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Dorsal as well as ventral striatal lesions affect levels of intravenous cocaine and morphine self-administration in rats

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Abstract

While the ventral striatum has long been implicated in the rewarding properties of psychomotor stimulants and opiates, little attention has been paid to the possible contribution of more dorsal regions of the striatum. We have thus examined the effects of lesions in three different striatal subregions on cocaine and morphine self-administration. Different groups of rats were trained to self-administer intravenous cocaine (1.0 mg/kg/infusion) or morphine (0.5 mg/kg/infusion) first under fixed ratio (FR) and then under progressive ratio (PR) schedules of reinforcement. Upon completion of the training, independent groups received bilateral electrolytic or sham lesions of the dorsal portion of the caudate-putamen (dCPu), the ventral portion of the caudate-putamen (vCPu) or the more ventral nucleus accumbens (NAS). Following recovery, they were tested for self-administration of cocaine (0.25, 0.5, 1.0 and 1.5 mg/kg/infusion) or morphine (0.125, 0.25, 0.5 and 0.75 mg/kg/infusion) under the PR schedule. The PR responding for each drug was significantly reduced in a dose-dependent manner following lesions of dCPu, vCPu and NAS. While the relative effectiveness of these lesions is likely to be specific to the conditions of this experiment, NAS lesions reduced self-administration of each drug to a greater extent than did dCPu or vCPu lesions.

Keywords

Cocaine self-administration; morphine self-administration; striatum; caudate putamen; nucleus accumbens; electrolytic lesion

It is well established that the rewarding properties of cocaine [6,22,26,39], opiates [8,25,39], and several other drugs of abuse [1,3,5,17,18,21,37,38] as well as natural rewards like food [33,34] and sexual contact [16] are dependent on the ventral striatum. In contrast, the dorsal striatum is thought to play an important role in stimulus-response habit learning [29,36] that may underlie one of the hallmarks of drug addiction – compulsive drug-seeking habit [11]. Consistent with such views, pharmacological inactivation of the dorsal striatum suppresses responding for cues associated with cocaine [7,12,24,27] and opiates [2]. Available

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evidence, nevertheless, suggests some involvement of the dorsal striatum in the rewarding properties of opiates [13,14], although no study to date has examined the involvement of this region in cocaine reward. To further understand the functional significance of different striatal compartments in drug reward, we have compared the effects of electrolytic lesions of the dorsal portion of the caudate putamen (dCPu), the ventral portion of the caudate putamen (vCPu) and the nucleus accumbens (NAS) on intravenous self-administration of cocaine and morphine maintained under a progressive ratio (PR) schedule of reinforcement [20]. A PR paradigm was used to avoid some of the difficulties of interpretation associated with traditional rate of drug self-administration paradigms [23,32].

The current experiments consisted of three phases: pre-lesion drug self-administration training, striatal lesion, and post-lesion drug self-administration testing. Ninety-two male Long-Evans rats (Harlan Sprague Dawley, Indianapolis, IN), weighing 300–350g at the time of surgery, were used. They were individually housed in a reverse cycle room (12-h light 12-h dark) and were tested during the dark period. Rats were randomly assigned to one of eight experimental groups defined by drug self-administration (cocaine or morphine) and lesion (dCPu, vCPu, NAS or sham) type, and were surgically implanted with an i.v. catheter. All procedures were conducted according to an approved IACUC (University of Chicago) protocol. Twelve rats were dropped because their catheters became non-patent or developed leaks through the course of the experiments.

Pre-lesion drug self-administration training began 3 days following surgery. Drug self-administration was conducted in fifteen operant chambers each equipped with a lever, a stimulus light and a liquid swivel system. Cocaine hydrochloride and morphine sulfate were obtained from Sigma, Inc. (Saint Louis, MO) and the National Institute on Drug Abuse (Bethesda, MD), respectively, and were dissolved in sterile saline (0.9% w/v). The training sessions were held daily and lasted 4 hours. In these sessions, reinforced presses on the lever delivered an i.v. infusion of drug (cocaine, 1.0 mg/kg/infusion or morphine, 0.5 mg/kg/infusion). Drug infusions were made in volumes of 0.07–0.13 ml/infusion (depending on the weight of the animals) at a rate of 1.6 ml/min. A cue-light above the lever was illuminated along with each infusion and remained illuminated for 15 seconds during which additional lever presses were recorded but did not lead to further infusions. An experimenter-delivered priming infusion of drug was given at the beginning of each training session. The initial training reinforcement schedule used was FR1; it was increased to FR2 once animals administered an additional 19 infusions within a 4 hour session for 2 consecutive days. Rats were then again required to self-administer an additional 19 infusions within a 4 hour session under FR2 for 2 consecutive days. Each FR training session lasted until the animal self-administered 19 infusions or until 4 hours elapsed. The number of training days was recorded and used for statistical analysis. Five animals did not satisfy the criteria within 14 days and were excluded from the study. Following training under the FR schedules, rats were trained under a PR schedule [20] for 3 days. Under this schedule, the number of responses required to obtain each successive infusion of the drug increased progressively. The number of lever-presses required to obtain each of the first 15 infusions was as follows: 1, 3, 9, 18, 30, 47, 71, 103, 145, 201, 274, 369, 493, 654, and 862. Each PR session lasted 4 hours or until 1 hour elapsed without a drug infusion. Priming infusions were not given during these sessions.

