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Effects of Lesions of the Caudate Nucleus on Morphine Dependence in the Rat

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LINSEMAN, M. A. *Effects of lesions of the caudate nucleus on morphine dependence in the rat.* PHARMAC. BIOCHEM. BEHAV. 5(4) 465–472, 1976. — Naloxone-precipitated withdrawal and oral self-administration of morphine were compared in morphine-dependent caudate-lesioned and sham animals, and drug-naive caudate-lesioned and sham animals. The lesion failed to suppress any signs of withdrawal in the dependent-lesioned animals as compared with the shams. However, the dependent-lesioned animals self-administered less morphine than their sham controls. The withdrawal results differed from others previously reported and it was hypothesized that the possibility of development of processes compensatory to the lesion among animals of this experiment, might account for the difference. The results were also discussed in relation to possible dissociation of mechanisms governing physical dependence and self-administration.

Caudate nucleus Striatum Morphine Opiate Dependence Withdrawal Naloxone Self-administration

THERE are now several converging lines of evidence to suggest that the striatum may be an important site of action of morphine in the brain. The highest proportion of opiate receptor binding is reportedly to be found in the striatum in rat [17,20]. Acute behavioral effects of morphine have been reported to be mediated via the striatum [1,2]. Neurochemically, acute administration of morphine and administration of naloxone to morphine-dependent animals have been found to alter neurotransmitter levels in the striatum [14, 15, 24]. Additionally, there is evidence that the behaviorally reinforcing effects of morphine may be mediated via this area of the brain [8,22]. There were, however, no neuroanatomical studies of the role of the caudate nucleus in regard to chronic behavioral effects of morphine, until Glick *et al* [11] recently reported that lesions of the caudate nucleus suppressed morphine withdrawal and morphine self-administration, two indices of morphine dependence, in the rat. The present experiment was also designed to assess the effect of caudate lesions on morphine dependence, though slightly different methods were chosen. The results have implications for the generality of the Glick *et al.* findings, which will be enlarged upon in the subsequent discussion.

METHOD

Animals

Sixty-four male Sprague-Dawley rats weighing approximately 400–450 g at the time of surgery were used in the experiment. These were randomly divided into 4 groups: Group 1, initially comprising 20 animals, received extensive bilateral caudate lesions and were made progressively dependent on morphine, eventually receiving a daily injection of 200 mg/kg (lesioned-morphine, LM Group); Group 2, also initially 20 animals, also underwent surgery for bilateral caudate lesions, but received only saline injections (lesioned-saline, LS Group); Group 3, 12 animals, received sham surgery and were made dependent upon morphine (intact-morphine, IM Group); Group 4, 12 animals, were sham-operated and received saline injections (intact-saline, IS Group).

Surgical Procedures

Animals were initially anesthetized with a dose of 50 mg/kg pentobarbital. Lesions were made via 0.010 in. dia. platinum-iridium electrodes insulated except for 0.5 mm at the tip. The cranium was removed bilaterally to allow penetration of the brain by the lesioning electrode at several loci within the caudate nucleus. The coordinates of these loci, calculated perpendicular to bregma from the skull surface, were: A +1.5, L 2.2, H 5.5 and 6.5 mm; A +1.5, L 3.5, H 6.0; A +0.5, L 2.2, H 6.0; and A +0.5, L 3.5, H 5.5. A lesion was made at each point by passage of a direct current of 2 ma for 20 sec. The lesions were monopolar with the second electrode attached to the animal's ear. More extensive damage was made in a small number of animals in each group by including similar bilateral lesions at A −1.0, L 3.9, H 5.5 as well. Sham animals were similarly treated except for insertion of the electrode.

Postoperatively, lesioned animals typically did not eat or drink, and required extensive care. This consisted initially of intragastric intubation of nutritional liquids (Metrecal, Enfalac) followed by feeding of wet mash, until eating of pellets and drinking resumed. This required from 3–24

days. A total of 7 animals, 3 in Group 1, and 4 in Group 2 died postoperatively. All animals were allowed a minimum of 23 days to recover before the beginning of morphine injections. Animals were fed so as to maintain their weights at 350–450 g.

Induction of Dependence

Morphine-treated animals were made dependent by a series of single daily intraperitoneal injections administered at approximately 9:30 a.m. beginning with a dose of 10 mg/kg. The dose was increased daily by 10 mg/kg up to 100 mg/kg, then every other day by 10 mg/kg until animals received 200 mg/kg/day. They were then maintained on single daily injections of 200 mg/kg for an additional 13 days before withdrawal tests were begun. Saline animals received equal volumes of 0.9% saline on the same injection schedule.

