before killing and thus is not included in the results. The biochemical results were analyzed with a one-factor analysis of variance, and individual means were compared with the Newman Keuls a posteriori test.

Results

The effects of 6-OHDA injections into the NAcc on cocaine and heroin self-administration are shown in Figs. 1 and 2. The time course effects of 6-OHDA-NAcc lesions on cocaine and heroin self-administration are shown in Fig. 1. Significant differences from the first trial preceding the lesion were seen on the first heroin trial postlesion and on all five postlesion cocaine trials ($P < 0.05$, $df = 40$, Dunnett's t statistic). The initial depression in response rates appeared either to be an effect of the surgical procedure or the interruption in testing, since a similar transient decrement (20%) was also observed in the sham-operated controls (see Fig. 2 top).

To compare the two treatments over time postlesion, the scores were transformed to percent of baseline and then subjected to an analysis of variance (Fig 2 bottom). The 6-OHDA lesions initially produced an attenuation in both cocaine and heroin self-administration on the first self-administration trial postlesion. Subsequently, heroin maintained responding, but with a time-dependent recovery, gradually increasing to 76% of prelesion baseline levels on average; in contrast, cocaine responding continued to decrease over trials (overall group effect: $F = 6.925$, $df = 1,8$, $P < 0.05$; group × trials interaction: $F = 3.302$, $df = 4,32$, $P < 0.05$; and with ARC sin transformation ($F = 10.483$, $df = 1,8$, $P < 0.05$; $F = 3.410$, $df = 4,32$, $P < 0.05$, respectively). By the fifth trial postlesion, cocaine self-administration rates were reduced to 30% of prelesion baseline levels, and this percent change was significantly different from that for heroin rates ($P < 0.05$, individual means comparisons on the fifth trial using a paired t-test, $t = 2.63$, $df = 8$). This decrease also did not recover in the three rats that were continued for five more cocaine trials (10 days). For the sham-operated rats, there was no significant difference in the response between cocaine and heroin postlesion (see Fig. 2 top). Analysis of variance revealed no group effect nor group × time interaction ($F < 1$). However, there was a significant increase in responding over time in both groups ($F = 4.817$, $df = 4,24$, $P < 0.05$).

To eliminate the possibility that the group differences in baseline rates of responding for postlesion heroin and

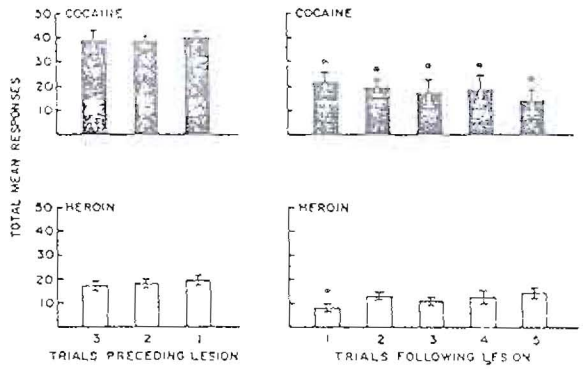

Fig. 1. Actual number of lever presses over the first five trials postlesion for cocaine and heroin self-administration. *Asterisks* indicate significant differencee from the first trial preceding lesion ($P < 0.05$, $df = 40$, using Dunnett's t statistic). *Vertical bars* represent standard error of the mean

