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Tegmental Pedunculopontine Nucleus Lesions Do Not Block Cocaine Reward

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PARKER, J. L. AND D. VAN DER KOOY. *Tegmental pedunculopontine nucleus lesions do not block cocaine reward.* PHARMACOL BIOCHEM BEHAV 52(1) 77-83, 1995.—Previous studies have implicated the tegmental pedunculopontine (TPP) nucleus in mediating the rewarding effects of opiates, food, and amphetamine, provided that animals are not in aversive motivational states induced by food—or drug—withdrawal. We wondered if bilateral TPP lesions could block the reinforcing effects of systemic cocaine in a place conditioning paradigm. Both lesioned and sham animals acquired cocaine place preferences. TPP-lesioned animals subsequently failed to acquire place preferences when conditioned with morphine, replicating previous data with TPP lesions. It is possible that our cocaine place conditioning protocol induced aversions during drug withdrawal, thus explaining the inability of TPP lesions to block conditioning. We looked for place aversions by conditioning animals at various times postinjection of cocaine. At no time point following drug withdrawal from cocaine were significant conditioned aversions observed. Cocaine's systemic motivational effects are mediated by a substrate separate from the TPP substrate underlying the rewarding effects of opiates, food, and amphetamine.

Withdrawal Reward Place conditioning Cocaine Tegmental pedunculopontine nucleus

COCAINE appears to be a powerful reinforcer (15). Cocaine maintains operant responding in every species tested so far, including rats (25), rhesus monkeys (37), squirrel monkeys (28), cats (2), and dogs (26). Cocaine maintains responding by various routes of administration, including intragastric (38), intralung (28), intranasal (9), and intramuscular (11). Progressive ratio studies found that the operant break point for cocaine was 2-16 times higher than that for amphetamine or methamphetamine (39). Furthermore, given the choice between cocaine and food monkeys preferred cocaine, and without experimental intervention they may have starved (1). Cocaine's powerful rewarding property has attracted attention with respect to its possible neurobiological substrate. Although dopamine holds a prominent role in the literature as a mediator of cocaine's rewarding action (17), in several place conditioning studies neuroleptics have been ineffective in blocking the conditioned place preferences produced by systemically administered cocaine (18,20,31). A possible site mediating the rewarding action of cocaine may be the tegmental pedunculopontine (TPP) nucleus. The TPP receives input from the nucleus accumbens (24), subpallidal area (32), and lateral hypothalamus (32,33), and is thought to constitute part of the mesencephalic locomotor region (29). Given that TPP nucleus lesions previously have been show to block the rewarding effects of amphetamine and morphine (6), we investigated the possible involvement of the TPP nucleus in the rewarding properties of cocaine. We used the place conditioning paradigm, which has the ability to measure the aversive and rewarding motivational effects of various stimuli (7,34).

Strong evidence has accumulated for a role of the TPP in motivation. Lesions of the TPP have blocked the motivational effects of food (4), heroin (23), morphine (4,6), and amphetamine (6). This effect appears due to a block in motivational effects, rather than a disruption in learning or memory. TPP lesions before conditioning block the acquisition of morphine place preferences; however, lesions after conditioning but before testing have no effect (6). In the same study (6), TPP-lesioned animals also learned place preferences for an environment paired with the administration of the peripheral opiate antagonist methylnaltrexone. Finally, if animals are drug dependent and in drug withdrawal, or food deprived, TPP lesions fail to block the rewarding actions of morphine, heroin, or food (3,4,23). In sum, the TPP appears to mediate the motivational properties of stimuli in drug naive or nondeprived animals, while leaving mechanisms of learning and memory intact.

For animals that have little previous drug exposure, the TPP is a critical site mediating the motivational effects of

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rewarding stimuli. To test further the generality of TPP involvement in reward, we asked if TPP lesions also would block the rewarding effects of cocaine in a place conditioning paradigm. Following the cocaine experiment, we later conditioned the same animals under morphine to verify behaviorally the phenotype of the lesion. Lesions were also checked histologically. Given the broad involvement of the TPP nucleus in mediating the effects of a number of rewarding stimuli, we hypothesized that TPP lesions would also block the motivational effects of cocaine in a place conditioning paradigm.