Withdrawal Testing

Withdrawal was precipitated by an intraperitoneal injection of 4 mg/kg naloxone hydrochloride. Animals were tested individually, 4 per day, beginning approximately 1 hour after the last maintenance injection and ending approximately 6 hours later. The order of testing within a day, as well as over days, was balanced across the 4 groups such that an equal proportion of animals in each group were tested after similar morphine-naloxone intervals, and after the same amount of morphine experience. A scoring procedure similar to that of Bläsig *et al.* [3] was used. An initial reading of rectal temperature was taken, following which the rat was placed into a Plexiglas box (17 × 22 × 23.5 cm) for observation. The observation period started 10 minutes prior to the naloxone injection and continued for 30 min following the injection. At the end of this time rectal temperature was again recorded.

The incidence of the following behaviors was counted. Circling (complete circles within the box, an index of locomotor activity); Rearing (standing on hind legs, an index of exploratory activity); Jumping (leaping onto the edge of the box, four feet off the ground at same time); Wet Dog Shakes; Teeth Chattering (episodes); Writhing (abdominal stretching).

The presence of the following signs was checked every 10 min: Scream-on-Touch, Hostility-on-Handling, Ptosis, Eye Twitching, Rhinorrhea, Lacrimation, Diarrhea, Penile Erection (ejaculation, presence of discharge), Salivation (or licking movements).

Oral Self-Administration Test

Animals were maintained on 200 mg/kg morphine for an additional 8 days following the last withdrawal test and prior to the self-administration test. The oral self-administration test was similar to those described previously by Cappell and Le Blanc [6] and Trafton and Marques [23]. The animals were subjected to 8 successive 5-day cycles as follows: Day 1, water deprivation, and the regular 200 mg/kg injection of morphine; Day 2, a single morphine solution of 0.5 mg/ml concentration to drink (forced morphine drinking), no drug injection (animals were therefore 24 hr drug-deprived as well as 24 hr fluid-deprived at the beginning of the day); Day 3, a single tube of water to drink placed on the side of the cage opposite to that of the morphine the day before, and a maintenance injection of morphine (i.e., such that the maintenance injection plus the amount of morphine drunk on Day 2 were equivalent to a dose of 200 mg/kg – this was done so the rats could not voluntarily withdraw from morphine); Day 4 choice drinking between one tube of water and one tube of morphine, placed in their respective positions of Days 2 and 3 (these positions were reversed on alternate cycles), no drug injection; Day 5, 2 tubes of water only, a maintenance injection of morphine as on Day 3. Fluid intake readings and refilling of tubes were done daily in the morning just prior to injection time. A summary of these procedures is found in Table 1.

TABLE 1

SUMMARY OF PROCEDURES

Day	Procedure
1-19	Surgery
20-42	Additional recovery time.
43-72	Daily A.M. injections, morphine animals receiving increasing doses of from 10 mg/kg to 200 mg/kg as described in text.
73-85	Additional daily A.M. injections, morphine animals receiving 200 mg/kg.
86-102	Withdrawal testing, daily injection schedule maintained.
103-110	Additional daily A.M. injections.
111-150	Oral self-administration test.
151 and following	Histology.

Histology

At the end of the self-administration test, all lesioned animals were given an overdose of pentobarbital, and perfused through the heart with physiological saline followed by a 10% formalin solution. The forward part of each brain was sliced into 50 μ sections. Alternate sections were mounted on slides and stained with a cresylecht violet stain.

Statistical Analysis

Since often the data were markedly skewed, the Mann-Whitney U-Test was used to compare groups in regard to temperature change, counted symptoms and self-administration. Fisher's Exact Test was used to compare groups in the case of checked sumptoms. If the dependence manipulation were effective, Group IM would differ from Groups IS. If the lesion altered the effect, Group LM would differ from Group IM. A significant difference was considered to be one with a $p \leq 0.05$ by a 2-tailed test.

