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Lesions of the Tegmental Pedunculopontine Nucleus: Effects on the Locomotor Activity Induced by Morphine and Amphetamine

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BECHARA, A. AND D. VAN DER KOOY. *Lesions of the tegmental pedunculopontine nucleus: Effects on the locomotor activity induced by morphine and amphetamine.* PHARMACOL BIOCHEM BEHAV 42(1) 9–18, 1992.—One of the important questions in the neurobiology of motivation asks how the incentive impact of stimuli acting on the limbic system of the forebrain are ultimately translated into action and approach behavior. Bilateral ibotenic acid lesions of the tegmental pedunculopontine nucleus (TPP) (a brainstem output of the limbic system that receives neuronal input from limbic forebrain and midbrain sites identified as primary sites for psychoactive drug reward) have been shown previously to block the acquisition, but not the retention, of morphine and amphetamine conditioned place preferences in formerly drug-naive rats. These results suggest a deficit in the processing of the unconditioned rewarding effects of these drugs. The TPP projects to widespread parts of the brain and spinal cord involved in various somatomotor responses. Thus, we investigated the role of the TPP in morphine- and amphetamine-induced locomotion as assessed in an open field. We report that TPP lesions blocked the locomotor excitation, as well as the conditioned hyperactivity, produced by amphetamine. TPP lesions also blocked the conditioned increase in locomotion, but not the catalepsy, produced by morphine. TPP lesions were behaviorally specific in that the analgesic properties of morphine in a tail-flick test were not attenuated, nor did the lesions affect the locomotion induced by naloxone-precipitated withdrawal in morphine-dependent animals. We suggest that the neural circuits mediating the acute rewarding effects of drug stimuli acting at forebrain sites exit the limbic system in the TPP region of the brainstem, where motivation gains access to (or is isomorphic with) motor systems that initiate approach and exploration.

Reward Limbic Opiates Stimulants Locomotion Brainstem

WHEN humans and laboratory animals are given access to opiates (such as heroin and morphine) or stimulants (such as amphetamine and cocaine), they frequently acquire an affinity for these drugs. Investigations aimed at unraveling the neurobiological substrates underlying the potent motivational effects of these psychoactive substances have revealed that several neural structures localized or connected to the limbic system of the brain are primary loci for mediating the rewarding properties of these drugs (22,43,51,53). Indeed, microinjection studies have revealed that the receptor sites where opiates and stimulants act to produce rewarding effects in drug-naive rats are in the limbic forebrain (i.e., nucleus accumbens and lateral hypothalamus) and midbrain (i.e., ventral tegmental area and periacqueductal gray) (10,32,48, 49,52). In addition, electrophysiological studies indicate that the reward information generated by electrical brain stimulation of these forebrain sites is carried through descending pathways of the medial forebrain bundle (MFB) to the midbrain (7).

Several lines of evidence now suggest that the appetitive motivational mechanisms activated more rostrally in the forebrain seem to operate via output pathways that descend at least to the level of the tegmental pedunculopontine nucleus (TPP) of the midbrain. Anatomical evidence indicates that the TPP region of the midbrain and pons receives neuronal inputs from all structures identified as positive reward sites via direct monosynaptic or indirect multisynaptic pathways traveling through the MFB (44,45). Bilateral ibotenic acid lesions of the TPP region block the acquisition, but not retention, of morphine and amphetamine conditioned place preferences in drug-naive rats (4). Similarly, bilateral electrolytic lesions placed in the midbrain tegmentum [infringing on the TPP area defined as critical for psychoactive reward (4)] depress bar pressing for electrical stimulation of the septal region (36,37) and of the lateral hypothalamus (8). On the other hand, anatomical evidence shows that the TPP is in a position to influence a variety of somatomotor responses since it projects directly to widespread parts of the brainstem reticular

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formation (29), the thalamus (16,40), the spinal cord (15,33, 44), and the basal ganglia and associated structures (12,19, 29,35,42). Furthermore, the TPP region appears to overlap the mesencephalic locomotor region, a region that facilitates locomotion when electrically stimulated in the decerebrate rat (39). Therefore, we hypothesized that the TPP region of the brainstem may serve as an anatomical substrate where appetitive motivational signals generated at more rostral levels of the brain exit the limbic system and gain access to motor systems that initiate behavioral acts. Thus, we tested our hypothesis by examining the effects of bilateral ibotenic acid lesions of the TPP on the locomotion induced by psychoactive drugs such as morphine and amphetamine. We predicted that TPP lesions would block the motor-activating properties of these drugs. The exploration of the neurobiological mechanisms underlying drug motivation and the elicitation of drug-seeking behaviors may prove to be relevant to the neurobiological bases of many adaptive behaviors such as exploration and food procurement (5,43). Indeed, the expression of many of these adaptive behaviors involves the activation of several limbic structures, as well as the translation of this limbic activity into locomotor behavior such as the approach to a prey or the escape from a predator (25).

Amphetamine produces unconditioned locomotor excitation in rats (18,21,53). When novel environmental stimuli are paired with amphetamine, these environmental stimuli acquire the ability to elicit conditioned hyperactivity in the absence of the drug (6,38,41,46). On the other hand, morphine has two unconditioned effects on locomotor activity that are separable by dose: a hyperactivity produced by low doses and a hypoactivity produced by high doses (1,2). However, it has been shown in rats that only the locomotor hyperactivity becomes conditioned to environments paired with high doses of morphine, even when the observed unconditioned effects are locomotor hypoactivity (30). We asked if the hyperactivity effects associated with these psychoactive drugs (as assessed in an open-field activity paradigm) would be blocked by TPP lesions.

