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Disruption of Cocaine and Heroin Self-Administration Following Kainic Acid Lesions of the Nucleus Accumbens

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ZITO, K. A., G. VICKERS AND D. C. S. ROBERTS. *Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens.* PHARMACOL BIOCHEM BEHAV 23(6) 1029–1036, 1985.—In previous experiments we have demonstrated that bilateral infusions of 6-hydroxydopamine (6-OHDA) into the nucleus accumbens result in a drastic reduction in the rate of cocaine self-administration. If this effect is due to the destruction of a presynaptic dopaminergic element in this nucleus, then selective removal of the postsynaptic neuron should also disrupt cocaine self-administration. This hypothesis was tested using the neurotoxin kainic acid. Bilateral kainic acid infusions into the nucleus accumbens resulted in a drastic destruction of cell bodies yet did not damage catecholamine innervation in areas anterior to the accumbens. The effects of these kainic acid infusions were evaluated in rats that had previously acquired cocaine self-administration behavior. These lesions were found to severely disrupt cocaine intake and the degree of damage produced in the accumbens was found to correlate (r=0.88) with postlesion cocaine intake. These lesions were additionally found to disrupt apomorphine and heroin self-administration. The possibility that these results are due to destruction of systems necessary for stimulant and opiate reward is discussed.

Cocaine Heroin Kainic acid Nucleus accumbens Self-administration

CURRENT pharmacological and lesion evidence suggests that mesolimbic dopamine (DA) is critically involved in the reinforcing properties of cocaine. Cocaine is said to be an indirect agonist at catecholamine receptors [8], due to its ability to inhibit the reuptake of dopamine (DA) and noradrenaline (NA). Accordingly, if this neurochemical effect is responsible for the behavioral actions of the drug, then removal of the presynaptic element should eliminate the drug action. This prediction has been confirmed in experiments employing the neurotoxin 6-hydroxydopamine (6-OHDA) [19,20,21].

Infusions of 6-OHDA into mesolimbic terminal fields in the nucleus accumbens [19,20] or into the DA cell bodies which project to the accumbens [21], produce a significant alteration in both rate and pattern of cocaine self-administration in rats. However, there is reason to believe that this disruptiion may not be due to denervation of the nucleus accumbens. First, although 6-OHDA lesions to the ventral tegmental area (VTA) cause lasting disruptions of cocaine self-administration, the amount of DA loss in the accumbens does not correlate with postlesion intake. In fact, animals with severe loss of DA from the nucleus accumbens have been observed to be capable of near normal cocaine self-administration [21].

Second, neuroanatomical studies have shown that axons originating in the ventral tegmentum course through the nucleus accumbens prior to synapsing in several areas anterior to the accumbens. These fibers of passage are likely to be destroyed by 6-OHDA infusions into the nucleus accumbens. This would have the net effect of disrupting amine content not only in this nucleus but additionally in other regions that normally would receive catecholamine innervation. Therefore, although the nucleus accumbens may be involved in the mediation of some of the rewarding effects of cocaine, we cannot rule out the possibility that neurochemical depletions in sites rostral to the accumbens may also play a role.

In support of this notion, there is some evidence to suggest that areas outside the accumbens may be involved in stimulant reward. Phillips and Rolls [17] have reported that monkeys will self-administer the stimulant, amphetamine, directly into the prefrontal cortex. Similarly, Goeders and Smith [10] have also reported intracerebral self-injection of cocaine into the frontal cortex in rats and have demonstrated that this behavior could be blocked by the DA antagonist, sulpiride.

In an attempt to identify the locus of the reinforcing action of cocaine, we employed the excitotoxin, kainic acid. Evidence suggests that kainic acid may cause selective destruction of perikarya while sparing fibers of passage [5, 12, 22]. We reasoned that if the rewarding effects of cocaine are produced by DA afferents to the nucleus accumbens, then kainic acid infusions in this region should disrupt cocaine self-administration. If, however, the rewarding effects are

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mediated by DA innervation of anterior sites, then the treatment would have no effect. The premise that fibers of passage through the nucleus accumbens are spared following the kainic acid lesions is crucial to the logic of this experiment. In the following series of experiments, we first demonstrate that the catecholamine innervation of anterior sites is not affected by kainate lesions. Subsequent behavioral studies reveal that not only do kainic acid accumbens lesions disrupt self-administration of cocaine, but also that responding for apomorphine and heroin are disrupted.