RESULTS

Histology

Lesioned animals sustained varying amounts of damage including almost total caudate destruction, to destruction primarily of the ventral area of the nucleus (see Fig. 1). Occasionally the lesions also spread slightly to the dorsal preoptic area and adjacent cortex. When the results of the subsets of animals with the most extensive damage were compared to those of their respective lesion groups as a

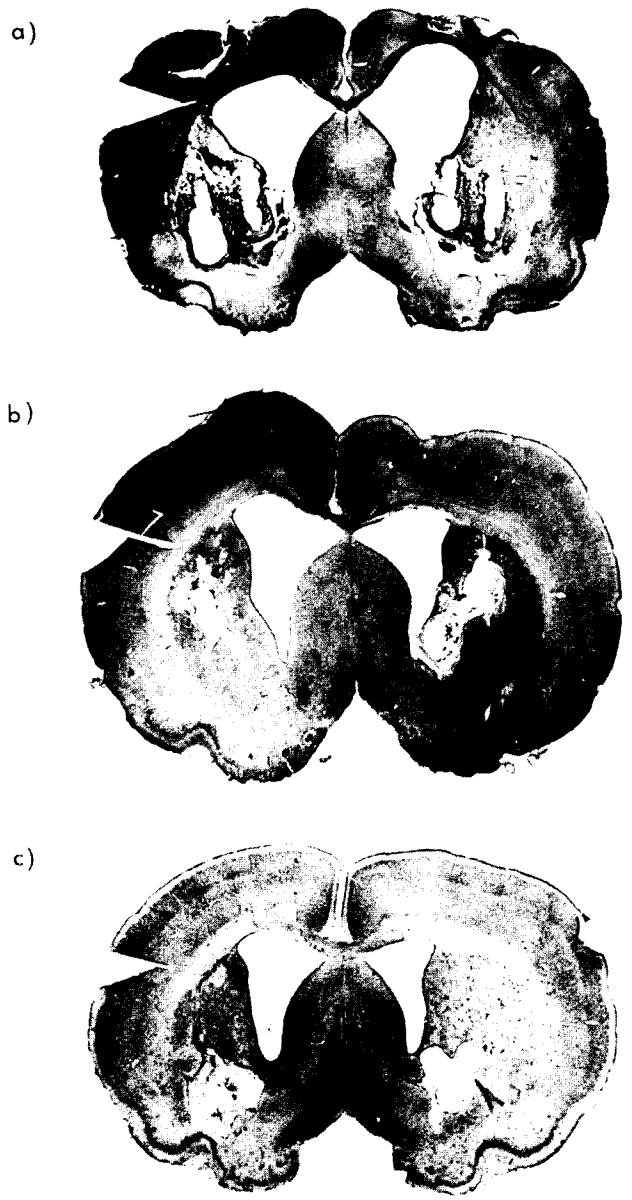

FIG. 1. Histological sections from three animals of the LM group, showing (a) almost total caudate destruction (b) substantial caudate destruction and (c) damage confined mostly to ventral caudate. The three types of lesions were approximately equally represented within the two lesion groups.

whole, however, no consistent differences were found. Accordingly, all animals were retained in Groups LM and LS for statistical analysis.

Morphine Injections

A number of animals died over the course of the experiment, often of apparent morphine toxicity. These included 8 animals before withdrawal testing (5 in Group LM, 2 in Group LS and 1 in Group IM), and an additional 6 animals before the completion of the self-administration test (3 in Group LM and 3 in Group IM). An additional 3 animals in Group LM could not be included in the self-administration test as they had reverted to eating only mash. Although the proportion of casualties in the lesioned morphine group was the largest, it did not differ significantly from that in the intact morphine group. The casualties in the LM Group, however, tended to be those animals with the most extensive lesions, such that no LM animals with lesions as represented in Fig. 1 (a) completed the final self-administration test, though several had completed withdrawal testing. When the withdrawal data of only those animals who completed the self-administration test as well were compared to the total who completed withdrawal, the results did not differ. Accordingly, the withdrawal results presented are for the combined number of animals.

Naloxone-Induced Withdrawal

Rectal temperature. The mean changes in rectal temperature for all groups from before to 30 min following naloxone are shown in Fig. 2. The change was significantly greater for Group IM than Group IS and for Group LM than Group LS, but Group LM did not differ from Group IM. That is, there was a significant drug effect, but the lesion had no effect.