TPP lesions did not block cocaine place conditioning. This result may have been obtained if our TPP-lesioned animals were suffering from cocaine withdrawal. Morphine- or heroin-dependent animals show place aversions to an environment paired with the absence of the drug at a time several hours after the last drug administration (4,23). TPP lesions do not block this aversive motivational state of withdrawal. Similarly, in animals in an aversive motivational state due to food withdrawal, TPP lesions do not block the place preferences produced by food (4). If animals are in an aversive motivational state induced by food—or opiate—withdrawal, then the rewarding effects of food or opiates are mediated by a substrate independent of the TPP (4). It is possible that our cocaine place conditioning protocol with TPP-lesioned animals could have induced an aversive motivational state at the time of conditioning, due to drug withdrawal since the last injection. Therefore, we determined how much cocaine exposure is required before animals begin to demonstrate an aversive motivational state during drug abstinence. Essentially, we tested if our drug regimen for place conditioning with cocaine in TPP-lesioned animals was sufficient to produce the aversiveness of drug withdrawal, a motivational state that does not depend on the TPP nucleus.

Conditioned place aversions produced by opiate withdrawal showed dose-dependent correlations with the doses of naloxone used to precipitate withdrawal, whereas overt behavioral symptomology failed to correlate (21). These data suggested that conditioned place aversions are a more sensitive indicator of the motivational effects of drug withdrawal than overt behavioral symptomology. Animals display conditioned avoidance of an environment paired with abstinence, and this procedure has been successful in detecting the aversiveness of food withdrawal (4,12), heroin withdrawal (23), and morphine withdrawal (3,4,21,23). Place conditioning may provide a direct assay of the motivational state of the animal and was utilized here to look at the consequences of cocaine drug abstinence. We predict that if there are motivational consequences of cocaine drug abstinence, then animals should show aversions to an environment previously paired with the absence of cocaine. To find this putative aversive withdrawal period we tried different drug protocols of cocaine preexposure in an attempt to build dependence, while conditioning at several different elapsed intervals after cocaine administration for each drug protocol. In summary, after determining whether TPP-lesioned animals could acquire cocaine place preferences, we then asked if different cocaine treatment protocols could induce aversive motivational states following injections of cocaine.

METHOD

Subjects and Drugs

Adult male Wistar rats, weighing 250–300 g (Charles River Laboratories), were allowed to acclimate to the vivarium on a 12L : 12D cycle (light between 0800 and 2000 h) for 1 week prior to the surgery. They were singly housed in wire suspended cages in a room kept at 22°C. They had free access to Purina rat chow and tap water. Conditioning procedures took place from 0800 to 1900 h. Cocaine HCl and morphine sulphate (BDH, Toronto) were made by dissolving in 0.9% saline. Cocaine HCl was made fresh daily. All injections were 2 ml/kg.

Surgery

Rats were given 1.0 ml of atropine subcutaneously (SC) and then anaesthetized with a 0.8 ml/kg dose of Somnotol intraperitoneally (IP). Each rat was placed in a stereotaxic apparatus, a scalp incision was made, and two small holes were drilled in the skull to allow the passage of a Hamilton (1 μl) syringe. Each rat was injected bilaterally in the TPP with 0.2 μl of 4% ibotenic acid solution (n = 9, lesioned group) or with the physiological saline vehicle (n = 9, sham group) over 20 min. The needle was left in place for an additional 5 min following each infusion. The injection coordinates for the TPP were (with mouth bar set at −3.3 mm below the interaural line) AP −7.8 mm posterior to bregma, L ±1.6 mm lateral to the midline, and DV −5.8 mm below the dura. At least 2 weeks were allowed for recovery from surgery, during which time the animals were handled for a few minutes each day.

Conditioning Procedures

After several days of handling animals were placed in a grey box for 5 min to familiarize them with the general conditioning apparatus. Animals were injected with either cocaine (10 mg/kg, IP) or saline, and immediately placed in one of two environments distinct with respect to color, odour, and texture (6,22) for 30 min. Conditioning was counterbalanced such that half of the animals in each of the sham and lesioned groups received cocaine six times in one environment and the other half in each group received cocaine six times in the other environment. Each animal received saline vehicle injections in its alternate environment. Animals were exposed to only one environment each day so that place conditioning under cocaine took a total of 12 days. One environment was a black lidless box with a black Plexiglas floor, wiped with 2% glacial acetic acid. The other environment was a white lidless box with a wire mesh floor holding wood chips. Animals were tested 10 days after the end of conditioning. Animals were tested by placing them in the centre of a large rectangular box. The box was composed of the two conditioning boxes described above, joined in the centre by a small grey area. The preference for each side was measured by recording the amount of time the animal spent in each environment in the course of a 10-min test period. An animal was considered in an environment when both front paws were in that compartment.