Upon completion of the training phase, rats received bilateral electrolytic lesions of the striatum: a Radionics Model RFG-4 lesion maker (Radionics, Burlington, VT) was used to deliver a 70°C stimulation for 120 seconds. The uninsulated tips of the monopolar probes were 0.4 mm in diameter by 0.4 mm in length. Two radiofrequency stimuli were applied per unilateral lesion at two different positions differing in D/V coordinates. The tips of the probes were aimed at dCPu (A/P = +1.6 mm, M/L = $\pm$ 2.4 mm, D/V = -4.4 and -5.0 mm),

vCPu (A/P = +1.6 mm, M/L = ± 2.4 mm, D/V = -5.8 and -6.4 mm) or NAS (A/P = +1.4 mm, M/L = ± 1.4 mm, D/V = -7.6 and -8.2 mm). The choice of these coordinates was influenced by the earlier findings of Glick and colleagues [13,14] showing that morphine self-administration is reduced following electrolytic lesions of the caudate nucleus, an area in that report roughly corresponding to the dCPu site in the present study, rather than by more contemporary neuroanatomical evidence of dorsolateral to ventromedial functional heterogeneity within the striatum [28]. For sham lesions, probes were lowered to the dCPu (5 rats), vCPu (5 rats) or NAS (6 rats), but stimulation was not applied. After the operation, rats were kept in the colony room for a 7 day recovery period. Three rats died following the lesion. Thus, all their data were excluded from the study.

Following recovery, all rats underwent post-lesion drug self-administration testing. The experimental procedures used in this phase were the same as those used in the pre-lesion PR training phase with the exception of the drug doses tested: four different doses of each drug were examined. Initially, rats were tested with the lowest dose (0.25 mg/kg/infusion cocaine; 0.125 mg/kg/infusion morphine) for two consecutive days. This was followed by testing with the second dose for two consecutive days (0.5 mg/kg/infusion cocaine; 0.25 mg/kg/infusion morphine), the third dose for two consecutive days (1.0 mg/kg/infusion cocaine; 0.5 mg/kg/infusion morphine), and the highest dose for two consecutive days (1.5 mg/kg/infusion cocaine; 0.75 mg/kg/infusion morphine). For each of the four doses, the total number of lever presses emitted across the two days of testing was averaged for each rat and these averages used for the statistical analyses.

Upon completion of all experimental procedures, the rats were anesthetized with sodium pentobarbital and received intracardiac perfusion of saline and 10% formalin. The brains were removed and coronal sections (40 μ m) were mounted onto gelatin coated slides, stained with cresyl violet, and examined under a microscope to identify the location and extension of the lesions. The size of each lesion (per hemisphere) was determined by examining the coronal section with the most extensive damage per plate using a scale. Lesions were mostly confined within the boundary of an intended target, although some variations in size were evident. Thus, pre-determined histological criteria were used to standardize the extent of lesions across all rats in all lesion conditions. The criteria for retention within each lesion condition were: (1) overall extent and location within the boundary of the intended target and (2) vertical length within a range of 1.2–1.8 mm. A total of seven animals (three from dCPu, two from vCPu, and two from NAS groups) were excluded because one or both of their lesions did not satisfy the criteria. The final number of rats retained for each of the eight experimental groups was as follows: cocaine-dCPu (11), cocaine-vCPu (9), cocaine-NAS (10), cocaine-sham (6), morphine-dCPu (11), morphine-vCPu (11), morphine-NAS (9) and morphine-sham (10).

Cocaine and morphine self-administration data were analyzed separately. The data obtained during the pre-lesion training under FR1 and FR2 (days to criteria) were analyzed with one-way between analyses of variance (ANOVA) with lesion type (4 levels: dCPu, vCPu, NAS or sham lesions) as the between factors. The data obtained during the pre-lesion training under the PR schedule (total numbers of lever-press) were analyzed with one-way between one-way within ANOVA with lesion type (4) as the between factor and days of training (3) as the within factor. The data obtained during post-lesion testing under the PR schedule (the average for each rat of the total number of lever presses emitted on each of the two test days for each of the 4 doses) were analyzed with one-way between one-way within ANOVA with lesion type as the between factor (4) and dose (4) as the within factor. The total number of lever presses rather than break point (final ratio achieved) was used for statistical analysis because the latter was derived by definition from an exponential function [20]. Post-hoc

comparisons were made when statistically appropriate. All analyses were conducted with Statistica (1999 edition) statistical software.