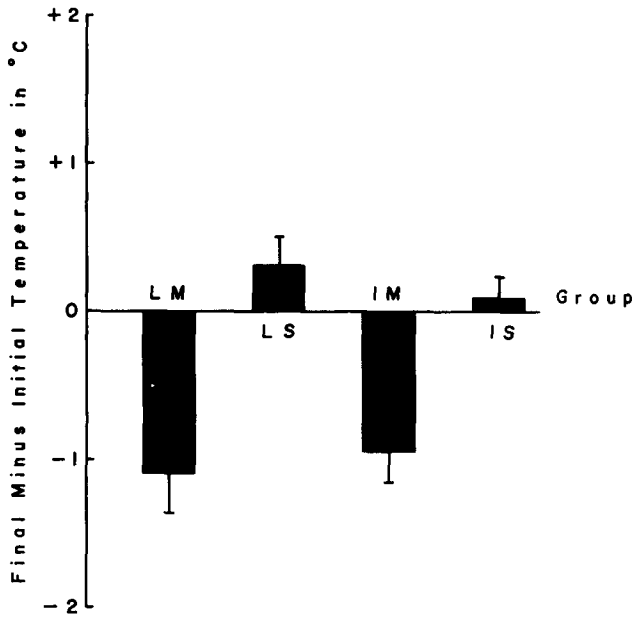

FIG. 2. Mean change in rectal temperature as measured 10 min prior to and 30 min following naloxone administration. The narrow bars above the histograms indicate the standard error of the mean. LM = Lesioned-Morphine, n = 13; LS = Lesioned-Saline, n = 16; IM = Intact-Morphine, n = 10; IS = Intact-Saline, n = 12.

Counted symptoms. The mean number of times per animal these symptoms occurred is illustrated in Fig. 3. Group IM differed significantly from Group IS in regard to jumping, teeth chattering, and wet dog shakes. The difference in writhing approached significance ($p<0.12$). Although often the mean frequency of symptoms in Group LM exceeded that of Group IM, the differences were not significant, probably due to the increased variability in the LM group. However, with regard to teeth chattering ($p<0.10$) and writhing ($p<0.06$) they approached sig-

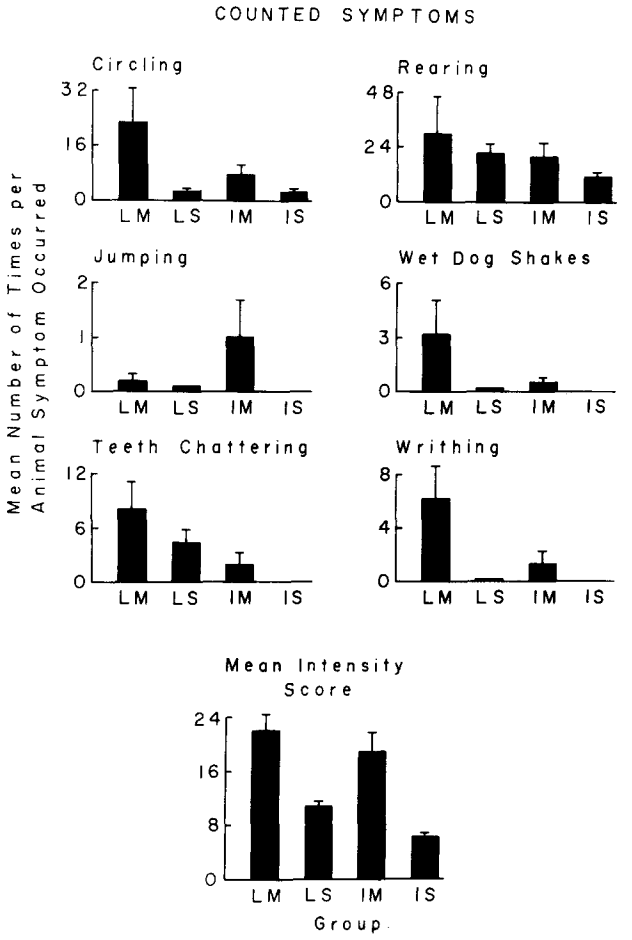

FIG. 3. Histograms showing, for each of the withdrawal symptoms that were counted, the mean number of times in each group the symptoms occurred, and the mean intensity scores (see text) for animals in each group. The narrow bars indicate the standard error of the mean. Key: same as above.

