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Kainic Acid Lesions of the Nucleus Accumbens Selectively Attenuate Morphine Self-Administration

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DWORKIN, S. I., G. F. GUERIN, N. E. GOEDERS AND J. E. SMITH. *Kainic acid lesions of the nucleus accumbens selectively attenuate morphine self-administration.* PHARMACOL BIOCHEM BEHAV 29(1) 175–181, 1988.—The influence of kainic acid lesions of intrinsic and efferent neurons of the central medial nucleus accumbens on responding simultaneously maintained by food, water and morphine self-administration was assessed. Rats were trained on a multioperant baseline to respond on three different levers that resulted in either a food pellet, the presentation of a water dipper or an infusion of morphine. While responding on the morphine lever was related to dose (0.83–13.2 mg/infusion), increasing concentrations of the drug had little or no effect on responding maintained by food and water before the lesion. Bilateral infusions of the neurotoxin into the nucleus accumbens decreased morphine self-administration but did not appreciably alter food or water intake. Food extinction probes before the lesion produced significant increases in drug intake and decreases in responding on the water lever, but the neurotoxin lesion attenuated the food extinction induced decrease in water intake. These data suggested that kainic acid lesions of the nucleus accumbens decrease the reinforcing efficacy of morphine but do not alter the reinforcing properties of food and water. The neuronal systems potentially involved in mediating the reinforcing effects of environmental events are discussed.

Morphine Self-administration Nucleus accumbens Kainic acid Food extinction
Operant behavior Concurrent schedules Food Water

INVESTIGATIONS using specific neurotoxin lesions of discrete brain regions have significantly increased our understanding of the neurobiological processes involved in the reinforcement of behavior by contingent drug administration. The neurotoxin, 6-hydroxydopamine (6-OHDA), has been used to selectively destroy dopamine containing neurons to provide data on the role of these neurons in the reinforcing properties of various drugs. 6-OHDA lesions of the nucleus accumbens decrease cocaine and amphetamine self-administration [13, 19, 21, 22] and increase responding maintained by contingent morphine injections [24]. These and other data suggest that the mesolimbic dopaminergic system is critically involved in drug self-administration and may also be involved in the neurobiological mechanisms by which many other environmental events (i.e., food and water) function as reinforcers [28]. Although the role of presynaptic dopaminergic innervations of the nucleus accumbens in drug reinforcement mechanisms has been examined, the importance of postsynaptic neuronal systems has not been as thoroughly investigated. Several other neurotransmitter systems within the nucleus accumbens however have been implicated in drug reinforcement processes. 5,7-Dihydroxytryptamine lesions of serotonergic neurons innervating the nucleus accumbens increase both amphetamine [13] and morphine [24] intake. Furthermore, other studies indicate that the nucleus accumbens is not the only brain region involved in the mediation of the reinforcing effects of drugs. For example, 6-OHDA lesions of the ventral tegmental area (VTA), which contains the dopamine cell bodies for the innervations of the nucleus accumbens, do not alway disrupt cocaine self-administration [20]. Not all of the dopaminergic axons originating in the VTA synapse in the accumbens and the ability of 6-OHDA lesions of the VTA to affect cocaine self-administration does not correlate with changes in dopamine levels in this structure [20]. These data suggest that other brain regions may be involved in drug reinforcement processes. Moreover, the demonstration that cocaine [6] is directly self-administered into the medial prefrontal cortex indicates that the nucleus accumbens is not the sole locus of drug reinforcement. Thus, efferents from the nucleus accumbens may play a role in modulating the reinforcing effects of drugs.

Kainic acid, a potent neurotoxin, has selective toxic effects which include destruction of cell perikarya while

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producing minimal damage to terminals or fibers of passage at the injection site [2,14]. Kainic acid lesions of the nucleus accumbens result in moderate depletions of glutamic acid decarboxylase at the injection site and in the ventral tegmental area [26] but do not reduce norepinephrine or dopamine content in the nucleus accumbens or at anterior sites [29]. Kainic acid destroys the intrinsic cholinergic and GABAergic neurons in the nucleus accumbens and the GABA feedback pathway from the nucleus accumbens to the VTA [29]. Therefore, this neurotoxin can be used to evaluate the role of neurons originating in the nucleus accumbens in mediating the effects of reinforcing stimuli. The central administration of kainic acid into this region has been reported to increase dopamine induced locomotor activity [4,8] and to decrease cocaine, apomorphine and heroin self-administration [29].