EXPERIMENT ONE

METHOD

Surgery

Thirty-two male Wistar rats (Woodlyn Farms) served as subjects. Immediately upon receipt from the supplier, animals were handled, housed in pairs and placed on a 12 hour light/dark cycle. All subjects were given ad lib food and water for the duration of the experiment. Subjects were divided into the following four treatment groups: (1) 6-OHDA and desmethylimipramine (DMI) and Pargyline; (2) 6-OHDA vehicle and DMI and Pargyline; (3) kainic acid; (4) kainic acid vehicle.

Animals that received Pargyline (50 mg/kg IP) and DMI (25 mg/kg IP) were injected with these agents 30 minutes prior to surgery. Animals were anaesthetized with Pentobarbital (60 mg/kg IP). Bilateral microinjections of either 6-OHDA (4 μg/μl, dosage expressed as the free base), kainic acid (0.5 μg/0.5 μl phosphate buffered saline, pH 7.2), or vehicle were directed into the nucleus accumbens. The coordinates from stereotaxic zero were: AP: +11.0 mm; ML: ±1.8 mm; DV: +2.7 mm. Injections were made simultaneously through two cannulae fashioned from 30 gauge needles, at the rate of 1 μl/3 min.

Assay

Two weeks following surgery, rats were sacrificed by decapitation and the brains were rapidly removed and dissected on ice. The prefrontal cortex, amygdala, olfactory tubercle and nucleus accumbens were dissected from 2 mm slices uniformly cut with a brain slicer (Research Instruments, San Diego, CA). Tissue samples were frozen in liquid nitrogen and stored in disposable tissue cassettes (Lab-Tek, Miles Laboratories), at −40°C for analysis 2–5 weeks later. Dopamine and noradrenaline levels were measured by high performance liquid chromatography (HPLC) using a modification of the method of Mefford [13].

Neurochemical Analysis

Regional NA and DA levels in kainic acid and 6-OHDA treated rats are presented in Fig. 1. Bilateral 6-OHDA injections produced depletions of both noradrenaline and dopamine in a variety of brain regions anterior to the site of injection. Relative to control lesions, the 6-OHDA treatment produced significant depletions of noradrenaline in the olfactory tubercle, $t(12)=2.17$, $p=0.05$, amygdala, $t(13)=4.44$, $p<0.05$, prefrontal cortex, $t(12)=3.24$, $p<0.05$; whereas significant reductions of dopamine were observed in the olfactory tubercle, $t(12)=3.6$, $p<0.05$, nucleus accumbens, $t(12)=12.88$, $p<0.05$, and prefrontal cortex, $t(13)=3.23$, $p<0.05$. By contrast, bilateral kainic acid injections into the nucleus accumbens failed to significantly deplete either noradrenaline or dopamine in any of the brain regions tested.