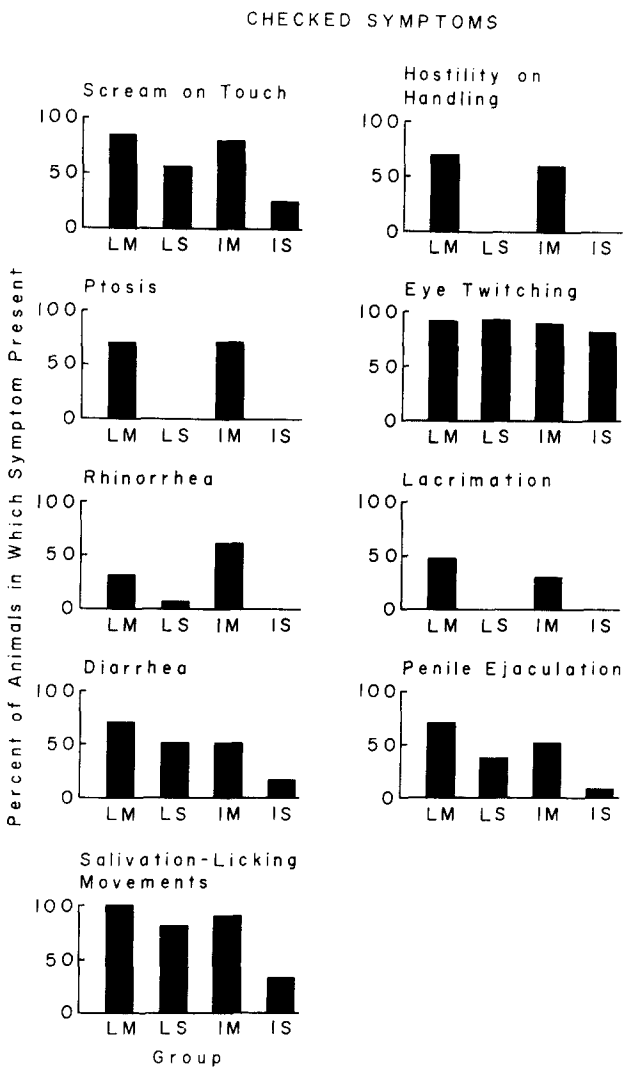

FIG. 4. Histograms showing, for each of the withdrawal symptoms whose occurrence was checked the percent of animals in each group in which they were present. Key: same as above.

nificance, the symptoms being more frequent among lesioned animals. Therefore, in several cases, there was a significant drug effect, but there was no evidence that it was diminished by the lesion. Group LS differed significantly from Group IS with regard to teeth chattering but this difference appeared to be a result of the lesion alone as it was present even before administration of naloxone.

Checked symptoms. The percent of animals in each group showing each of these symptoms is illustrated in Fig. 4. Group IM differed significantly from Group IS with regard to scream-on-touch, hostility-in-handling, ptosis, rhinorrhea, diarrhea, and salivation. In no case did Group LM differ from Group IM; that is, there was often a significant drug effect, but again the lesion did not alter it.

Overall intensity score. In addition, an overall score of the intensity of withdrawal was computed by adding one point for each symptom occurring within each 10 min period postnaloxone (15 symptoms × 3 10-min periods, allowing a maximum score of 45 per animal). This considered both the total number of symptoms an animal manifested and the duration of time in which they were present (see Fig. 3). The mean intensity score for Group IM was greater than that of Group IS, and that of Group LM, greater than Group LS. There was no difference between Groups LM and IM. In addition, the Group LS score was greater than that of Group IS but this difference was primarily due to the increased frequency of teeth chattering in the LS Group, which appeared to result from the lesion alone.

Order of Testing. Although the order of testing for withdrawal on each day was balanced across groups, it is possible that different symptoms might predominate when withdrawal is precipitated at different intervals following the last morphine injection. The lesion might have an effect at a particular interval and such a difference would be obscured by combing the data. Accordingly, animals of the IM Group who were tested at the first two intervals were compared to those tested at the final two intervals with regard to all symptoms. There was a tendency among several symptoms toward greater frequencies at the longer