There are difficulties inherent to investigations of the effects of neurotoxin lesions on drug self-administration and other operant behaviors since it is not always possible to identify the behavioral mechanisms that have been altered by a selective neurotoxin lesion. For example, a lesion that results in the altered self-administration of a particular drug may do so by interfering with at least four distinct processes. The lesion may alter the unconditioned effects of the drug, the reinforcing efficacy of the drug, the motoric capabilities of the subject or may produce non-specific alterations in the central mechanisms of reinforcement. The determination of the specific effects of a neurotoxin lesion therefore requires evaluating the effects of the lesion on responding maintained by different drug doses as well as on responding maintained by other reinforcers. This study provides an analysis of the selective effects of kainic acid lesions of the nucleus accumbens on morphine self-administration. Behavioral specificity was investigated by determining the effects of the lesion on responding concurrently maintained by food, water and intravenous morphine. In addition, complete dose-effect curves for self-administration both before and after the lesion indicated that the lesion resulted in a specific attenuation of the reinforcing efficacy of morphine without affecting responding maintained by food or water.

METHOD

Subjects

Twelve adult male inbred rats developed from the Fischer 344 strain weighing between 275–325 g at the beginning of training were used. The subjects were adapted to an operant conditioning chamber and to random tone and light presentations before training.

Apparatus

The rats were continuously housed in a standard operant conditioning chamber containing three retractable levers, a stimulus light directly above each lever, a tone source, a pellet dispenser, a water dipper and a motor-driven syringe pump. An additional light mounted above the Plexiglas® chamber was illuminated from 5:00 p.m. to 5:00 a.m. to provide a reversed 12 hour light/12 hour dark cycle.

Behavioral Procedure

The training procedure has been described in greater detail elsewhere [5]. Briefly, the subjects were initially trained to respond on two levers under a concurrent chained fixed-ratio 1, fixed-ratio 9 schedule of food and water reinforcement (conc chain FR1, FR9). A third lever was continuously retracted during initial training. The first response on either extended lever resulted in the retraction of the other. Nine additional responses on the extended lever resulted in the presentation of the chosen reinforcer (either food or water) and retraction of that lever. If the ratio was not completed within 100 sec (limited hold or LH), the extended lever was retracted. The two levers were reintroduced into the chamber 30 sec after a reinforcer presentation or the elapse of the LH (time out or TO).

The rats were then surgically implanted with chronic jugular catheters and were placed in operant conditioning chambers and made physically dependent on morphine over a 12-day period by delivering hourly infusions of morphine in the absence of the response lever. The dose ranged from 0.41 mg/infusion on the first day and was doubled every third day to 3.3 mg/infusion on the ninth day. A lever was then introduced, and the rats were trained to respond under an FR10 schedule of intravenous morphine administration (3.3 mg delivered over 5.5 sec). After stable rates and patterns of morphine intake were observed, the rats were returned to the original three lever chamber. A morphine reinforcer option was then added to the initial food and water schedule, and all three levers were extended into the chamber. Responding on the third lever resulted in infusions of morphine. Subsequent responding was maintained under a conc chain FR1, FR9, LH 100″, TO 30″ schedule of food, water and morphine presentation.

Surgical Procedure

Each rat was implanted with a chronic jugular catheter and bilateral guide cannulae into the nucleus accumbens. The guide cannulae (23 gauge stainless steel tubing) were implanted stereotaxically at the following coordinates: 9.5 mm A to lambda, 1.2 mm L, 5.1 mm V [11]. The cannulae were permanently cemented to the skull with dental cement, and a stainless steel 30 guage stylet was inserted in each cannula.

Morphine

Morphine sulfate was dissolved in a bacteriostatic 0.9% sodium chloride solution containing 0.83 USP units/ml of sodium heparin. Dosages were determined as the salt, and a range of doses from 0.83 to 6.6 mg/infusion were investigated. Morphine presentations consisted of a 0.2 ml infusion delivered over 5.5 sec concurrent with a 30-sec tone presentation.