Tpp lesions block the conditioned place preferences produced by morphine and amphetamine (4). Given that TPP lesions may similarly attenuate the locomotor effects of these drugs, we sought to investigate whether TPP lesions would modify the locomotor activity induced by action on motivational systems independent of the TPP-mediated reward system. In related work, we have shown that although bilateral ibotenic acid lesions of the TPP blocked the conditioned place preferences produced by morphine and amphetamine in drug-naive animals (4) these same TPP lesions failed to attenuate the conditioned place aversions induced by opiate withdrawal in opiate-dependent animals (5). Thus, we investigated the effects of TPP lesions on the locomotor activity induced by naloxone-precipitated withdrawal in opiate-dependent animals. Given that moderate and high doses of morphine produce postinjection catalepsy, and that analgesia is produced by the administration of even low doses of opiates (1,2), we also asked if the cataleptic or analgesic (as assessed in a tail-flick test) effects of morphine were modified by the TPP lesions.

METHOD

Subjects

All animals used in these experiments were adult, male Wistar rats (Charles River) weighing between 350–450 g. Subjects were housed individually in suspended grey wire cages in a room kept at a temperature of 22°C and lit from 0900–2100 h. Purina Rat Chow was available ad lib throughout the experiments. Water was also continuously available.

Surgery and Histology

Different groups of rats were anesthetized with 0.8-ml/kg doses of Somnotol. Each was placed in a stereotaxic apparatus, a scalp incision was made, and two small holes were drilled in the skull to allow passage of a needle. Each rat was either bilaterally injected with 0.2 μl 4% ibotenic acid solution via a 1-μl Hamilton microsyringe over 25 min (lesion groups) or with physiological saline (sham groups). The needle was left in place for 5 min following infusions. The injection coordinates (with the mouthbar set at -3.3 mm below the interaural line) were AP -7.8 mm posterior to bregma, L $\pm$ 1.6 mm lateral to the midline, and DV -5.8 mm below the dura for the TPP. At least 2 weeks were allowed for recovery from surgery before any experiments were begun. During the recovery period, each rat was handled for a few minutes on each of several days.

At the end of the behavioral experiments, all operated rats were deeply anesthetized with Somnital and perfused through the heart with isotonic saline followed by 10% formalin. Brains were removed, postfixed in 15% sucrose, and then 32-μm cryostat sections were cut. Sections were mounted on gelatin-coated slides and stained with cresyl violet to verify the placement and extent of the lesions. Sections were examined and photographed in bright-field microscopy.

Behavioral Paradigms

Locomotor activity. The test apparatus consisted of an unpainted wooden box (60 × 60 × 60 cm) fitted with a stainless steel wire grid floor with 1-cm spacing. The floor was divided with lines into 16 15-cm squares by placing white tape underneath the grid. Locomotor activity was scored as the total number of lines crossed by the point on the skin midway between the rat's ears (in both the rostrocaudal and mediolateral planes) during a 2-min period prior to SC injection of an appropriate dose of amphetamine, morphine, or saline vehicle. After allowing 2 min for drug absorption, the total number of lines crossed was then counted during another 2-min period. Tests were run under normal lighting conditions with the box located so that there were no obvious shadows in the corners. The rat's activity was monitored by the experimenter peering over the top of the box. All rats employed in the present study were well handled prior to the start of the experiment.

This method for assessing locomotor activity is similar to a method previously described as very sensitive to drug-induced changes in locomotion (30). The experimenter simply traced the rat's activity on a paper template of the floor of the locomotion test box. This experimenter was blind as to the sham or lesion condition of the animal, but the behavior of the animals made it impossible for the experimenter to be completely blind to the drug vs. saline treatment of the animal. The number of lines crossed were then counted on each template under conditions where both the drug and lesion treatments were unknown to the experimenter.

Catalepsy. The test apparatus consisted of a stainless steel bar positioned 12 cm above a wire grid floor. Each rat was first injected with an appropriate IP dose of morphine or saline vehicle and immediately returned to the home cage. Fifteen min later, each injected rat was tested for catalepsy. The catalepsy test involved placing the forepaws on the stainless steel bar. The latency (s) to withdraw the forepaws from

the bar was taken as a measure of the cataleptic effects of the injected drug.

Tail-flick. Each rat received an injection of either morphine or its saline vehicle (SC) 15 min prior to immersion of the distal half of the tail into a water bath at 52°C. The latency (s) to flick the tail was recorded for each rat and taken as a measure of analgesia. A ceiling of 20 s was selected, after which time rats that had not flicked the tail were removed from the water bath and a score of 20 s was recorded.

Locomotion after TPP Lesions

Morphine and amphetamine hyperactivity. Separate sham vehicle (n = 8) and lesion vehicle (n = 8) groups were injected with saline vehicle. Separate sham amphetamine (n = 7) and lesion amphetamine (n = 5) groups were injected with amphetamine (1 mg/kg SC). Two other separate sham morphine (n = 7) and lesion morphine (n = 5) groups were injected with morphine (16 mg/kg, SC). Once per day, each rat was placed in one corner of the open-field box and allowed to explore freely for 2 min prior to drug injection. At the end of the 2-min preinjection period, each rat was lifted out of the box and injected with saline, amphetamine, or morphine and then immediately returned to the open-field box for 4 min. Pre- and postinjection activity scores were recorded as described above on the third day of injections for each group.