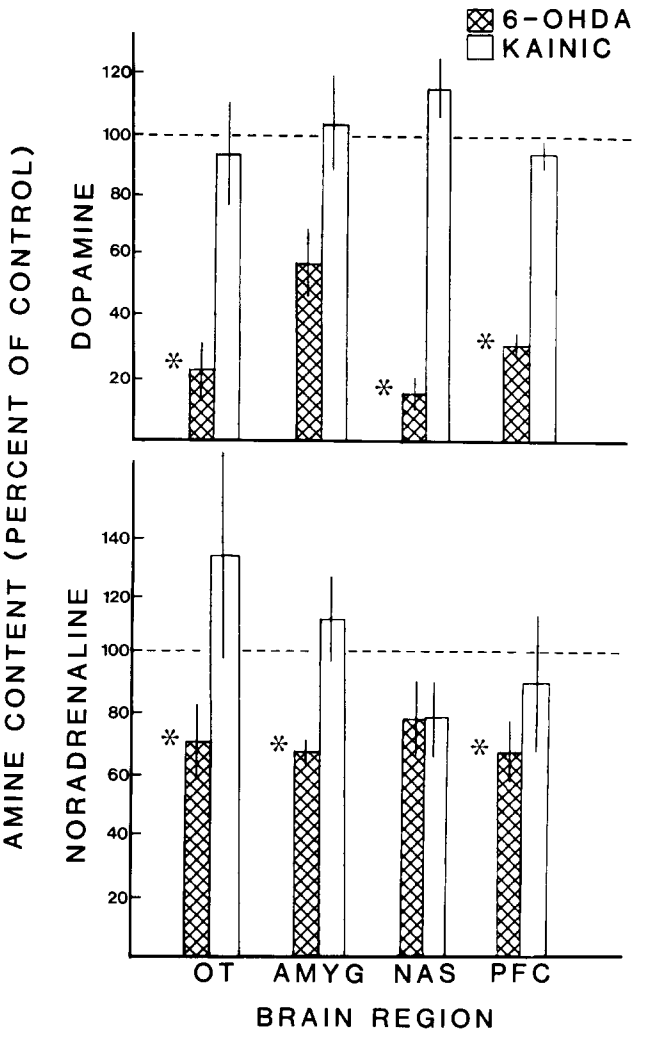

FIG. 1. The effect of kainic acid or 6-hydroxydopamine infusions into the nucleus accumbens on dopamine and noradrenaline content in various areas of the rat brain. Bars represent mean (±SEM) amine levels presented as percent of respective control values. Abbreviations: OT: olfactory tubercle; AMYG: amygdala; NAS: nucleus accumbens; PFC: prefrontal cortex. Asterisks indicate a significant difference compared to the respective sham operated control group.

These results clearly demonstrate that these two techniques produce very different effects. Although both neurotoxins interfere with normal function in the nucleus accumbens, 6-OHDA infusions concomitantly cause reductions in catecholamine content in other brain regions that also receive catecholaminergic innervation. In contrast, the kainic acid treatment fails to produce any noticeable changes in either noradrenaline or dopamine content in other forebrain areas. This suggests to us that kainic acid would be useful in separating the effects of damage to fibers of passage from lesions of the nucleus accumbens.

EXPERIMENT TWO

In the second experiment, the effect of bilateral kainic

TABLE 1

THE EFFECTS OF KAINIC ACID ON COCAINE SELF-ADMINISTRATION*

Subject Number	Accumbens Damage (Rank Order)	Percent of Prelesion Cocaine Intake
SA255	1	15
SA242A	2	10
SA241	3	54
SA243	4	33
SA242B	5	34
SA239	6	81
SA250	7	58

*Pearson r=.76; $df=5$; $p<0.025$.

TABLE 2

THE EFFECTS OF KAINIC ACID ON APOMORPHINE SELF-ADMINISTRATION

Subject Number	Accumbens Damage (Rank Order)	Percent of Prelesion Drug Intake	
		Apomorphine	Cocaine
SA382	1	34	44
SA390	2	18	3
SA349	3	28	27
SA368	4	55	39
SA358	5	25	10

acid lesions of the nucleus accumbens was evaluated in animals trained to self-administer cocaine. Adult male Wistar rats served as subjects. Following a one week acclimatization period each animal was deprived of food for 24 hours and trained to press a lever for food. This procedure was used to increase the probability that subjects would respond on the lever in the drug cage and, therefore, be more likely to learn the drug reinforced response. Following this training procedure each animal was anaesthetized and implanted with a chronic silastic cannula into the right jugular vein according to the method of Roberts *et al.* [19]. Each subject was then placed in its own individual test chamber where it lived for the remainder of the study with ad lib food and water.

The day following cannula implantation, rats were given access to a lever mounted on the side wall of their self-administration cage for 4 hours each day (approximately two hours into the dark phase). Every depression of the lever produced a 4 second intravenous infusion of 0.1 ml cocaine (0.5 mg/injection which corresponds to approximately 1.5 mg/kg/injection). Drug infusions were coincident with the onset of a white stimulus light which remained on for 20 seconds. During this period the lever was inactive.

Twenty animals that revealed stable (±10%) cocaine intake over 4 consecutive days received bilateral kainic acid lesions of the nucleus accumbens as outlined in the previous experiment. In all cases, surgery followed one day of cocaine deprivation. Subjects were given four days to recover from kainic surgery before being given access to cocaine.

RESULTS AND DISCUSSION

Anatomy

Our data are based on seven subjects that remained healthy, with patent cannula, who also displayed stable rates of self-administration prior to kainic acid surgery. The histological results were rank ordered independently by two observers blind to the behavioral results. Considerable variability was observed in the severity of accumbens damage following the kainic acid infusions. In some subjects only minimal damage to the nucleus was found; identifiable by a small population of glial cells, the majority of which were concentrated along the cannula track and at the site of the injection. Despite this variability several common features of such lesions could be identified. In almost all cases some degree of damage to striatal tissue was observed although the amount of spread dorsal into the ventral caudate did not appear to be directly related to the degree of damage in the accumbens. In fact, a near total loss of cells in the accumbens could be attained with only minor effects on the striatum.