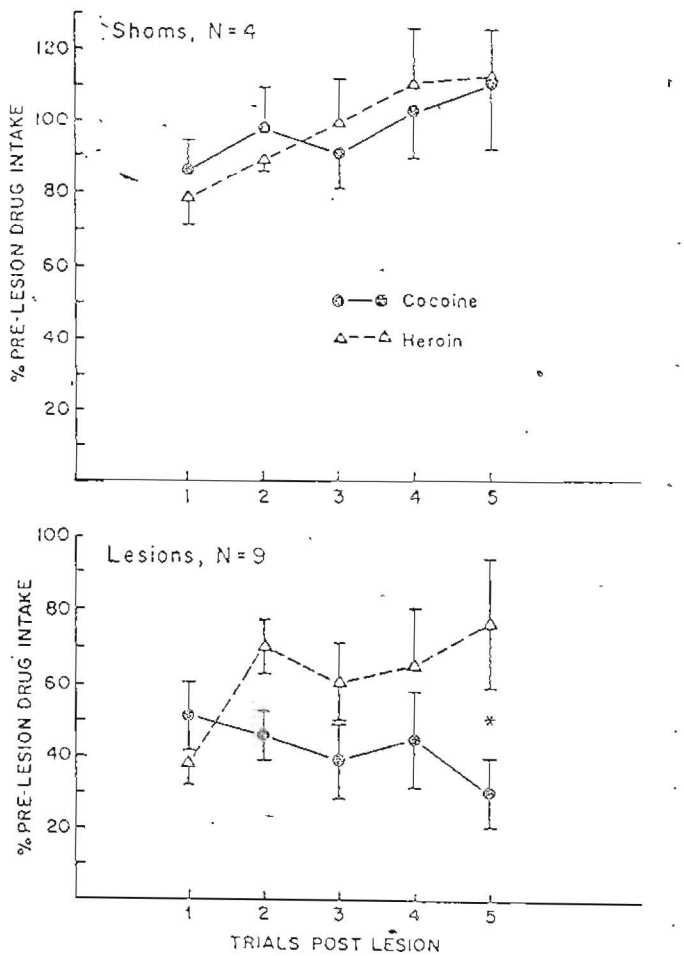

Fig. 2. Top: Percent of presurgery cocaine and heroin intake over the first five trials postlesion for the rats receiving sham lesions. Both cocaine and heroin increased significantly overtime (see text). *Vertical bars* represent standard error of the mean. *Bottom:* Percent of prelesion cocaine and heroin intake over the first five trials postlesion for rats receiving NAcc 6-OHDA lesion. Cocaine responding showed a trial dependent decrease, whereas heroin self-administration showed a trial-dependent recovery. *Vertical bars* represent standard error of the mean. *Asterisk* indicates significant difference between the two drugs $P < 0.05$, paired t-test