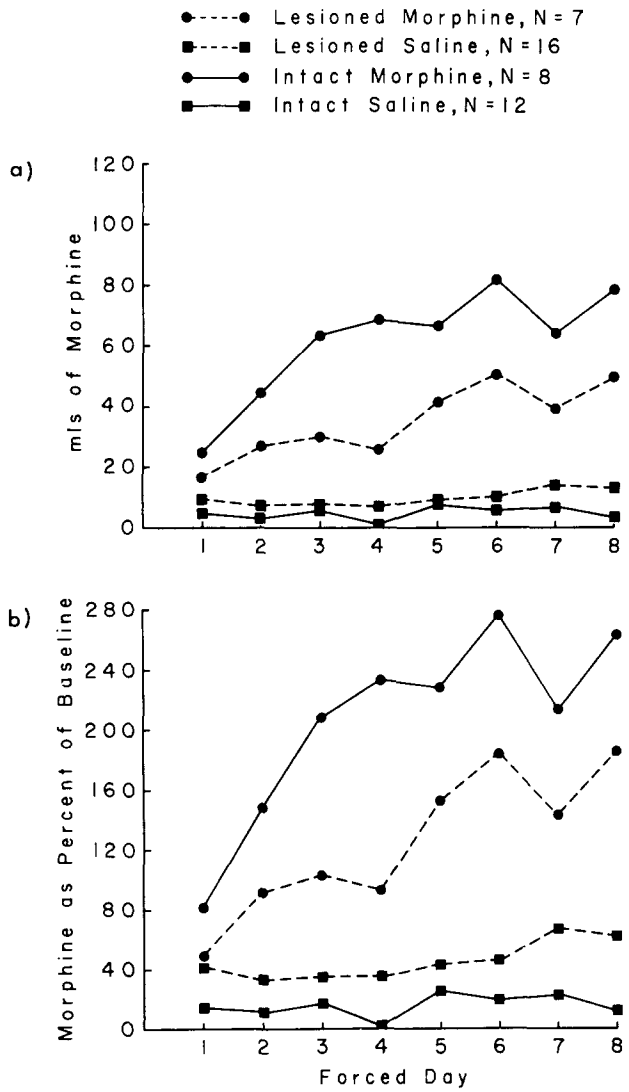

FIG. 5. Mean amounts of morphine drunk by each group on forced morphine days, expressed (a) as absolute amounts and (b) as a percent of the mean amount of water drunk on the 5 days immediately preceding morphine treatment.

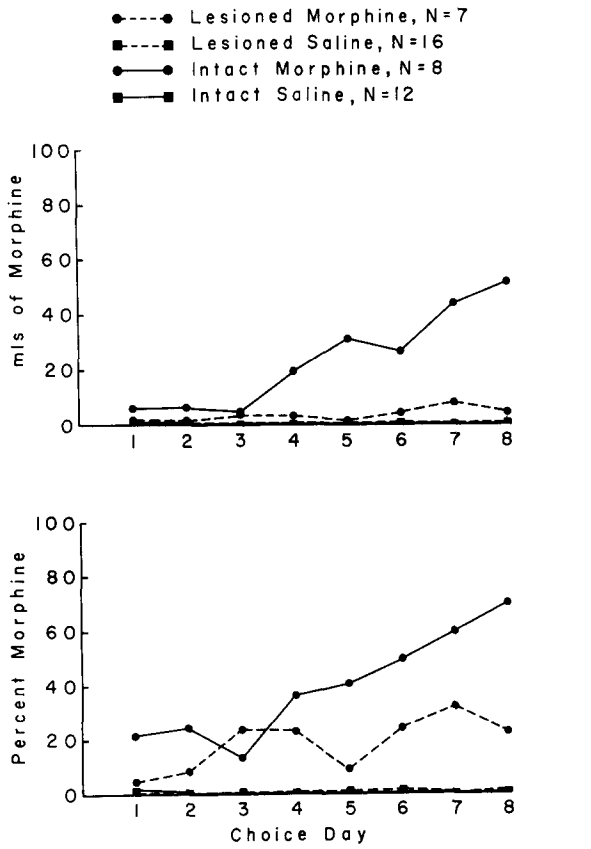

FIG. 6. Mean amounts of morphine drunk by each group on choice days expressed (a) as absolute amounts and (b) as a percent of the total amount of fluid consumed on that day. It is difficult to discriminate the curves of the LS and IS Groups from the abscissa as the amounts drunk by them were zero, or approximately zero, on all choice days.

intervals but only in the case of diarrhea and the total intensity score was it significant. A similar comparison among animals of the LM Group had similar results with the exception that there was no significant difference in total intensity scores at early and late intervals. However, the total intensity scores of the LM Group at the early interval was not so great as to be significantly different from those of the IM animals.

Oral self-administration test. The results of the 8 days of forced morphine drinking are illustrated in Fig. 5, those of the choice drinking days, in Fig. 6. On the forced days, the morphine drunk is shown both in absolute terms, and as a percent of the mean amount of water drunk on the 5 days that immediately preceded morphine treatment, to correct for possible overall differences in fluid consumption. Similarly, morphine drunk on choice days is shown both as absolute amounts and as percent of total fluid consumption on the choice days.

Statistically, on forced drinking days, in regard to absolute amounts of morphine (data in Fig. 5a), Group IM consistently drank more than Group IS: Group LM drank more than Group LS on Days 2, 3, 5, 6, and 8 and over the 8 days combined. Group LM, however, also drank less than Group IM on Days 3, 4, 5, 6, 7, and 8 and over the 8 days combined.

When the percent scores (Fig. 5b) were considered, Group IM still consistently drank significantly more morphine than Group IS. Group LM, however, drank more than Group LS on Days 5, 6, and 8 and over the 8 days combined; and Group LM, less than Group IM on Days 3 and 7 and over the 8 days combined.