Single Dose Study

Two rats were allowed to self-administer one dose of morphine (3.3 mg/infusion) before (243F) or after (307A) the lesion. A complete dose-effect curve was determined before the lesion for 307A and a complete curve was determined after the lesion for 243F.

Dose-Effect Study

Dose-effect relationships were evaluated in five additional subjects. Dose-effect determinations were made by replacing the daily morphine dose (3.3 mg/infusion) with another dose of morphine or saline for 24 hours, beginning at the start of the dark cycle (5:00 a.m.). At least two determinations of each dose or vehicle were made, and a minimum of 2–3 days elapsed between each probe to allow a return to baseline responding.

Food Extinction

The effects of eliminating food deliveries were studied with four rats exposed to the dose-effect manipulations, both before and after the kainic acid lesion. In addition, two of these rats were given a sham lesion and exposed to food extinction before the neurotoxin lesion. These probes were initiated at 5:00 a.m. and were terminated 24 hours later. Double determinations were made with each animal before and after the lesion and 3–4 days were allowed between each probe until baseline responding was observed.

Kainic Acid Lesion

Chemical lesions were made by the bilateral microinjection of kainic acid through injection cannulae inserted into the guide cannulae. On the day of lesion, the animals were anesthetized with diazepam (30 mg/kg) and sodium thiopental The stylets were removed, and injection cannulae (30 gauge stainless steel tubing that extended 0.5 mm beyond the end of the guide cannula) which were attached to a 1 μl microsyringe by PE tubing were inserted into each guide cannula. A 0.2 μl injection of 2 μg kainic acid in artificial CSF was then made over 6 minutes using a precision microinfusion pump that delivered 0.033 μl of solution per minute. The injection cannulae were removed after an additional 10 minutes, and the stylets were replaced. Artifical CSF alone was used for sham lesions. During the 48 hours immediately following the lesion, the rats were placed in a housing chamber without response levers, given unrestricted access to food and water, and response independent infusions of morphine (3.3 mg/inj) at a rate approximating their prelesion daily intake. The rats were then returned to the three lever schedule contingency. The effects of a sham lesion were determined in 4 rats that were later lesioned with kainic acid. One of these rats died after the lesion.

Histology

Cannulae placements were verified after the rats were sacrificed by immersion in liquid nitrogen. Frozen brain sections (16 or 32 microns) were cut and stained with Luxol Fast Blue and cresylecht violet for identification of both cell bodies and myelinated fiber bundles [10]. Location and extent of lesions were determined by assessment of the location and size of gliosis by light microscopy.

Data Analysis

Data obtained the day immediately before a manipulation were compared to values observed during the manipulation to evaluate experimental effects. For the dose-effect determinations, each dose was evaluated at least twice in each subject as were the food extinction sessions. These replications occurred before the lesion, after the vehicle lesion and a third time after the kainic acid lesion. A repeated measures analysis of variance followed by individual paired t comparisons were used to test for statistically significant effects.

RESULTS

Prelesion

The data from 4 of the 12 rats have been omitted because the rats did not survive the neurotoxin lesion. The relative percentage of ratios completed or reinforcers delivered as a consequence of responding on the three available levers was calculated for the baseline drug condition (3.3 mg/infusion). Sixty-eight percent of the reinforcers delivered over a 24-hour period were food deliveries. Twenty-eight percent of the completed ratios occurred on the water lever, and 4 percent of the reinforcers delivered were morphine infusions. Although the mean number of ratios completed on the three levers was different, local rates and temporal patterns were very similar. When the rats were responding on any of the three levers, high rates of responding were typically observed. A large number of consecutively completed ratios (runs) occurred on the food lever while runs on the water lever were shorter. Very few runs occurred on the morphine lever. The rats had mean daily intake of 14 g of food, 13 g of water and 56 mg of morphine.

TABLE 1

NUMBER OF RATIOS COMPLETED ON THE FOOD, WATER, AND MORPHINE LEVER BEFORE AND AFTER THE NEUROTOXIN LESION FOR THE TWO SUBJECTS IN THE SINGLE DOSE STUDY

Subject		Morphine Pre	Morphine Post	Food Pre	Food Post	Water Pre	Water Post
243F	Mean	17.8/4.4		465.8/419.4		113.2/140.2	
	SD	(4.4)/(0.54)		(33.1)/(49.8)		(24.1)/(73.1)	
307A	Mean	11.0/2.9		375.9/360.3		133.4/149.2	
	SD	(3.4)/(1.7)		(44.0)/(55.2)		(38.7)/(44.9)	

Data were collected during exposure to the 3.3 mg/infusion dose. Only the difference in morphine responding is significantly different ($p<0.0001$, independent observation t-test).