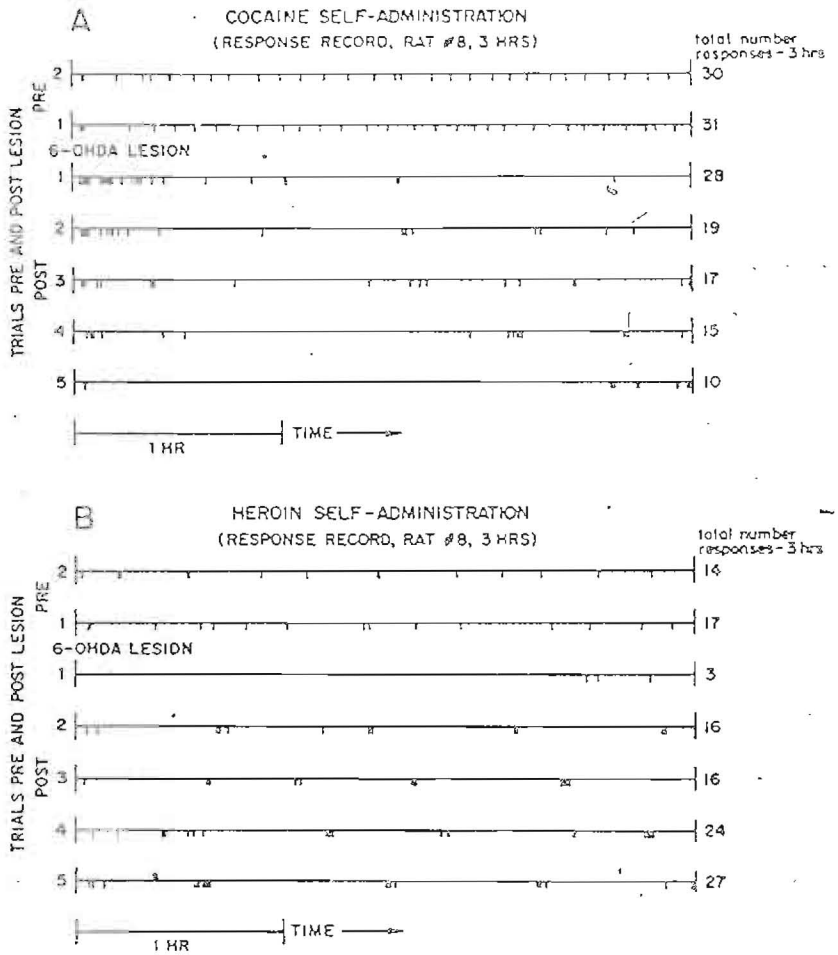

Fig. 3 A, B. Titration response records for IV heroin and cocaine self-administration of rat no. 10, pre- and postlesion. Note the extinction-like response on the first cocaine postlesion trial, followed by general response cessation on the remaining cocaine trials postlesion. In this rat an initial depression of responding was followed by a general recovery of heroin self-administration

cocaine could explain the treatment effects, individual response records were examined for those animals displaying approximately equal prelesion response rates for cocaine and heroin infusions. In three such animals, heroin responses were distinctly higher than cocaine responses postlesion, demonstrating an absolute as well as relative difference in responding.

Examination of responding postlesion using the event recorder charts (Esterline Angus) showed differences in the pattern between cocaine and heroin maintained responding. Whereas cocaine responding often showed extinctionlike bursts, particularly at the beginning of a session, heroin responding continued with a regular spacing of responses (Fig. 3). The bursts in responding observed with cocaine seen at the beginning of a session are similar to those observed during extinction where saline is substituted for the cocaine; thus, they may reflect the nonrewarding properties of cocaine postlesion. The regular spacing of heroin lever pressing postlesion was difficult to distinguish from prelesion responding with the possible exception of more of a tendency to respond in bursts (see Fig. 3). Whether this pattern reflects a partial decrease in the reinforcing properties of heroin or an alteration in the ability of the rat to move about (given the decreased locomotor behavior observed in rats in operant situations following NAcc 6-OHDA lesions; Robbins et al. 1983) is unknown at this time.

The 6-OHDA lesion resulted in a 94% depletion of DA in the NAcc, but no significant decrease in the anterior striatum (Table 1). DOPAC levels followed the same pattern as DA, but norepinephrine levels actually increased in both regions compared to unoperated controls; however, if the sham-operated animals are used as the appropriate control group, norepinephrine in the NAcc actually was decreased in the lesion group by 51%. The four sham-operated animals showed similar values as the controls, except in the NAcc where there was an actual increase in DA, DOPAC, and norepinephrine (Table 1). This increase may reflect some sprouting or other neurochemical compensation following the sham-injection damage.

Discussion

The present study was designed to examine the specificity with which the destruction of a major terminal field of the mesolimbic DA projection would alter self-administration of either cocaine or heroin in rats. An important factor in the present study was that effects of each lesion could be

Table 1. Levels of DA, DOPAC, and norepinephrine following 6-OHDA lesions of the NAcc (ng/mg protein, mean ± SEM)

	NAcc	Anterior striatum
DA		
Unoperated controls ($N = 8$)	54.7 ± 3.3	107.7 ± 5.7
Sham lesion ($N = 4$)	75.3 ± 3.6*	102.8 ± 0.8
6-OHDA lesion ($N = 8$)	3.5 ± 0.6*	90.5 ± 13.8
Lesion percent of control	6%	84%
DOPAC		
Unoperated controls ($N = 8$)	13.4 ± 1.1	54.7 ± 3.8
Sham lesion ($N = 4$)	21.3 ± 4.3*	35.3 ± 7.4
6-OHDA lesion ($N = 8$)	0.2 ± 0.1*	36.3 ± 7.1
Lesion percent of control	1%	66%
Norepinephrine		
Unoperated controls ($N = 9$)	1.344 ± 0.34	0.71 ± 0.18
Sham lesion ($N = 4$)	4.03 ± 1.20*	0.94 ± 0.16
6-OHDA lesion ($N = 9$)	1.97 ± 0.48**	0.80 ± 0.23
Lesion percent of control	147%	113%