On choice days, in regard to absolute amount of morphine drunk (Fig. 6a), Group IM drank more than Group IS on Days 2 through 8 and over the 8 days combined; Group LM, more than Group LS on Days 2, 4, 7 and over the 8 days combined; but Group LM less than Group IM on Days 5, 6, and 8 and over the 8 days combined. These differences remained when the percent scores (Fig. 6b) were considered with the exception of the difference between the LM and IM groups on Day 6.

In summary, the morphine-treated animals drank more morphine than the saline-treated animals — there was a

significant drug effect. However, lesioned morphine-treated animals drank less morphine than the intact morphine-treated animals.

DISCUSSION

Lesions of the caudate nucleus did not alter naloxone-induced withdrawal in morphine-dependent rats, but they did suppress oral self-administration of morphine in the same dependent rats. These results appear different from those of Glick *et al.* [11] in regard to withdrawal but are consistent with those in regard to self-administration.

Lesions sustained by animals of this experiment were generally larger than those described by Glick *et al.* so that the discrepancy in withdrawal results would not appear to be due to size of lesion, larger lesions generally resulting in greater, not lesser, effects [11]. The control morphine-treated animals showed significantly more withdrawal symptoms than did the saline-treated animals, indicating the drug manipulation had been effective. However, particularly in regard to counted symptoms, the absolute frequencies were often small indicating that a less than maximal withdrawal syndrome was induced. Nevertheless, if a manipulation were to reduce the intensity of withdrawal one would expect it to be even more apparent at a developing rather than at an asymptotic phase of withdrawal when the overall intensity could be so great as to mask the effect. The lesion, in this experiment, however, never reduced the intensity of withdrawal – there was even some indication it may have enhanced it. There is in fact a recent report that pimozide (a dopamine receptor blocker) enhanced some symptoms of morphine withdrawal [8].

This experiment, however, also differed from that of Glick *et al.* [11] in that a greater length of time of recovery from the lesion was allowed prior to morphine administration, morphine was administered over a greater period of time, and there was, consequently, a greater length of time between lesion and withdrawal. The manner in which morphine was administered was also different – i.e., discrete injections of increasing doses over at least six weeks, as opposed to continuous exposure for three days.

Wikler [25] has recently drawn a distinction between acute and chronic lesions, referring to the amount of time prior to testing they are made. He suggested that in the case of chronic lesions, it was possible that a restitution of function might occur. Since the time between lesion and withdrawal was much greater in this experiment than in that of Glick *et al.*, it is possible that the longer interval was sufficient for some mechanisms, compensatory to the lesion, to have developed in the brain resulting eventually in the full expression of the withdrawal syndrome. The possibility of development of compensatory processes has been raised by others. Blasig *et al.* [4], in an analogous neurochemical study, reported that, whereas acute depletion of catecholamines just prior to naloxone-induced withdrawal suppressed withdrawal symptoms, chronic depletion during induction of dependence did not. They hypothesized that the formation of additional receptor sites during the morphine experience may have accounted for the withdrawal in spite of the chronic lesion.

Wikler [25] also distinguished between acute and chronic dependence – the former resulting from one exposure to the drug (continuous infusion, pellet implant), the latter, from multiple exposures over some period of time. Martin and Eades [19] reported there were quantitative and qualitative differences in precipitated withdrawal between acute and chronically dependent dogs, and hypothesized that different mechanisms may be responsible for these syndromes. Thus, it is possible that these results and those of Glick *et al.* may differ not only because compensatory mechanisms may have developed among animals of this experiment, but also because the mechanisms of dependence initially induced may have been different as well.

It is interesting to note that some of the symptoms of withdrawal occurred even in the lesioned-saline animals. It was observed here and previously [18] that some symptoms – eye twitching, licking, penile discharge – sometimes occur when naloxone is given to sham saline animals. Stimulation of the caudate nucleus reportedly has inhibitory effects [5,16] and a lesion could therefore result in some release from inhibition. It is possible, therefore, that the withdrawal symptoms in the LS group, especially teeth chattering, could be a result of an increased responsiveness of the animals in the absence of normal caudate inhibition.

Although the lesion did not suppress withdrawal, it did reduce oral self-administration of morphine by the morphine-pretreated animals relative to the intact morphine animals. This difference was not a result of overall differences in fluid consumption between the two groups since their baseline water intake was not different (LM, 28.2 ml/day; IM, 30.8 ml/day; n.s.), and the difference was still significant when the percent scores were considered. The lesioned-saline animals who completed the self-administration test, however, had a significantly lower baseline (LS, 21.9 ml/day; IS, 28.4 ml/day; $p<0.05$) than did the intact-saline animals but this was not reflected in differences in morphine consumption between the groups. The baseline consumption levels of LM animals who completed withdrawal, however, was 23.7 ml, significantly less than the IM baseline, and comparable to the LS group. However, as mentioned previously, LM animals with the most severe lesions (and consummatory deficits) did not complete the self-administration test, such that the baselines of the remaining LM animals and the IM animals were not different.