Ventricular enlargement was also a predominant feature in the kainic acid lesioned animals. This effect may have been due to either a shrinkage of surrounding neural tissue near the site of injection or a general encephalitic response to the lesion itself. By far, the most consistent and drastic feature produced by these lesions was an atrophy of the base of the brain which appeared to be directly related to the amount of cell loss in the accumbens.

Cocaine Self-Administration

The mean (±S.E.M.) daily intake for the group prior to the lesion was 4.32±0.18 ml. This corresponds to 43.2 infusions per 4 hour session. Kainic acid infusions of the nucleus accumbens were found to cause a reduction in the rate of cocaine self-administration (see Table 1). Moreover, the degree of cellular degeneration in the nucleus accumbens was observed to significantly correlate with both postlesion rate of cocaine self-administration for individual animals (Pearson r=0.76; $df=5$; $p<0.025$). Subjects with minimal cell damage to the accumbens displayed only minor disruptions of their prelesion intake, whereas animals with complete lesions drastically declined in response rate and often ceased to respond altogether.

At least three possible reasons may be put forth as to why these animals do not respond for cocaine following kainic acid lesions. Firstly, destruction of accumbens perikarya may have rendered cocaine nonreinforcing. Alternatively, the kainic acid treatment may have produced a non-specific effect on self-administration. Finally, it remains possible that these lesions altered the motoric capabilities of subjects, such that they were unable to initiate or perhaps maintain a stable response rate. If subjects were to self-administer another agent this would eliminate the last two possibilities.

After the first few subjects displayed a decrease in response rate following the lesion, the remaining subjects were allowed access to apomorphine. Following the completion of cocaine testing, these animals were offered apomorphine at 0.033 mg/injection (approximately 0.1 mg/kg/injection) with the change in drug solution occurring at the beginning of each new test session. None of these subjects acquired a

stable pattern of self-administration. Responding was at very low levels in all subjects with one subject failing to respond at all.

However, it remains possible that the neurons that possess the critical receptors for mediating the reinforcing effects of apomorphine were also destroyed by kainic infusions. The absence of prelesion response rates for apomorphine in these subjects did not permit a reliable assessment of the effects on apomorphine self-administration. We decided to systematically investigate the effects of kainic acid lesions in a separate experiment.

EXPERIMENT THREE

This experiment was designed to evaluate the effects of kainic acid lesions to the nucleus accumbens on apomorphine self-administration. If kainic acid destroys neurons upon which apomorphine is thought to exert its effects, then it would be predicted that animals would not self-administer apomorphine. If, however, these cells are robust with respect to kainic acid, apomorphine self-administration should remain unaffected.

METHOD

Twenty-two male adult Wistar rats served as subjects. Animals were handled, housed and cannulated as previously described. Following intravenous cannulation rats were given access to cocaine. Animals that showed stable cocaine intake after four consecutive days were then given access to apomorphine. Only subjects that exhibited at least four days of stable apomorphine responding (less than 10% variability) were prepared for intracerebral infusions of kainic acid.

Rats were deprived of apomorphine for one day prior to surgery. All animals received kainic acid injections into the nucleus accumbens as described previously. On the fifth day postlesion, animals were tested for self-administration of apomorphine for a period of six days. Regardless of whether subjects would self-administer this agent, animals were then given access to cocaine for at least four days. Following all behavioral testing animals were transcardially perfused and their brains were prepared for histology as previously described. The mean percent of prelesion intake of apomorphine (postlesion days 5–9) and cocaine (postlesion days 11–14) were determined for each subject.

RESULTS AND DISCUSSION

Anatomy

Only subjects that formed stable baselines on both apomorphine and cocaine were used for kainic acid surgery. Unfortunately, more than half of the subjects were discarded due to the development of stereotypy while self-administering apomorphine. These stereotypies took the form of perseverative responding or gnawing on the lever, which often resulted in drug overdose. Competing stereotypic response patterns, therefore, interfered with their ability to regulate their intake of apomorphine. Such side effects have been reported elsewhere in both rats and rhesus monkeys self-administering apomorphine [6,9].

In those subjects that completed successfully all phases of the experiment, we noted considerable variability in the extent of accumbens damage. However, in all cases the cannula placement was as desired. In general, all subjects displayed a slight enlargement of the lateral ventricles and traces of neuronal destruction in the most ventral portion of the striatum. Most subjects showed some evidence of cell survival, particularly in the anterior portion of the accumbens, although to varying degrees. In two subjects, the nucleus accumbens had shrunk to such an extent that the base of the brain atrophied considerably.