* Signigificantly different from unoperated controls, $P < 0.05$ Newman-Keuls test

** Significantly different from sham lesion rats, $P < 0.05$ Newman-Keuls test

measured on the two independent drug variables almost simultaneously. Thus, differential effects could not be attributed to dissimilar DA depletion levels, since for each subject, the lesion had specific effects on the self-administration of cocaine and heroin, which were compared within individuals to prelesion rates. Such DA lesions produced a time-dependent decrease in cocaine self-administration, whereas responding for heroin steadily approached control levels. Thus, these results have direct implications as to the neural substrates responsible for the reinforcing properties of both psychomotor stimulants and opioids and suggest that the reinforcing properties of heroin are at some point independent of the dopaminergic neural systems mediating the reinforcing properties of cocaine.

A differentiation of substrates for the reinforcing properties of opioids and psychomotor stimulants is consistent with the results of many pharmacologic studies. For example, DA antagonists block intravenous psychomotor stimulant self-administration and opioid antagonists have similar effects on heroin reinforced responding (Goldberg et al. 1971; Yogel and Wise 1975, 1976; Weeks and Collins 1976; De Wit and Wise 1977). Moreover, opioid antagonists do not prevent the self-administration of cocaine, and DA antagonists do not block heroin reinforced self-administration except at motor impairing doses (Ettenberg et al. 1982). The present study using a within-subjects design and a neurochemically specific lesion lends further specificity to this distinction.

The rats also showed a significant change in the pattern and regularity of postlesion responding. Presumably after the lesion, the animals have to learn that on one day their response will no longer produce reinforcement (cocaine self-administration) and the next day response will have reinforcing consequences (heroin self-administration). An example of this is seen in Fig. 3. In this case, when the animal first self-administered cocaine postlesion an extinction-like response occurred (Fig. 3, first cocaine trial postlesion). On the following day no responding for heroin was seen until the final hour of the test period (Fig. 3, first heroin trial postlesion). Heroin-reinforced responding, however, recovered in this particular rat to levels above prelesion rates and a temporal pattern of responding was maintained. One could hypothesize that the animal received inadequate reinforcement on the first self-administration trial postlesion and thus carried this experience on to the next day's trial. Note the regular titration of responses on the remaining heroin trials (Fig. 3, bottom). Curiously, for this animal more heroin responses were made at each bout, whereas cocaine-reinforced responding was irregular throughout all remaining sessions.

Commensurate with this hypothesis, some of the cocaine responding on postlesion trials 3, 4, and 5 could perhaps be explained by reinforcement received when responding for heroin of the alternate days, thus creating a delayed extinction effect on cocaine reinforced responding. If this hypothesis were true, responses for the reinforcing effects of cocaine would decrease slowly over time. Indeed, in the time frame of this study, animals showed a consistent decline in postlesion responding for cocaine, whereas heroin reinforced responses were observed to increase towards preoperative levels.

While the present results are consistent with the hypothesis that DA in the region of NAcc mediates the reinforcing effects of cocaine, several other possibilities must be considered. First, it could be argued that a lesion-induced potentiation of the reinforcing effects of cocaine was responsible for reduced self-administration rates. This view is unlikely because lesioned animals failed to maintain time-dependent or titrated responding throughout each session (Fig. 3). Second, it is possible that 6-OHDA induced lesions created motor deficits that disrupted the lever press responding (Fibiger et al. 1976); however, 6-OHDA lesions of the NAcc have been reported to have only transient effects in animals responding for food and no effect on apomorphine self-administration (Roberts et al. 1977, Robbins et al. 1983). Third, it is possible that destruction of the DA terminals in the NAcc attenuates self-administration of both cocaine and heroin, but that heroin is reacquired due to the drug's analgesic properties (i.e., heroin may reduce the pain or discomfort resulting from the 6-OHDA lesion but cocaine does not). Although no such differential effects were observed in the sham-operated rats of the present study, the best test for this hypothesis would be to pair cocaine with a nonanalgesic self-administered drug in the same experimental design. A more likely possibility is that by destroying DA terminals in the region of the NAcc, one eliminates some of the pharmacologic sites through which the action of cocaine is mediated, thereby reducing its reinforcing properties.