The number of lines crossed during the preinjection period were taken as a measure of the conditioned locomotor effects of the drug. A previous study used a similar preinfusion period to look at conditioned locomotor effects with considerable sensitivity (30). Furthermore, our preliminary observations revealed that longer preinjection periods eventually resulted in habituation to the box and cessation of locomotor activity. Most importantly, since the preinjection activity scores reflect the conditioned effects (if any) of the drug, these conditioned effects should be expressed upon the exposure of the animal to the conditioned environment. Therefore, the 2-min preinjection period was considered sufficient for measuring conditioned locomotor effects. On the other hand, the number of lines crossed during the last 2 min of the postinjection period were considered a measure of the unconditioned locomotor effects of the drug. Assessing the unconditioned effects of drugs after allowing only 2 min for drug absorption may be questioned in view of the fact that the peak effects of morphine and amphetamine occur after longer periods of time. However, it has been shown that unconditioned locomotor effects of morphine can be revealed when allowing only 30 s for drug absorption (30).

All sham and TPP-lesioned rats used for this experiment had been previously trained and tested for morphine or amphetamine conditioned place preference approximately 6 weeks earlier (4). Rats were assigned to the six separate groups of the present experiment randomly with respect to their previous drug exposure (a maximum of four morphine or amphetamine injections spread equally over 8 days). None of these rats had previous experience in locomotor tests. It is important to note that the previous place conditioning experiments with these animals allowed direct comparison within the same animals between the effects of the lesions on reward and locomotion. However, the previous drug exposure during place conditioning could have modified the subsequent drug conditioning during the present locomotor tests. Nevertheless, the previous brief drug exposure was equivalent for both the sham and lesion groups and thus should not effect the interpretation of the lesion effects in the present locomotor activity study.

Since the aim of the present study was to ask if TPP lesions block the locomotor effects produced by amphetamine and morphine, we selected high doses of morphine and amphetamine that are well above the threshold doses for producing locomotor effects. These high doses were also chosen because previous dose-response analyses demonstrated that TPP lesions blocked the rewarding effects of doses as high as 10–20 mg/kg morphine and 1 mg/kg amphetamine in drug-naive rats (4,5). Therefore, the present study employed similarly high doses of morphine (16 mg/kg) and amphetamine (1 mg/kg). Most importantly, a previous study showed that only the locomotor hyperactivity of morphine (16 mg/kg) becomes conditioned to environments paired with morphine, even when the observed unconditioned effects are locomotor hypoactivity (i.e., catalepsy) (30). We employed this same dose of morphine in the present locomotor study.

Locomotion after naloxone-precipitated withdrawal. Separate sham (n = 5) and lesion (n = 5) groups were made physically dependent on morphine by daily injections of morphine (20 mg/kg, IP injected three times daily) over a period of 14 days (5). On the test day, each animal was allowed to explore the box for 2 min prior to an injection of naloxone (1 mg/kg, IP). Two minutes after naloxone injection, the locomotor activity of each rat was recorded for 2 min in a manner similar to that described above.

Morphine catalepsy. Separate sham (n = 8) and lesion (n = 8) groups were injected with morphine (15 mg/kg, IP) 15 min prior to the catalepsy test. Separate vehicle sham (n = 8) and vehicle lesion (n = 8) groups were injected with the saline vehicle. These sham and lesioned rats participated in a place conditioning study approximately 4 weeks earlier (4). The maximum drug exposure of these rats prior to this experiment was four drug injections (methylnaltrexone) spread equally over 8 days. None of these rats had previous morphine or catalepsy test experience.

Morphine Analgesia after TPP Lesions

Separate groups of sham (n = 9) and lesion (n = 7) rats were administered morphine (1.5 mg/kg, SC) 15 min prior to tail-flick testing, as described above. Two other separate groups (sham, n = 9; lesion, n = 7) were administered saline vehicle instead of morphine prior to the tail-flick test. These sham- and TPP-lesioned rats used in this experiment were from groups that were place conditioned and tested 4 weeks earlier for morphine or amphetamine place preference (4). Rats were assigned to the four separate groups of the present experiment randomly with respect to their previous drug history (a maximum of four morphine or amphetamine injections spread equally over 8 days). None of these rats had previous tail-flick test experience.

Since the aim of this experiment was to ask if the deficits induced by TPP lesions would extend to the analgesic effects of morphine, we chose a low dose of morphine to test the effects of the lesions on a just above threshold dose of morphine for producing motivational, locomotor, and analgesic effects (4,5,30,50).

RESULTS

Rats with ibotenic acid lesions of the TPP region appeared normal under superficial visual examination and maintained normal body weights compared to sham-lesioned animals. All animals whose behavioral data were included in the statistical analyses were histologically verified for lesions that encompassed significant portions of the TPP region bilaterally. The TPP extends as far rostrally as the caudal substantia nigra

and retrorubral field and as far caudally (in close association with the ascending limb of the brachium conjunctivum) as the fourth cranial motor nucleus and the rostral parabrachial nucleus (15,31,34). Dorsally, the TPP extends as far as the cuneiform nucleus and laterally as far as the lateral lemniscus and associated nuclei (31,34). The pontine tegmental field and rubrospinal tract form the ventral boundaries of the TPP (31,34), whereas the PAG and the decussation of the brachium conjunctivum form its medial boundaries (31). TPP neuronal perikarya are found dorsal to, ventral to, and intermingled with the ascending fibers of the brachium conjunctivum. The lesions and their boundaries were relatively easily defined in Nissl sections by the loss of neuronal perikarya and gliosis. Histological sections of some TPP lesions at the level of the decussation of brachium conjunctivum are shown in Fig. 1.