Single Dose

The infusion of kainic acid into the nucleus accumbens produced a significant decrease in the number of ratios completed on the morphine lever. Morphine intake in the rats exposed to one dose (3.3 mg/inj) either before or after the lesion decreased from a mean of 13.6 [95% confidence interval (C.L.), 2.7] before the lesion to 3.7 (95% C.L., 0.9) after the kainic acid was administered. The acutal mean dosage of morphine decreased from 45.4 mg/day to 12.3 mg/day. The lesion did not change the number of ratios completed on either the food or water levers (Table 1).

Dose Effect

The effects of substituting several doses of morphine for the training dose (3.3 mg/infusion) are shown in Figs. 1, 2, and 3 for responding on the drug, food and water levers, respectively. Increasing the dose of morphine available for a 24-hour period from 0.83 mg/inj to 13.2 mg/inj resulted in dose related decreases in the number of ratios completed on the morphine lever with a modest increase in drug intake. At the 0.83 mg dose, the rats had a mean daily drug intake of 27.8 mg while at the 13.2 mg dose, 35.0 mg was the mean dosage injected over a 24-hour period. Responding on the food or water lever was not significantly altered by changes in the morphine dose (see Figs. 2 and 3). Substitutions of saline for morphine resulted in an increase in responding on the morphine lever, a modest decrease in the number of ratios completed on the food lever and an extreme decrease in water intake. The vehicle lesion did not significantly alter drug, food or water intake at the training dose or shift the dose-effect curves for these three reinforcers.

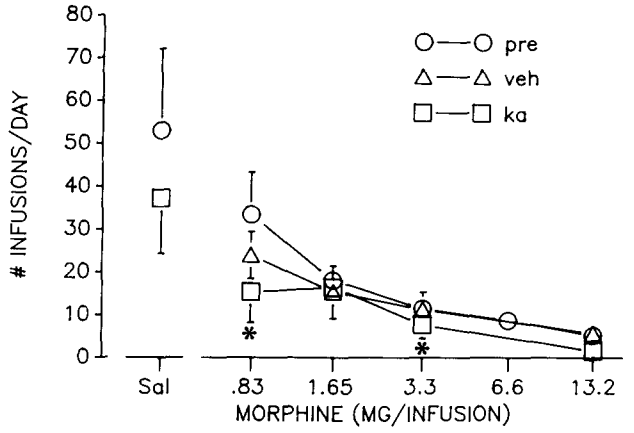

FIG. 1. Morphine intake. Dose-effect relationship for intravenous morphine self-administration before the lesions (open circles), after the vehicle lesion (open triangles) and after the kainic acid lesion (open squares). The values indicate the mean number of injections during 24 hr. The verticle lines above the circles indicate +1 S.D., the verticle lines below the squares depict −1 S.D. and the verticle lines around the triangles indicate ±1 S.D. Post-vehicle and kainic acid lesion intake was compared to pre-lesion responding. The significance of the differences between means determined with Student's *t*-test were: *=$p<0.001$.

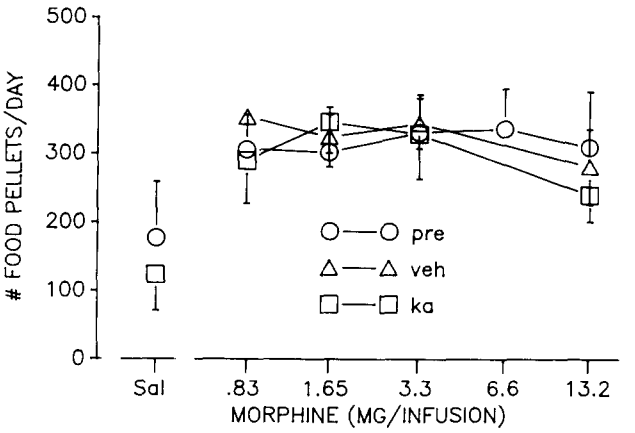

FIG. 2. Food intake. Dose-response curve depicting the effects of different self-administered morphine doses on food maintained responding. Details are the same as for Fig. 1, but there were no statistically significant differences.