The observation of a decrease (approximately 20%) in heroin-maintained responding postlesion might be interpreted as a partial decrease in the reinforcing properties of heroin. Consistent with this hypothesis is a recent observation that conditioned place preference produced by heroin can be attenuated by approximately 30% with a similar NAcc lesion (Spyraki et al. 1983). However, given the curious problem that cocaine-induced place preference cannot be attenuated by neuroleptics or NAcc lesions (Spyraki et al. 1982); interpretations based on this paradigm must for the moment be made with caution. Indeed, an alternate explanation for the decrease in heroin maintained responding in the present study is that destruction of the presynap-

tic DA terminals in the NAcc actually increases the reinforcing properties of heroin. This hypothesis is based on the monotonic inverse function relating drug dose to self-administration rate for stimulants and opiates (Thompson and Pickens 1970, Schuster and Thompson 1969) and the assumption that our dose is located in the middle of this function (DeWit and Stewart 1983, also preliminary dose-response studies in our laboratory support this hypothesis). Only dose-response studies or more sophisticated measures of drug reinforcement can resolve this question.

Several alternatives exist that could explain how the reinforcing nature of various drugs are neurally mediated. First, reinforcing properties of all drugs could be ultimately mediated by one neurotransmitter system in series with other neural systems (Wise 1980). In this case, an independent variable that affects one drug or pathway should similarly affect the other. Second, reinforcing properties of specific drugs could be mediated via specific neurotransmitter completely independent, but parallel to each other. In this case, an action that affects one drug should not similarly affect others. Third, reinforcing actions of a given drug could be mediated by interactions of both types. For example, as with the motor excitation produced by opioid peptides, the reinforcing properties of opioids may be mediated by opioid receptors in series with and independent of the midbrain DA systems (Joyce et al. 1981). Indeed, the results from the present study support a parallel hypothesis: at some level opioid reinforcement is mediated by systems separate from psychomotor stimulant reinforcement. The identification of the specific receptors and neurochemical systems involved in this reinforcing property of opioids is the challenge of future research.

Acknowlegements. This work was supported in part by grants-in-aid from a series of U.S. corporations and foundations including Amoco Foundation, Conoco Inc., Mobil Oil, PPG Industries Foundation, and Union Oil Co. of California. Support was also provided by NIDA grant 01785 and NIAAA grant 03504. During the period of this work AE held a J. Aron Foundation Fellowship and was a Medical Research Council of Canada Postdoctoral fellow. We thank Lynne Randolph for performing the catecholamine assays and Nancy Callahan for manuscript preparation.

References

Bozarth MA, Wise RA (1981a) Heroin reward is dependent on a dopaminergic substrate. Life Sci 29:1881–1886

Bozarth MA, Wise RA (1981b) Intracranial self-administration of morphine into the ventral tegmental area in rats. Life Sci 28:551–555

Davis WM, Smith SG (1975) Effect of haloperidol on (+)-amphetamine self-administration. J Pharm Pharmacol 27:540–542

Deneau GA, Yanagita T, Seevers MH (1969) Self-administration of psychoactive substances by the monkey. Psychopharmacologica 16:30–48

DeWit H, Wise RA (1977) Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine or phenoxybenzamine. Can J Psychol 31:195–203

DeWit H, Stewart J (1983) Drug reinstatement of heroin-reinforced responding in the rat. Psychopharmacology 79:29–31

Ettenberg A, Pettit HO, Bloom FE, Koob GF (1982) Heroin and cocaine intravenous self-administration in rats: Mediation by separate neural systems. Psychopharmacology 78:204–209

Felice JJ, Felice JD, Kissinger PT (1978) Determination of catecholamine in rat brain parts by reverse-phase ion pair liquid chromatography. J Neurochem 31:1461–1465

Fibiger HC, Carter DA, Phillips AG (1976) Decreased intracranial self-stimulation after neuroleptics or 6-hydroxydopamine: Evidence for mediation by motor deficits rather than by reduced reward. Psychopharmacology 47:21–27