TPP Lesion Effects on Locomotion

Behavioral observations. Animals tested under the influence of amphetamine did not express any stereotyped behavior, at least during the time of assessing the postinjection locomotor scores (i.e., 2–4 min after the amphetamine injection). Although amphetamine is known to induce stereotopy and other behaviors such as sniffing and gnawing, our observations suggest that these behaviors may occur later, perhaps closer to the peak effects of the drug. On the other hand, the behavior exhibited by opiate-dependent rats treated with naloxone involved an initial period of hyperlocomotion (starting approximately 1–3 min after the naloxone injection and lasting for 2–3 min). This was followed by a severe withdrawal syndrome (approximately 5–6 min after the naloxone injection) characterized by repetitive circling and jumping, teeth-chattering, writhing, wet-dog shakes, and diarrhea that lasted about 5 min. Finally (approximately 10 min later), animals became immobile and confined to one corner of the box. It is important to note that because our postinjection scores were taken during the 2- to 4-min period after the naloxone injection many of the later appearing circling, jumping, and writhing behaviors described above did not contribute to the locomotor counts.

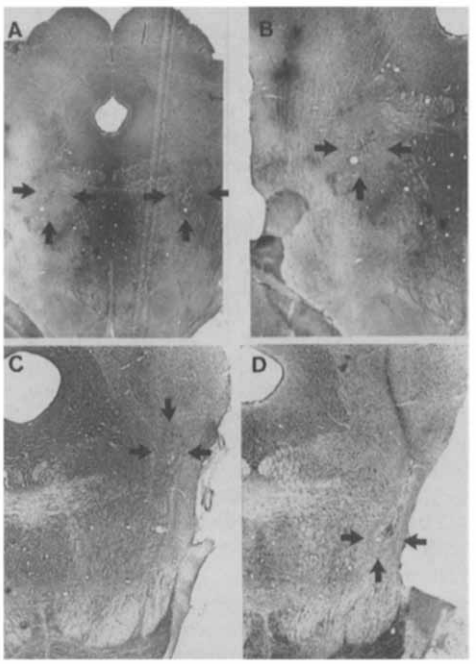

FIG. 1. Photomicrographs of Nissl-stained frontal sections through similar rostrocaudal levels of the pons show various bilateral ibotenic acid lesions (arrows) in the region of the TPP. The lesions showed gross bilateral symmetry as shown in (A). Higher magnification photomicrographs show (B) ventromedial, (C) dorsolateral, and (D) ventrolateral lesions of the TPP. TPP lesions situated in the ventromedial TPP region (i.e., A and B) were effective lesions in producing locomotor deficits. Lateral lesions (i.e., C and D) are less effective in producing locomotor or motivational (4) deficits. The effective lesions appear to destroy a greater percentage of TPP cells with descending than with ascending projections (4,15), in comparison to the lateral lesions that appear to spare the TPP cells with descending projections and primarily destroy the TPP cells with ascending projections (4,15).

Morphine and amphetamine hyperactivity. Two general points are revealed by the changes in activity counts over the three trials (Table 1). First, vehicle sham rats appeared to be more active than vehicle-lesioned rats during exploration of the test box on the first trial. The activity scores from all sham rats on the first day trial, prior to injection of saline vehicle, morphine, or amphetamine, were significantly higher than the similar activity scores observed across all lesioned animals, $t(38) = 2.4$, $p < 0.05$. However, within the saline vehicle control group the activity of the vehicle sham rats decreased over the three trials down to the level of locomotor activity shown by the vehicle-lesioned rats. Second, morphine and amphetamine sham rats showed increments over the three trials in locomotor activity prior to each drug injection, reflecting the acquisition of conditioned hyperactivity as a function of the repeated exposure to drugs in the text boxes. Thus, the morphine sham rats showed significantly higher activity scores, $t(6) = 5.5$, $p < 0.05$, on their third, compared to first, preinjection trials. The amphetamine sham rats showed a smaller, but still significant, $t(6) = 3.7$, $p < 0.05$, increase in activity scores on their third, compared to first, preinjection trials. These changes in preinjection activity scores over trials contrasted with those of postinjection periods. The locomotor activity scores observed after each drug injection did not change over trials within either the morphine sham or amphetamine sham groups. We suggest that the postinjection activity scores reflect primarily the unchanged unconditioned locomotor effects of the injected drugs.

Bilateral lesions of the TPP region blocked the unconditioned (postinjection) and conditioned (preinjection) hyperactivity seen after three amphetamine injections, and also blocked the conditioned (preinjection) hyperactivity seen after three morphine injections (Fig. 2A). Separate three-way analyses of variance (ANOVA's) comparing the locomotor scores from the vehicle and amphetamine groups of sham- and TPP-lesioned rats, during the pre- and postinjection periods on the first, second, and third trials, revealed a significant interaction of amphetamine with lesion and with testing period on the first, $F(1,24) = 5.5$, $p < 0.05$, second, $F(1,24) = 7.8$, $p < 0.05$, and third, $F(1,24) = 8.5$, $p < 0.05$ trials. Similar, separate three-way ANOVA's comparing the locomotor scores from the vehicle and morphine groups revealed a significant interaction of morphine with lesion and with testing period on the second, $F(1,24) = 9.9$, $p < 0.05$, and third, $F(1,24) = 14.8$, $p < 0.05$, but not on the first, $F(1,24) = 1.2$, $p > 0.1$, trials.