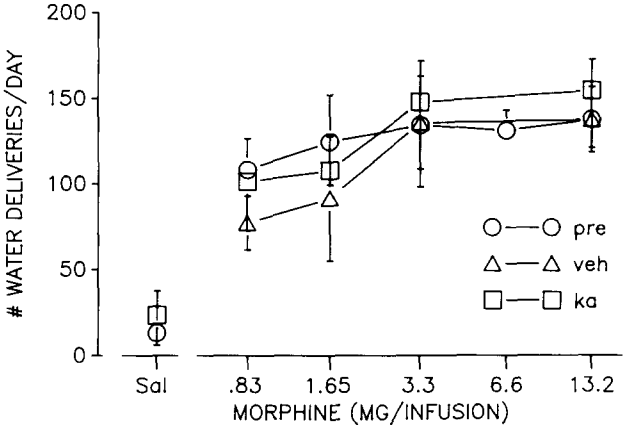

FIG. 3. Water intake. Dose-response curve illustrating the effects of morphine dose and responding on the water lever. Details are the same as for Fig. 1. No. significant differences were observed.

Kainic Acid Lesion

Four of the subjects died following the kainic acid lesion of the nucleus accumbens. Their data were not included in the results reported in this study. Complete dose-effect curves both before and after the neurotoxin lesion were determined in 5 rats, three of which had previously received the vehicle lesion. The effects of the neurotoxin lesion on responding maintained by morphine, food and water are shown in Figs. 1, 2 and 3 respectively. With two exceptions, the neurotoxin lesion did not significantly alter responding on the food or water lever when the training dose or other doses of morphine were available. The neurotoxin lesion did slightly decrease the number of ratios completed on the food lever when 6.6 mg of morphine or saline was available. However, the kainic acid lesion significantly decreased morphine intake at the training dose as well as the lowest dose investigated (0.83 mg/infusion). The number of ratios completed on the morphine lever and morphine intake decreased from a mean of 11.5 injections (38.0 mg) to 7.7 injections per day (25.5 mg) when the training dose was available. A 54% decrease in morphine intake was also observed at the 0.83 mg/inj dose. The neurotoxin lesion also decreased the number of ratios completed on the morphine lever during saline substitutions.

Food Extinction

The effects of eliminating food deliveries (food extinction) for a 24-hour period were evaluated in 4 rats both before and after the kainic acid lesions. Food extinction probes were also determined in 2 of the 4 rats following vehicle lesions which preceded kainic acid lesions. Morphine intake was significantly increased during all food extinction probes (Fig. 4). The mean number of ratios completed on the drug lever was decreased by the kainic acid lesion both before and during food extinction probes.

Figure 5 shows that responding on the food lever was not significantly affected by food extinction probes before or after the vehicle lesion. However food extinction after the kainic acid lesion did result in a slight but not statistically significant decrease in the number of ratios completed on the food lever. Food extinction probes before the kainic acid lesion resulted in significant decreases in the number of water presentations during extinction sessions (Fig. 6). The mean number of ratios completed on the water lever decreased from 127.4 to 32.9 before the vehicle or neurotoxin lesion. Food extinction sessions which followed the neurotoxin lesion did not result in a statistically significant decrease in responding on the water lever.

Histology

All the injection cannula were placed into the nucleus accumbens. In most subjects, only minimal damage to the nucleus accumbens was found. Two subjects showed moderate gliosis in the nucleus accumbens, and in one of these rats, gliosis was also observed in the olfactory tubercle. Since these histological assessments were made a relatively long time following the neurotoxin lesions, it is likely that the gliosis may have disappeared. These standard histological