Goldberg SR, Woods JH, Schuster CR (1971) Nalorphine-induced changes in morphine self-administration in rhesus monkeys. J Pharmacol Exp Ther 176:464–471

Jonsson LE, Anggard E, Gunne LM (1971) Blockade of intravenous amphetamine euphoria in man. Clin Pharmacol Ther 12:889–896

Joyce EM, Koob GF, Strecker R, Iversen SD, Bloom FE (1981) The behavioural effects of enkephalin analogues injected into the ventral tegmental area and globus pallidus. Brain Res 221:359–370

Konig JFR, Klippel RA (1970) The rat brain, a stereotaxic atlas of the forebrain and lower parts of the brain stem. Krieger Publishing, Huntington, NY

Lyness WH, Friedle NM, Moore KE (1979) Destruction of dopaminergic nerve terminals in nucleus accumbens: Effect on *d*-amphetamine self-administration. Pharmacol Biochem Behav 11:663–556

Phillips AG, LePaine FG (1980) Reinforcing effects of morphine microinjection into the ventral tegmental area. Pharmacol Biochem Behav 12:965–968

Pickens R, Meisch R, Dougherty JA (1968) Chemical interactions in methamphetamine reinforcement. Psychol Rep 23:1267–1270

Pickens R, Harris WC (1968) Self-administration of *d*-amphetamine by rats. Psycopharmacologia 12:158–163

Pickens R, Meisch RA, Thompson T (1978) Drug self-administration: an analysis of the reinforcing effects of drugs. In: Iversen LL, Iversen SD, Snyder SH (eds) Handbook of psychopharmacology, vol 12. Plenum Press, New York, pp 1–37

Roberts DCS, Corcoran ME, Fibiger HC (1977) On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacol Biochem Behav 6:615–620

Roberts DCS, Koob GF, Klonoff P, Fibiger HC (1980) Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacol Biochem Behav 12:781–787

Robbins TW, Roberts DCS, Koob GF (1983) The effects of *d*-amphetamine and apomorphine upon operant behavior and schedule-induced licking in rats with 6-hydroxydopamine-induced lesions of the nucleus accumbens. J Pharmacol Exp Ther 224:662–673

Schuster CR, Thompson T (1969) Self-administration of and behavioral dependence on drugs. Ann Rev Pharmacol 9:483–502

Schwartz AS, Marchol PL (1974) Depression of morphine-seeking behavior by dopamine inhibition. Nature 248:257–258

Spyraki C, Fibiger HC, Phillips AG (1982) Cocaine-induced place preference conditioning: lack of effects of neuroleptics and 6-hydroxydopamine lesions. Brain Res 253:195–203

Spyraki C, Fibiger HC, Phillips AG (1983) Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology 79:278–283

Thompson T, Pickens R (1970) Stimulant self-administration by animals: some comparisons with opiate self-administration. Fed Proc 29:6–11

Weeks JR (1972) Long term intravenous infusion. In: Myers RD (ed) Methods in psychobiology, (vol 2). Academic Press, London, pp 155–168

Weeks JR, Collins RJ (1976) Changes in morphine self-administration in rats induced by prostaglandin E and naloxone. Prostaglandins 12:11–19

Werner TE, Smith SG, Davis WM (1976) A dose-response comparison between methadone and morphine self-administration. Psychopharmacologia 47:209–211

Wise RA (1980) The dopamine synapse and the notion of "pleasure centers in the brain". Trends Neurosci 3:91–94

Woods JH, Schuster CR (1968) Reinforcement properties of morphine, cocaine, and SPA as a function of unit dose. Int J Addict 3:231–237

Yokel RA, Pickens R (1973) Self-administration of optical isomers of amphetamine and methylamphetamine by rats. J Pharmacol Exp Ther 1887:27–33

Yokel RA, Wise RA (1975) Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. Science 187:547–549

Yokel RA, Wise RA (1976) Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. Psychopharmacology 48:311–318

Received March 11, 1983; Final version February 10, 1984