Multiple comparison tests on the locomotor activity scores from the vehicle sham and vehicle-lesioned rats on their third saline vehicle trials revealed no significant differences between their activity scores during the preinjection period, $t(14) = 0.6$, $p > 0.1$, nor during the postinjection period, $t(14) =$

TABLE 1

LOCOMOTION COUNTS OVER THE THREE TRIALS

	No. of Lines Crossed in 2 min					
	Preinjection (mean ± SEM)			Postinjection (mean ± SEM)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Vehicle						
Sham	12 ± 3	8 ± 2	7 ± 2	14 ± 3	7 ± 2	2 ± 1
Lesion	7 ± 2	8 ± 2	5 ± 2	6 ± 2	3 ± 1	3 ± 1
Morphine						
Sham	13 ± 2	17 ± 1	39 ± 5	4 ± 1	2 ± 1	3 ± 1
Lesion	9 ± 1	7 ± 1	8 ± 1	3 ± 1	1 ± 1	1 ± 1
Amphetamine						
Sham	10 ± 1	13 ± 1	14 ± 1	27 ± 3	29 ± 2	26 ± 4
Lesion	8 ± 1	6 ± 1	8 ± 2	7 ± 1	6 ± 1	3 ± 2

Locomotion counts over trials on 3 days using separate groups of sham- and TPP-lesioned rats injected with saline vehicle, morphine (16 mg/kg), or amphetamine (1 mg/kg). Both sham- and TPP-lesioned groups treated with saline vehicle showed decrements in the number of lines crossed over the three trials during both the pre- and postinjection periods. In contrast, sham, but not TPP-lesioned, groups treated with morphine or amphetamine showed increments in the number of lines crossed over the three trials during the preinjection period. Sham, but not TPP-lesioned, groups treated with amphetamine showed large increases in the number of lines crossed during the postinjection compared to the preinjection periods. No difference was observed between the morphine-treated groups during the postinjection period.

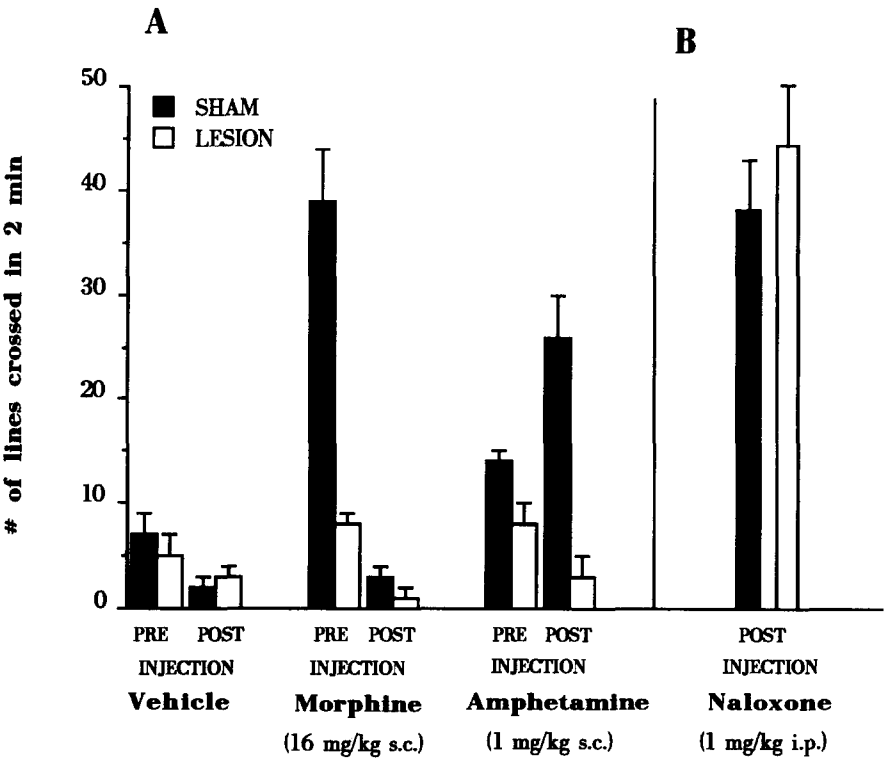

FIG. 2. (A) Effects of bilateral sham or ibotenic acid lesions of the TPP on the locomotor effects produced before (preinjection) and after (postinjection) the third administration of morphine, amphetamine, or saline vehicle (as measured in an open-field box). (B) Effects of bilateral sham or ibotenic acid lesions of the TPP on the postinjection locomotor effects produced by naloxone- (1 mg/kg, IP) precipitated withdrawal in opiate-dependent rats. Bars represent means ± SEM for five to eight rats.

0.7, $p > 0.1$ (Fig. 2A). In contrast, after three amphetamine injections significant differences were revealed between amphetamine sham and amphetamine lesion groups during both the preinjection, $t(10) = 2.9, p < 0.05$, and postinjection periods, $t(10) = 4.1, p < 0.05$. These differences between the sham amphetamine and lesion amphetamine groups were also evident in the postinjection periods on the first, $t(10) = 4.9$, $p < 0.05$, and second, $t(10) = 10.7$, $p < 0.05$ trials and in the preinjection period on the second, $t(10) = 3.5, p < 0.05$, but not the first, trial. Furthermore, after three amphetamine injections amphetamine sham groups were significantly more active than vehicle sham groups during both the preinjection, $t(13) = 2.8$, $p < 0.05$, and postinjection, $t(13) = 5.4$, $p < 0.05$, periods. On the other hand, after three amphetamine injections the pre-, $t(11) = 0.7$, $p > 0.1$, and postinjection, $t(11) = 0.1$, $p > 0.1$, locomotor activity scores of the amphetamine lesion group did not differ significantly from those of the vehicle-injected groups. Together, these results demonstrate that TPP lesions abolished the unconditioned locomotor excitation, as well as the conditioned hyperactivity, produced by amphetamine.