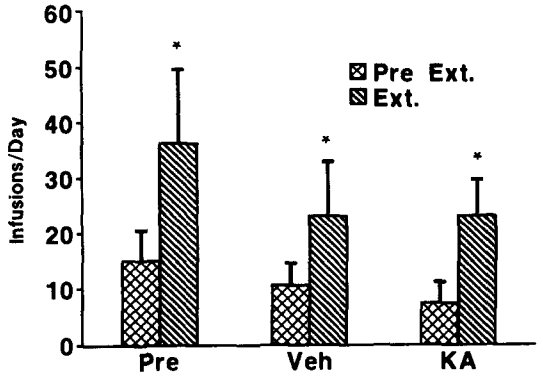

FIG. 4. Food extinction drug intake. Bar histogram indicating the effects of food extinction on drug intake. The left, center and right pairs of bars show the number of infusions delivered over a 24 hour period before the lesion, after the vehicle lesion and after the kainic acid lesion, respectively. The data presented are means and 99% confidence intervals. The significance of the differences between means determined with Student's paired *t*-test were: *=$p<0.05$.

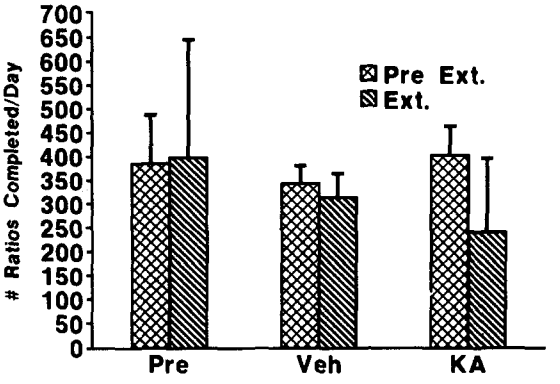

FIG. 5. Food extinction. Histogram illustrating the effects of food extinction on the number of ratios completed on the food lever. Details are the same as for Fig. 4. No significant differences were observed.

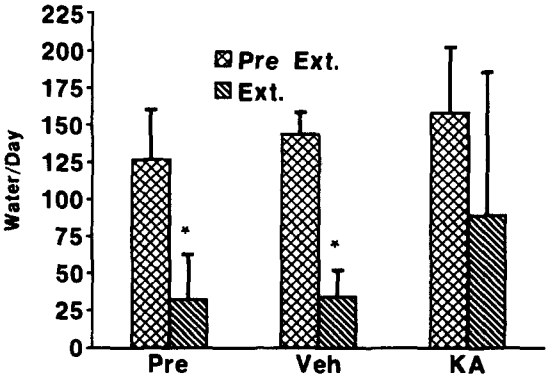

FIG. 6. Food extinction water intake. Bar graph illustrating the effects of food extinction on water intake. Details are the same as for Fig. 4. *=$p<0.001$.

procedures may provide data that result in an underestimation of the cell loss or shrinkage to the nucleus.

DISCUSSION

Kainic acid lesions of the nucleus accumbens decreased morphine self-administration while having little or no disruptive influence on responding maintained by food or water. Morphine intake was attenuated for a relatively long period (up to 121 days) following the lesion and showed no indication of recovery to pre-lesion levels before the rats were sacrificed. Since responding on the food and water lever was not significantly altered, the lesion did not appear to interfere with the rats' ability to respond. Therefore, the decrease in responding on the morphine lever was not a non-specific motoric effect. Moreover, the selective effect on morphine self-administration suggested the lesion did not affect a general reinforcement system. The lesion did not appear to alter the effects of morphine on response rates since the post-lesion dose-effect curve determination for food and water was not significantly changed. Therefore, the kainic acid lesion had a specific effect on the reinforcing efficacy of the drug. However, both the post-lesion dose-effect curve and the effects of food extinction on morphine self-administration indicate that morphine was still an effective reinforcer after the lesion.

The kainic acid lesion of the nucleus accumbens appears to have attenuated the reinforcing efficacy of morphine. The modest decrease in drug self-administration at the training dose and the much greater decrease in drug intake at the lowest dose support this conclusion. The decrease in the reinforcing efficacy of morphine was dose related. However, the lesion did not alter drug intake at the highest dose, suggesting that the effects of this dose could override the mechanisms involved in the lesion induced diminished reinforcing efficacy of the drug.