It could be, however, that the reduced intake of morphine in lesioned animals might simply result from increased motor incapacitation – that is, that the effects of morphine and lesion might summate so as to make the LM animals less capable of performing the motor acts necessary for drinking. This would be difficult to refute on the basis of only the forced days data. However, it could not account for the low levels of morphine consumed by the LM animals on choice days, since they had already previously shown they were, in fact, capable of drinking several times that amount on the forced days.

It is also possible that the lesioned animals might drink less morphine than the intact animals if the lesion made them more sensitive to the aversive properties of the morphine solution. This could manifest itself in either of two ways. First, the lesioned animals could be more sensitive to the unconditioned aversive properties of the solution, i.e., the bitter taste. This would not seem to be true since there was no significant difference in morphine consumption between the lesioned and their respective control groups on first exposure to morphine (Forced Day 1), which could be considered largely a measure of their response to the unconditioned aspects of the solution. The

significant differences between groups LM and IM appeared on later exposures when the animals would have had time to associate the taste of the solution with its pharmacological effect.

Alternatively, the lesioned animals could have developed a greater conditioned aversion to the morphine solution than the intact animals, or it may not have been attenuated as greatly by pretreatment with morphine. The latter is possible since the oral self-administration procedure has characteristics of a taste aversion paradigm – the morphine solution is a novel solution, and the psychoactive effects would presumably follow its ingestion. In addition, it has been shown that pretreatment with morphine can attenuate such an aversion [7]. In this experiment, it is difficult to tell whether a conditioned taste aversion played a part since there is no evidence of it among animals of the non-pretreated LS and IS groups; the possibility may have been overshadowed by the effects of unconditioned properties of the solution. That the increased consumption of morphine among the pretreated LM and IM groups is not simply the reversal of a conditioned taste aversion is attested to by the fact that final consumption levels not only exceeded the initial morphine consumption levels, but the daily water baselines as well.

Reduced oral self-administration of morphine in previous experiments has been interpreted as reflecting a decreased level of dependence [6], a deficit in avoidance behavior [23], decrease in reinforcement properties of the solution [12,26] or increased sensitivity to the rewarding properties of the solution [12]. Glick *et al.* [11] interpreted decreased intravenous self-administration in caudate animals as increased sensitivity to the reinforcing properties of the morphine, since lesioned animals would self-administer smaller doses than intact animals. On the basis of the present results alone, one could not distinguish between decreased reinforcing efficacy and increased sensitivity to reinforcing effects. Perhaps one could do so, however, in an additional experiment, using the oral self-administration model, by observing changes in responses to decreasing concentrations of morphine solutions between lesioned and sham animals once their consumption had reached asymptotic levels.

It is interesting that the lesion had different effects on withdrawal from morphine and on morphine self-administration in already dependent animals. That is, even though the chronic lesion failed to suppress withdrawal, possibly because of recovery of function in that respect, it still reduced self-administration, i.e., any such functional deficits were not restored. Similarly, it has been reported, in one instance, that chronic lesions of the cingulate cortex, an adjacent area of the brain, had negligible effects on morphine withdrawal in chronically dependent animals [26], and in another, that chronic cingulate lesions reduced self-administration of morphine in dependent animals in a test similar to that used here [23]. It is possible that the oral self-administration tests were more sensitive than the withdrawal tests. However, it is also possible that the processes governing the two phenomena are at least, in part, separable – that morphine is administered not only to allay incipient withdrawal, but has independently reinforcing properties, with a different neural basis, as well. Perhaps also pretreatment can increase the probability of self-administration in ways other than by inducing physical dependence. Glick and Charap [10] also previously reported a dissociation of the two processes. That is, lesions of the posterior hypothalamus which suppressed morphine withdrawal, nevertheless increased morphine self-administration. Behaviorally, also, there is evidence of dissociation as opiates are reportedly self-administered in amounts believed to be too small to create any physical dependence [11,21].

In summary, the results of this experiment both limit and extend the generality of the Glick *et al.*, findings. That is, chronic lesions of the caudate nucleus failed to suppress any sign of withdrawal from morphine in chronically dependent as opposed to pellet-implanted animals. However, the same lesions effectively reduced oral morphine consumption in the same dependent animals. The previous report [11] was of a suppression of intravenous self-administration in non-dependent animals.

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