In the case of morphine significant differences were revealed on the third trial between morphine sham and morphine lesion groups during the preinjection, $t(10) = 5.0$, $p < 0.05$, but not during the postinjection period, $t(10) = 1.0$, $p > 0.1$. These differences between the sham morphine and lesion morphine groups were observed in the preinjection period, $t(10) = 5.2$, $p < 0.05$, but not the postinjection period, of the second trial. No significant differences between the sham morphine and lesion morphine groups were observed in either the pre- or postinjection periods on the first trial. After three injections of morphine, sham rats showed significantly more locomotion prior to the morphine than prior to the vehicle injections, $t(13) = 6.3$, $p < 0.05$. After three injections of morphine, the locomotor activity of the TPP-lesioned morphine group did not significantly differ from that of the vehicle-injected group during either the pre-, $t(11) = 0.9$, $p > 0.1$, or postinjection, $t(11) = 1.3$, $p > 0.1$, periods. These results suggest that TPP lesions induced a deficit in the conditioned hyperactivity produced by morphine. Morphine produced unconditioned locomotor effects (i.e., catalepsy) during the postinjection period that did not seem to be blocked by TPP lesions. However, it can be argued that the low postinjection baseline activity scores in the vehicle-injected groups render this paradigm relatively insensitive for the detection of opiate catalepsy. Therefore, a further examination of this issue was pursued in a later experiment.

Hyperactivity after naloxone-precipitated withdrawal. TPP lesions did not affect the hyperactivity associated with naloxone-precipitated withdrawal in opiate-dependent rats (Fig. 2B). A simple *t*-test on the scores from sham- and TPP-lesioned animals treated with naloxone did not reveal a significant difference, $t(8) = 1.0$, $p > 0.1$. Most importantly, the fact that the locomotor scores observed in these withdrawn TPP-lesioned animals were higher than those observed with amphetamine or morphine in TPP-lesioned rats suggests that TPP lesions do not cause gross impairments in locomotor activity that nonspecifically limit the locomotor scores of TPP-lesioned animals.

Morphine catalepsy. TPP lesions proved to have no effect on the catalepsy induced by morphine (Fig. 3). An ANOVA on the scores from vehicle and morphine groups of sham- and TPP-lesioned rats revealed a significant main effect of drug treatment, $F(1,28) = 100.6$, $p < 0.05$, but no effect of lesion

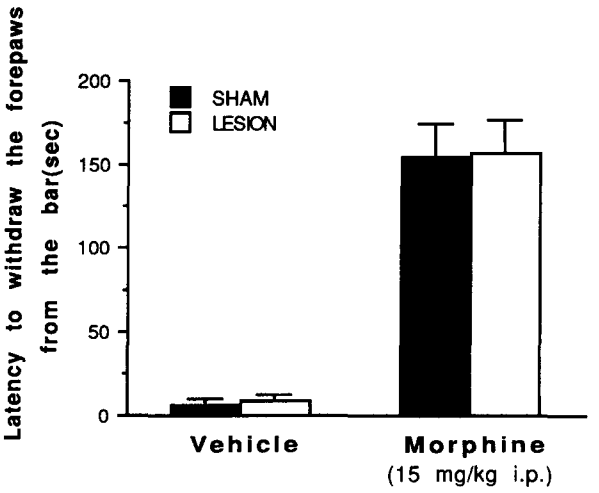

FIG. 3. Effects of bilateral ibotenic acid or sham TPP lesions on the catalepsy produced by morphine, measured by the latency to withdraw the forepaws from a bar hanging 12 cm above the floor. Bars represent means ± SEM for eight rats.

nor any significant interaction of lesion with drug treatment. The latency to withdraw the forepaws from the bar hanging 12 cm above the floor depended on whether morphine or saline vehicle was injected but not on the presence of sham or TPP lesions. These results demonstrate that the TPP is not a part of the neural circuit underlying the cataleptic effects of morphine. Taken together, the open-field and catalepsy results demonstrate that the locomotor deficits caused by TPP lesions were restricted to the stimulant and were not seen on the depressant effects of psychoactive drugs.

TPP Lesion Effects on Morphine Analgesia

TPP lesions did not interfere with the neural mechanisms underlying morphine (1.5 mg/kg, SC) analgesia (Fig. 4). An ANOVA on the data from the sham vehicle, lesion vehicle,

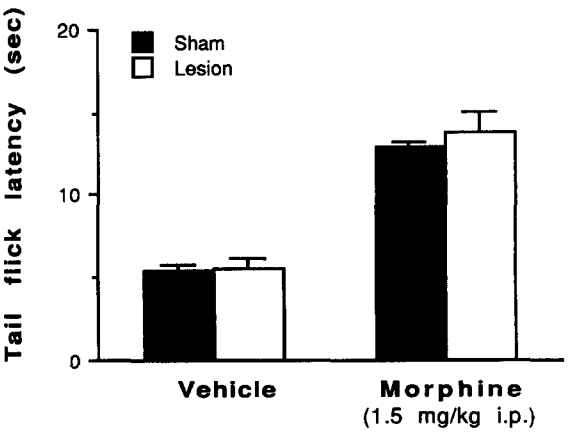

FIG. 4. Effect of sham or TPP lesions on the analgesia produced by morphine or its vehicle in naive rats using the tail-flick test. Bars represent means ± SEM for seven to nine rats.

sham morphine, and lesion morphine groups revealed a significant main effect of drug treatment, $F(1,28) = 73, p < 0.05$, but no effect of lesion nor any interaction of lesion with drug treatment. That is, the latency to flick the tail depended on the injection of morphine or saline vehicle but not on the presence of the sham or ibotenic acid lesions. These findings demonstrate that the TPP is not critical in mediating opiate analgesia. Interestingly, the tail-flick latencies after saline vehicle injections were equally short in both the sham and lesion groups, suggesting that TPP lesions do not produce a generalized impairment in all basic movements (i.e., the ability to flick the tail). Rather, the TPP deficit may be specific to a higher form of motor behavior, the locomotor excitation induced by psychoactive drugs and perhaps novelty (see the Discussion section).