Self-Administration

Our data (see Table 2) are based on the five rats that remained healthy, with patent cannulae, for at least 14 days of postlesion testing. The mean (±S.E.M) apomorphine intake for these subjects was 2.53±0.1 ml. The mean (±S.E.M.) intake for cocaine was 2.9±0.3 ml. As can be seen, bilateral kainic acid infusions resulted in a severe alteration in both rate and pattern of cocaine and apomorphine self-administration. However, we were unable to correlate the amount of cell loss in the accumbens with postlesion intake of either apomorphine or cocaine due to the small number of subjects that completed all phases of the experiment.

Nevertheless, the results of this experiment suggest that kainate lesions of the nucleus accumbens are capable of abolishing stimulant reinforcement caused by "direct" or "indirect" action on DA receptors. Consistent with the hypothesis that the DA receptor in the nucleus accumbens mediates the reinforcing effects of both cocaine and apomorphine, neither the rate or pattern of self-administration of apomorphine is altered following 6-OHDA infusions into the nucleus accumbens [19,20]. Lesions produced by the neurotoxin 6-OHDA differ from kainic acid in terms of their type of neuronal destruction. Whereas the former would have destroyed terminals and fibers of passage through this nucleus, the results from our initial neurochemical study suggest that kainic acid destroyed postsynaptic dopamine receptor sites only. Accordingly, apomorphine would not have a receptor through which it could exert its pharmacological effects. Thus, we would not expect our animals to self-administer apomorphine.

The question still remains as to whether these animals were indeed capable of responding since both apomorphine and cocaine appeared to be equally affected by removal of cells in the nucleus accumbens. If we could demonstrate self-administration of a non-stimulant, then we could be fairly confident that our lesions are producing a specific effect on stimulant self-administration rather than causing any non-specific effects on responding or any general disruption of drug self-administration *per se*. Due to pharmacological evidence which suggests that heroin and cocaine intravenous self-administration are mediated by separate neural systems [7], we decided to evaluate the effects of kainic lesions on this behavior. If the substrates for opiate reinforcement are distinct from those underlying stimulant reward, then it should be possible to find lesions which affect self-administration of stimulants but not that of opiates.

EXPERIMENT FOUR

METHOD

The effect of kainic acid lesions to the nucleus accumbens on heroin self-administration was examined in male Wistar rats. Animals were cannulated and housed as in previous experiments. Following intravenous cannulation, all animals were first given access to cocaine to initiate self-administration behavior. Once it was demonstrated that animals would self-inject cocaine, the drug solution was