The animal's previous drug history with respect to other drug doses could also have modified the effects of the lesion. The kainic acid lesion produced a marked decrease in drug self-administration in the two rats that were exposed to a single dose of morphine before or after the lesion. This effect can be contrasted with the more modest decrease in drug intake observed at the same dose in animals with more extended training. Other studies have reported that kainic acid lesions of the nucleus accumbens also decrease the self-administration of cocaine, heroin and apomorphine [29]. Therefore, the lesion appears to produce a non-drug specific decrement in the reinforcing efficacy of stimulants and opiates. However, a quantitative differential effect on cocaine and heroin self-administration was reported to occur in rats self-administering both drugs [29].

There are several general neurobiological explanations for the effects observed in this study. The neurotoxin lesion may have altered regional blood flow or metabolism, induced changes in drug dependence or withdrawal or altered the biochemcial interaction of the drug with receptors necessary for reinforcement. The integration of data collected from neurotoxin lesion studies investigating other behaviors and brain regions suggests a more specific and perhaps more testable explanation for these effects. Recent studies have suggested that there are anatomical interconnections between the ventral tegmental area and the substantia nigra. The nucleus accumbens receives projections from both the substantia nigra and the ventral tegmental area [15]. These neuroanatomical interconnections have been shown to be behaviorally relevant. The destruction of dopamine containing neurons in the nucleus accumbens reduces spontaneous activity [12], whereas electrolytic [9,12] and kainic acid lesions increase spontaneous motor activity [8]. Therefore,

dopaminergic innervations of the nucleus accumbems appear to be excitatory to spontaneous locomotor activity while the efferents of neurons in the nucleus accumbens have an inhibitory influence [9]. Regulation of locomotor activity could occur in part via a ventral tegmental area-accumbens-substantia nigra-system. The effects of kainic acid lesions on water intake during food extinctions also suggest the possibility of a behaviorally relevant interconnection within this system. Water intake by rats is markedly decreased during periods of food deprivation. However, kainic acid lesions of both striatal neurons [22] and the nucleus accumbens (see Fig. 5) increased water intake during food deprivation. The anatomical interconnections between these areas may also be involved in reinforcement mechanisms. The response contingent electrical stimulation of the ventral tegmental area results in increased neuronal activity in the substantia nigra [18], thus indicating a neuronal involvement of these two areas related to the delivery of a reinforcing stimulus.

Recent studies have provided data indicating that dopaminergic mechanisms are involved in the reinforcing effects of opiates. Heroin conditioned place preference is attenuated following the administration of neuroleptics [1] and by dopaminergic lesions of the nucleus accumbens [25]. 6-OHDA lesions of the nucleus accumbens also increase morphine self-administration [24]. Morphine is self-administered directly into the ventral tegmental area [1] and the nucleus accumbens [16], areas extensively innervated by dopaminergic terminals. Moreover, morphine administration has been shown to increase dopamine turnover in the striatum [7,23]. Kainic acid lesions of the striatum further enhance morphine induced increases in dopamine turnover in this area, possibly through the destruction of the GABAergic striato-nigra negative feedback system [7]. Therefore several neurotransmitter systems and pathways are likely involved in the reinforcing effects of opiates and lesions of these systems should influence the conditioned and unconditioned effects of these drugs.

Kainic acid and 6-OHDA lesions of the nucleus accumbens have opposite effects on spontaneous locomotor activity and morphine self-administration. 6-OHDA lesions decrease locomotor activity and increase morphine self-administration while kainic acid lesions increase locomotor activity and appear to decrease morphine self-administration. Dopaminergic transmission is implicated in the effects of both of these lesions. 6-OHDA lesions decrease dopamine by directly destroying dopamine containing neurons. Kainic acid lesions may actually increase dopaminergic activity by destroying a negative feedback loop to the ventral tegmental area. This increased dopamine turnover may reduce the amount of morphine that is necessary to further increase dopamine levels, thus resulting in compensatory decreases in drug intake. The increase in dopamine turnover in these systems is probably only a minimal change since there was no effect on food and water maintained responding and since the increased doses of morphine could overcome this deficit.

The present data indicate that there may be specific neuronal systems that mediate the reinforcing effects of drugs. Moreover, these systems may be differentiated from systems responsible for the reinforcing effects of food and water. Efferents of the nucleus accumbens are involved in the neurobiological processes mediating the effects of morphine. Furthermore, the neurobiological process mediating the reinforcing effects of drugs appear to involve interactions between the nigrostriatal and mesolimbic dopamine systems.

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