Anatomy of TPP Lesions

The vast majority of TPP-lesioned animals had lesions that were centered in the ventromedial region of the TPP (Fig. 1A, B). Only one TPP lesion (from the lesion vehicle locomotor group) was placed in the dorsolateral TPP (Fig. 4C) and another lesion (from the lesion morphine locomotor group) fell more ventrolaterally (Fig. 4D). In a previous study (4), we established that this variation in lesion sites corresponds to the degree of motivational deficit and to a certain extent to the origin of various efferent projections from the TPP. Specifically, TPP-lesioned rats that failed to show any behavioral deficits in the morphine or amphetamine place preference tests (4) proved to have lesions that fell more laterally (either dorsolaterally or ventrolaterally). In contrast, rats with TPP lesions that included the more ventromedial areas (and thus ventral to the decussation of the brachium conjunctivum) tended to show complete blockade in the same place preference tests (4). In the present study, the TPP-lesioned rats with ventrolateral lesions (from the lesion morphine locomotor group) showed conditioned locomotor scores similar to the sham rats (preinjection scores on day 1 = 9, day 2 = 19, day 3 = 36). In contrast, the TPP-lesioned rats with ventromedial lesions showed a complete blockade of the morphine-conditioned hyperlocomotor effects. Although the data from rats with lesions that included the lateral areas of the TPP suggests that these lesions were behaviorally ineffective (4), the data from these two rats (one with a dorsolateral and one with a ventrolateral lesion) were not excluded from the behavioral analyses in the present study. Only data from rats with unilateral lesions or lesions that were placed completely outside the boundaries of the TPP were not included in the behavioral analyses.

Our ventromedial lesion sites in the TPP were shown to overlap a larger percentage of the TPP neurons with descending than with ascending projections (4,15). Nevertheless, these same lesions also destroyed a significant population of the TPP cells with ascending projections (4,15) so no absolute conclusion can be drawn concerning the directionality of the TPP efferents underlying the locomotor deficits observed in the present study. TPP lesions did not extend as far rostrally as the red nucleus, substantia nigra, and the caudal part of the ventral tegmental area, nor did the lesions extend as far caudally as the parabrachial nucleus.

DISCUSSION

TPP lesions blocked the locomotor excitation, as well as the conditioned hyperactivity effects, induced by amphetamine. Furthermore, TPP lesions abolished the conditioned increase in locomotion but not the catalepsy induced by morphine. TPP lesions did not modify the hyperlocomotor activity associated with naloxone-precipitated withdrawal in opiate-dependent animals. The deficit caused by TPP lesions showed a further behavioral specificity in that the analgesic properties of morphine were spared by the lesions, even though morphine produces profound analgesic effects at the dose used to induce locomotor effects. Thus, lesions of the TPP caused a specific behavioral deficit that was restricted to the stimulant effects of psychoactive drugs on locomotor behavior in non-drug-dependent animals.

Immunocytochemical procedures have established that many cells within the TPP in the rat are cholinergic (13,31,34). Moreover, the distribution of cholinergic TPP cells overlaps the distribution of sites producing locomotion after electrical stimulation in both the cat and the rat (13). However, our effective lesions for producing locomotor deficits extended further medially and ventrally than the distribution of the largest concentration of cholinergic cells in the TPP (15,33). Thus, the critical lesions encompassed a ventromedial area of the TPP that corresponds to a population of mostly noncholinergic neuronal perikarya with axons descending to the ventromedial medulla and spinal cord (15,33,34). This area contrasts with the lateral portion of the TPP (especially the dorsolateral portion) that contains the majority of the cholinergic neurons, which have diffuse ascending projections to the thalamus and the forebrain (15,40).

Although morphine has two unconditioned effects on locomotor behavior (i.e., hyperactivity and hypoactivity), only one of these two unconditioned effects (i.e., hypoactivity or catalepsy) was directly examined in the present study. However, in so far as the conditioned hyperactivity effects of morphine (which are blocked by TPP lesions) reflect the conditioning of unconditioned morphine hyperactivity (30), we suggest that TPP lesions are blocking the unconditioned hyperactivity produced by morphine. In another paradigm, TPP-lesioned rats were clearly capable of remembering the conditioned properties of stimuli (places) associated with morphine if the conditioning preceded the lesions (4). After the extinction of the conditioned place preferences in these rats, sham (but not TPP lesioned) rats reacquired conditioned preferences for places paired with morphine. These results strongly suggest that TPP lesions disrupt the unconditioned, but not conditioned, motivational effects of morphine. In a similar vein, we hypothesize that TPP-lesioned rats failed to express the conditioned hyperactivity induced by morphine because conditioning fails as a result of the TPP lesions disrupting the neural processes mediating the unconditioned locomotor excitation induced by the drug. The same argument can be made concerning the amphetamine locomotor results. The fact that TPP lesions blocked the unconditioned hyperactivity effects of amphetamine, as well as the conditioned hyperactivity effects of both morphine and amphetamine, should, therefore, not be taken as evidence that both the conditioned and unconditioned locomotor effects of the drug reflect the activation of an identical neural system in the brain.