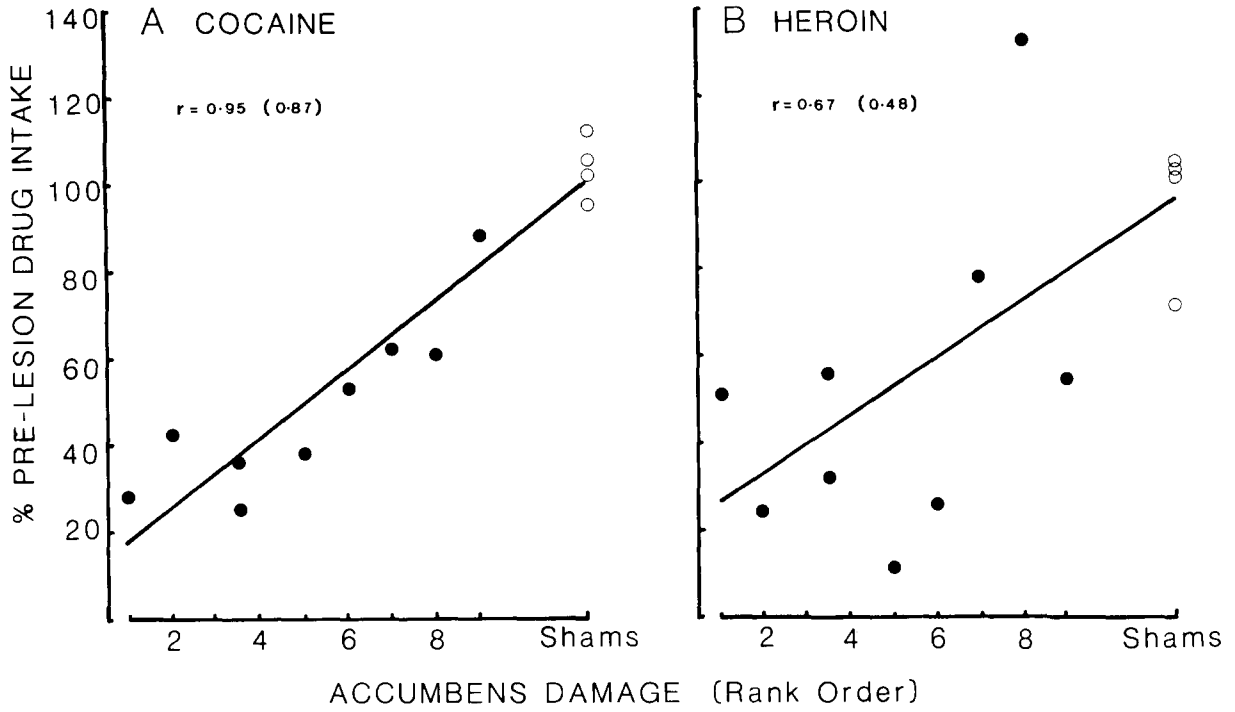

FIG. 2. Correlations between damage to the nucleus accumbens and postlesion intake of cocaine (A) and heroin (B) intake. The brains were rank ordered following histological examination of Nissl stained sections. Postlesion drug intake was calculated as a percentage of baseline (prelesion) cocaine intake for the mean of days 5–9 postlesion and heroin intake for the mean of days 12–16.

changed to heroin (0.6 mg/kg/injection) for subsequent sessions. Animals that displayed relatively stable heroin intake for four consecutive days (less than 15% variability) were then permitted to self-administer cocaine. Only animals that exhibited stable cocaine intake for four consecutive days (less than 10% variability) were prepared for further surgery.

All rats were deprived of cocaine for one day prior to intracerebral infusions. Fifty-six subjects received bilateral kainic acid injections. Eight subjects were prepared for bilateral kainic acid vehicle infusions. The parameters of injection were as previously outlined. Following a four day recovery period, animals were again given the opportunity to self administer cocaine. Regardless of whether subjects would self-administer cocaine, all animals were changed to heroin on the eleventh day post kainic infusions. Rats that would self-administer heroin, regardless of their response rate, were given access to the drug for at least five days. Following all behavioral testing animals were transcardially perfused and their brains prepared for histology. The percent of prelesion intake of cocaine (postlesion days 5–9) and heroin (postlesion days 12–16) were determined for each subject.

RESULTS AND DISCUSSION

Anatomy

The brains of the 13 animals (nine kainic, for shams) that completed all phases of the experiment were rank ordered for the amount of cell loss in the nucleus accumbens. No damage was observed to neurons in the nucleus accumbens in animals that received sham infusions. In these subjects only remnants of the cannula penetration were evident, outlined by a thin layer of glial cells. This was in direct contrast to the neuronal damage observed in kainic acid subjects. Again, although extensive variation in the severity of brain damage was noted among these animals, there were several prototypical signs of kainic acid infusions.

Of the 13 brains examined, six cases of ventricular enlargement, six cases of atrophy of the olfactory tubercle and six cases of damage to the ventral portion of the striatum were noted. These effects were not found in all the same six subjects, however. Some animals revealed only one or two of these symptoms while only three subjects possessed all three. Although these animals all had greater than 50% cell loss in the accumbens, complete lesions to this nucleus were possible without such adverse effects. We were not able to detect any evidence of secondary damage to areas distal to the site of injection (e.g., hippocampus) as has previously been reported with kainic acid [24,29].

Self-Administration

The mean (±S.E.M.) daily intake/4 hr session prior to the lesion for cocaine and heroin were 3.59±0.18 ml and 2.8±0.51 ml, respectively. Bilateral kainic acid lesions to the nucleus accumbens resulted in a drastic alteration in both rate and pattern of self-administration of cocaine. As in the previous experiment, the amount of cell loss in the accumbens correlated ($r=0.87$; $df=7$, $p<0.001$ (excluding shams); $r=0.95$; $df=11$, $p<0.005$ (including shams)) with postlesion cocaine intake (see Fig. 2). Subjects that sustained extensive neuronal damage reduced their rate of responding to very low levels whereas subjects with less damage were far less affected. Regardless of their postlesion rate, all subjects that sustained some cell destruction in this nucleus were dis-