No group differences were observed prior to the striatal lesions. The ANOVA conducted on the data obtained during training for cocaine and morphine self-administration revealed no significant group differences in the number of days to reach the training criteria or in the number of responses under the PR schedule. The average number of days ($\pm$ SEM) needed to achieve the FR1 and FR2 training criteria together was 8.22 ($\pm$ 0.22) for cocaine and 7.58 ($\pm$ 0.31) for morphine. The average number ($\pm$ SEM) of lever presses across the three days of PR training was 95.23 ($\pm$ 13.68) for cocaine and 21.71 ($\pm$ 1.82) for morphine. The PR schedule used was originally developed to study the self-administration of psychomotor stimulants and relies on an exponential function to generate a requirement for an increasing number of responses for each successive infusion [20]. This, in turn, may have accounted for the lower levels of lever-pressing for morphine, relative to cocaine, observed in the current study. However, despite these lower levels of responding, this schedule nonetheless produced the expected dose-dependent effects with morphine: as with cocaine, higher break points were attained with higher doses in the sham lesion rats.

Lesions of all striatal subregions (dCPu, vCPu, or NAS) decreased PR responding for cocaine (Figure 2A) and morphine (Figure 2B). For cocaine, there were significant effects of lesion [$F_{3,32}=5.50$, $p<0.01$] and dose [$F_{3,96}=9.76$, $p<0.001$] and a significant lesion X dose interaction [$F_{9,96}=2.88$, $p<0.01$]. Similarly for morphine, there were significant effects of lesion [$F_{3,37}=7.98$, $p<0.001$] and dose [$F_{3,111}=14.25$, $p<0.001$], but the lesion X dose interaction did not achieve statistical significance [$F_{9,111}=1.02$, ns]. Post-hoc Tukey HSD tests revealed that rats with dCPu, vCPu, or NAS lesions lever-pressed significantly less than the sham lesion controls for cocaine ($p<0.05$ – 0.001) and morphine ($p<0.01$ – 0.001) in a dose-dependent manner.

These findings complement earlier studies [13,14] to suggest that lesions not only of the ventral (NAS) but also of the dorsal (dCPu and vCPu) striatum decrease the rewarding impact of cocaine and morphine. It is unlikely that lesion-induced motor deficits can account for the decreased PR responding observed following lesions of the caudate putamen in the present experiments as dorsal striatal lesions fail to affect food self-administration maintained under a PR schedule [9]. The present results are also consistent with the finding that rats will work for electrical stimulation of the ventral as well as the dorsal striatum, and that there are no major parametric discontinuities in effectiveness of brain stimulation reward at the borders of these structures [19]. Indeed, rats will work for electrical stimulation at the level of the cells of origin of both the mesocorticolimbic and the nigrostriatal dopamine systems [4] projecting respectively to the ventral and dorsal striatum [1,3,14,18]. Taken together with the present results, these findings suggest that drug reward is mediated by a dorsal-ventral continuum of the striatum.

In the current study, the lesions at the three sites were similar in size, but more ventral lesions caused stronger depression in responding. This may be due in part to the fact that compared to restricted lesions of the larger dCPu and vCPu, a larger proportion of the relatively smaller NAS was damaged by the restricted lesions of this site. It is also possible that lesions of the dCPu and vCPu could have reduced responding to a greater extent if rats in the present experiments had been afforded substantially more training. It has been argued that high levels of training lead to the progression of drug-seeking from initially voluntary to compulsive and the increasing control over behavior by drug associated cues via stimulus-response habits mediated by dorsal striatal mechanisms [10,11]. It remains to be determined what neuroadaptations dorsal striatal structures might undergo as they evolve from sites mediating drug reward to sites mediating stimulus-response habits. These neuroadaptations

need to be deciphered as drug associated cues represent the only external embodiment of central drug effects [30,31,35], making an understanding of how they control behavior critical.

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Figure 1. Illustration of the extent of the striatal lesions in rats that self-administered cocaine (A) and morphine (B). The smallest (black fill) and largest (gray fill) lesions of dCPu, vCPu, and NAS are depicted. The line-drawings are modified from Paxinos and Watson [15]. The numbers to the right indicate distance from bregma. The size of the lesions in each hemisphere was determined by examining the coronal section with the most extensive damage per plate.

Figure 2.

Bilateral lesions of the dCPu, vCPu, or NAS reduced subsequent cocaine (A) and morphine (B) self-administration under a progressive ratio schedule of reinforcement. Data are shown as group mean (+SEM) total number of lever presses for each of the four different doses of cocaine and morphine tested. Responding was reduced for both drugs in a dose-dependent manner. *, $p < 0.05$ – 0.001 , significantly different from sham lesion controls as determined by post hoc Tukey HSD comparisons following significant ANOVA. $n = 6$ – 11 /group.