TPP lesions block both the acute rewarding (4) and locomotor excitatory effects (present study) induced by morphine and amphetamine in previously drug-naive rats. These findings raise the question of whether the motivational and motor-activating properties of these drugs result from their action on a common neural system or from their action on

two separate neural systems that are processed in series or that interact at some different processing point. Most neural and pharmacological manipulations that modify the motivational effects of psychoactive drugs have been shown to effect, in a similar manner, the locomotor excitation induced by the same drugs (53). These findings support the Glickman and Schiff (14) biological theory of reinforcement suggesting that reinforcement evolved with and is isomorphic with the activation of the neural pathways underlying species-typical approach behaviors. In line with this theory, our results would suggest that the activation of this appetitive locomotor system in the TPP occurs through excitation generated by psychoactive drugs acting in the forebrain and descending via the medial forebrain bundle. Activation of the TPP would then constitute a necessary condition for these drugs to have rewarding impact, at least in previously drug-naive animals. In addition, we hypothesize that activation of the TPP may also be a necessary condition for other (nondrug) rewarding stimuli (such as novel environmental stimuli) to have appetitive motivational impact. Indeed, our results reveal that sham rats are somewhat more active than TPP-lesioned rats during initial explorations of the test box. We predict that these differences in exploratory behavior would be even more pronounced if rats were exploring environments rich in potential survival resources such as food and water. Nevertheless, it is important to note that TPP lesions do not cause nonspecific motor deficits that limit locomotor activation in these animals under all circumstances. When locomotor activity is induced by naloxone action on a separate motivational system (3,5) underlying opiate withdrawal in dependent animals, locomotor activation in TPP-lesioned rats can reach the levels seen in sham animals treated with morphine or amphetamine.

Other studies have indicated that the neural processes mediating the motivation and locomotion induced by psychoactive drugs are dissociable. Certain pharmacological manipulations have been shown to block the locomotor stimulant effects of psychoactive drugs without influencing the motivational effects of the drug as assessed in a conditioned place preference paradigm (9,11,24). For example, progabide (a GABA mimetic drug) attenuated the locomotor stimulant effects of amphetamine, but did not influence the conditioned place preferences produced by the drug (11). Similarly, haloperidol (a dopamine antagonist) attenuated the locomotor stimulation produced by methylphenidate (a dopamine agonist), but did not effect the conditioned place preferences produced by the drug (24). If partially separate neural substrates subserve the motivational and locomotor excitatory effects of psychoactive drugs, then our results suggest that motivational and locomotor processes must overlap in the TPP region of the brainstem. There is also anatomical and behavioral evidence suggesting that interactions between limbic and motor processes may occur in the nucleus accumbens of the forebrain, which receives efferent fibers from many limbic regions including the amygdala, hippocampus, and cingulate gyrus (25). Since there is a major output pathway that arises within the nucleus accumbens and projects down to the subpallidal region (17,25), it has been proposed that activity within this projection reflects an integrated activity of limbic and motor information arising from within the nucleus accumbens (25). Given the major output from the subpallidal area to the TPP region (44), our results may suggest that the appetitive locomotor information generated by rewarding stimuli acting on the limbic system of the forebrain exit the subpallidal region and are ultimately translated into changes in motorneuron activity and into action via the TPP region of the brainstem. It is important to note, however, that such a nucleus accumbens–ventral pallidum–TPP pathway is not necessarily the only route by which appetitive locomotor activity generated by drug stimuli acting on the forebrain could reach the TPP.

The notion that the TPP region is critical for mediating both the appetitive (4) and the hyperlocomotor (present study) effects of morphine and amphetamine does not mean that it is also critical for the properties of these drugs which exert subjective sensory effects known to humans as the "rush" (20). In rats, it has been suggested that morphine has distinct cueing or discriminative properties (23) that perhaps model the subjective rush reported by humans. However, these internal cueing effects of morphine were separable from the motivational effects of the same drug. Indeed, combined neural and pharmacological manipulations that blocked the motivational effects of opiates in drug-naive rats did not effect the discriminative effects of morphine (23). These results suggest that the discriminative properties of opiates are neurobiologically separable from their TPP-mediated appetitive and motivational properties that lead to action. That is, it may be possible to experience the subjective discriminative effects of the drug without necessarily seeing the expression of their objective appetitive locomotor effects.

While several authors have concluded that the nucleus accumbens and subpallidal region provide an anatomical substrate for the expression of integrated limbic/motor function, there are conflicting reports concerning the next putative link in the neuronal circuit carrying this information. In addition to the major output from the subpallidal region to the TPP, there is another neural projection from the subpallidal region to the mediodorsal thalamus (26,54). Locomotor activity elicited by injections of picrotoxin into the subpallidal region was reduced by the administration of procaine (a local anesthetic) to the TPP, but not by the administration of procaine to the mediodorsal thalamus (27). In contrast, locomotor activity elicited by the subcutaneous administration of apomorphine (a dopamine agonist) was reduced by bilateral electrolytic, as well as ibotenic acid, lesions of the mediodorsal thalamus, but not lesions of the TPP (47). Our results are consistent with findings of Mogenson and Wu (27) that the TPP region provides the next link in this appetitive locomotor circuitry.

A resolution of these contradictory ideas might come from the suggestion that each of the pathways to mediodorsal thalamus vs. TPP may play separate roles in eliciting appetitive locomotion. Mogenson and Wu (28) suggested that the projection to mediodorsal thalamus may contribute to behaviors such as hoarding, which depend on more cognitive function. On the other hand, our recent work suggests that there are two independent neural substrates that subserve the motivation for incentive stimuli under deprivation (such as hunger or withdrawal in the case of opiates) vs. nondeprivation conditions (3,5). We suggest that the discrepancy in TPP vs. mediodorsal thalamic lesion effects on locomotor behavior may reflect a fundamental difference in the motivational mechanisms that can lead to locomotion.

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