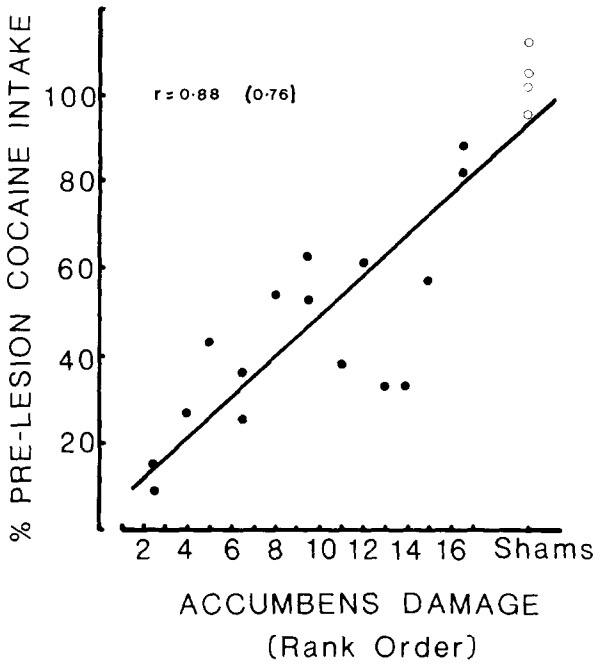

FIG. 3. Correlation between damage to the nucleus accumbens following bilateral kainic acid infusions and postlesion intake for subjects in Experiments 2 and 4. The brains were rank ordered following histological examination of Nissl stained sections. Postlesion cocaine intake was calculated as a percentage of baseline (prelesion) drug intake for the mean of days 5–9 postlesion.

rupted in their pattern of intake. This was characterized by irregular responding, sometimes in bursts. Not only did these lesions produce more variability in the pattern of responding within a single session, but day to day responding for cocaine also became more variable. None of these animals displayed an extinction-like pattern of responding nor were there any indications that recovery had or would occur.

Surprisingly, bilateral accumbens lesions also decreased responding for heroin in all animals, although the correlation between heroin and cocaine intake was not significant ($r=0.39$; $df=7$, $p>0.05$). The amount of accumbens cell loss and postlesion rate was, however, significant ($r=0.67$; $df=11$; $p<0.05$ (including shams); $r=0.49$; $df=7$; $p>0.10$ (excluding shams)). At the completion of all drug testing, in an attempt to demonstrate that these lesions did not produce any adverse motoric effects, four subjects were removed from their test cages, deprived of food for 24 hours, and given a 15 minute operant session during which they could bar press for food pellets. All of these subjects demonstrated high levels of stable responding, bar pressing at least 100 times in a single 15 minute test period. Animals continued to respond at this level for four consecutive sessions.

In contrast to the drastic effects produced by kainic acid treatment, responding in rats that received vehicle infusions failed to reveal any behavioral effects. Postlesion intake of both heroin and cocaine was unaffected. These animals continued to respond with the same general pattern and rate as they had done prior to surgery.

GENERAL DISCUSSION

Our main finding was that bilateral infusions of kainic acid into the nucleus accumbens severely disrupt cocaine self-administration. Moreover, the degree of damage produced in the nucleus accumbens was found to correlate with postlesion cocaine intake. When the animals from Experiments 2 and 4 are combined, the Pearson correlation was calculated to be 0.88 (see Fig. 3). Animals with the most severe cell loss reduced their responding for cocaine to extremely low levels or failed to respond altogether.

These studies were designed to test whether the nucleus accumbens contains the critical receptors responsible for the mediation of cocaine's reinforcing effects. Had the kainic lesions not disrupted cocaine self-administration, then decreases observed following 6-OHDA lesions [19, 20, 21] could not implicate the nucleus accumbens as the critical site. Rather, such effects would have indicated that in the process of destroying dopamine terminals, essential fibers of passage were damaged. It may then have been hypothesized that disruptions in cocaine self-administration were critically dependent upon denervation of structures anterior to the accumbens. Such regional depletions were, in fact, confirmed in our first experiment following 6-OHDA accumbens injections.

There are several explanations for our results. First, it is possible that the animals were incapable of responding for the drug due to motor impairment. We feel this explanation is unlikely because animals did not appear either akinetic or ataxic. While some subjects were incapacitated immediately after the lesion, and some animals died or were sacrificed before cocaine testing, those animals that remained in the study did not have an unhealthy appearance. To demonstrate that they were indeed capable of the motor response, some were trained to bar press for food. These animals were quite capable of pressing a lever over 100 times in 15 minutes. This exceeds by far the response requirements for normal self-administration behavior. Taken together, this evidence fails to convince us that any motor debilitating effects produced by the lesion were sufficient to account for the decrease in self-administration behavior.

A second explanation for the reduction in cocaine intake observed following kainic acid lesions may be that the animals were suffering from a general malaise which may have prevented self-administration of any drug. In order to examine whether the observed effects were specific to cocaine, a separate group of animals was tested for apomorphine self-administration (Experiment 3). The results of this experiment indicated that the disruption also extended to the direct acting agonist. Since apomorphine self-administration was also reduced, it did not provide an adequate control for a possible nonspecific effect of the treatment. In our final experiment the effects of kainic acid were tested in animals that were trained to self-administer both cocaine and heroin. The opiate was chosen because it is readily self-administered by rats and it represents a drug class quite different from the psychomotor stimulants. Kainic acid lesons of the nucleus accumbens reduced the intake of both cocaine and heroin. These data would seem to demonstrate that the effects of kainic acid are non-specific. However, closer examination of the data and the literature indicate that the results may be more intriguing.

Self-administration of cocaine and heroin were differentially suppressed after the lesion. In some animals heroin was affected more than cocaine, while in other animals the reverse was true. The correlation between the suppression of heroin and cocaine intake was not significant ($r=0.39$; $df=7$; $p>0.05$). Had the kainic acid treatment produced a non-

specific depressant effect, then one would expect that the intake of both drugs would be depressed equally (in the same animal) and that postlesion intake of heroin and cocaine should, therefore, correlate. The fact that this was not the case suggests that the reason for the differential effect on cocaine and heroin self-administration is more complicated than a general non-specific action.

Recent data indicates that dopaminergic mechanisms may be involved in opiate reward. The most convincing evidence comes from the demonstration that morphine is self-administered directly in mesolimbic dopamine-rich brain regions. For example, Bozarth and Wise [3] have shown that rats will self-inject morphine directly into the VTA, an effect that is naloxone reversible. Additional support comes from the finding that opiate receptors appear to be located either on or proximal to dopaminergic cell bodies in the VTA [18,23]. It has also been demonstrated that rats will self-inject morphine directly into the nucleus accumbens, an area that receives extensive innervation from these dopamine neurons [15]. Whether adjacent areas such as the lateral hypothalamus do [14], or do not [1], support such behavior remains controversial. Additionally, intrahypothalamic kainic acid infusions do not disrupt intravenous self-administration of heroin [4].

The involvement of a dopaminergic component in opiate reward is strengthened by the finding that animals will acquire a place preference following morphine microinjections directly into the VTA [16] or the nucleus accumbens [26]. Heroin induced place preference produced by peripheral drug injections has also been reported to be attenuated following neuroleptic pretreatment [2] and by 6-OHDA lesions of the nucleus accumbens [25].

While these data seem to indicate a correlation between DA and opiate reward, some authors argue that stimulant and opiate reinforcement are mediated by distinct systems. Ettenberg *et al.* [7] have demonstrated that manipulations that affect the self-administration of stimulants do not similarly affect opiates and vice versa. In spite of these pharmacological data it seems possible that dopamine and opiate systems may interact anatomically. The fact that certain lesions can at times affect both has led to the suggestion that opiate reward may be "serially" related to dopaminergic neurons [27,28]. This hypothesis could possibly be used to explain the disruption we observed in heroin self-administering animals. If opiates act on VTA cells, it follows that destruction of the neurons postsynaptic to the DA cells might also disrupt behavior.

Probably the most striking confirmation that the accumbens is responsible for the mediation of the rewarding effects of stimulants is the recent work of Hoebel *et al.* [11]. These authors have reported that rats will learn to self-administer amphetamine directly into the nucleus accumbens. By contrast, Goeders and Smith [10] failed to demonstrate cocaine self-injection into the accumbens. Whether there is some procedural difference which may account for this discrepancy or whether the important difference is the choice of drugs (amphetamine vs. cocaine) is unclear. If it is due to drug selection, this would yield the surprising conclusion that the rewarding effects of cocaine and amphetamine are mediated at different locations.

While the present data indicate a role for the nucleus accumbens in psychomotor stimulant reward, they do not rule out the possibility that other areas may also contribute. It is likely that not all the reinforcing effects are mediated at the level of the accumbens. We need not restrict our thinking to fibers of passage through this nucleus but should consider the efferents of the accumbens as well in future studies.

ACKNOWLEDGEMENTS

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