Two weeks following the cocaine place conditioning, animals were next conditioned with morphine to verify the phenotype of the lesion. Animals were conditioned in a similar manner to that above for cocaine, except that they spent an hour in the conditioning boxes, in line with the longer time course of action of morphine. Half of the animals received morphine (5 mg/kg, IP) in the same environment as they received cocaine. The other half received morphine in the same environment where they had previously received saline during the cocaine place conditioning phase. Saline was given in the non-morphine-paired compartment. The conditioned prefer-

ences of the animals were tested 10 days after the end of conditioning to avoid any residual drug effects, which could disrupt their performance during the test.

Using additional groups of animals, we looked for the aversiveness of cocaine withdrawal. The withdrawal place conditioning procedure used was similar to that employed previously with morphine (3). At various time points following an injection of cocaine, animals were placed in one of two environments distinct with respect to color, odor, and texture for 1 h. Animals were consistently placed in the same environment postinjection for a total of four pairings, with half of the animals conditioned to either environment. Animals were never conditioned in their alternate environments in this procedure. Animals were injected every other day, to allow us to sample time points greater than 20 h following cocaine administration. In our paradigm, animals do not show a preference or aversion for novel compartments to which they have not been exposed before (4,5).

Drug naive animals had no preexposure to cocaine prior to the withdrawal conditioning phase. A total of four previously drug naive groups were conditioned four times each, at different times after 35 mg/kg IP cocaine injections: 6 h (n = 8), 11 h (n = 8), 16 h (n = 7), and 20 h (n = 6). Our first chronic drug protocol involved animals that were given 35 mg/kg IP injections of cocaine once daily for 10 days. Injections occurred at a random time each day. After this preexposure phase to cocaine, groups of animals were conditioned four times each at 6 h (n = 8), 11 h (n = 7), 16 h (n = 16), 20 h (n = 15), 24 h (n = 13), and 32 h (n = 15) after 35 mg/kg injections of cocaine (IP). The second chronic drug protocol preexposed animals to cocaine at a dose of 20 mg/kg injected three times daily for 12 days. Animals were given 40 mg/kg injections and paired eight times with an environment at a 0.5 h (n = 8), 3 h (n = 8), 13 h (n = 5), 16 h (n = 14), and 19 h (n = 7) postinjections. To keep the cumulative cocaine exposure during conditioning the same as during preexposure (60 mg/kg day), animals received maintenance dose injections (20 mg/kg) 4 h after place conditioning. As a procedural control for the sensitivity of the paradigm for aversive motivational effects, a separate group of previously drug naive animals (n = 8) received a low dose of naloxone (1 mg/kg, IP) four times in one of the two environments and were not exposed to the alternate environment. Naloxone has been shown previously to produce clear conditioned place place aversions (22). The naloxone group received saline injections at the same times the groups in the second chronic drug protocol above were injected during the preexposure phase with cocaine. The place conditioning score was measured as the difference between the amount of time spent on the paired side minus the time spent on the novel, neutral side.

Histology

At the end of the behavioral study, sham and lesioned animals were deeply anaesthetized with Somnotol and perfused transcardially with isotonic saline followed by 10% formalin. Brains were removed and postfixed in 20% sucrose in 10% formalin solution, and 32-μm cryostat sections were cut. Sections were mounted on gelatin-coated slides and Nissl stained to verify the placement and extent of the lesions. Sections were examined and photographed under brightfield microscopy.

RESULTS

A two-way ANOVA on the times spent on the cocaine paired side and the saline paired side of the place conditioning apparatus from the sham- and TPP-lesioned groups (Fig. 1) revealed a significant main effect of drug, $F(1, 15) = 23.6$, $p < 0.05$, but no significant main effect of lesion, $F(1, 15) = 0.21$, $p > 0.05$, nor a significant interaction, $F(1, 15)) = 0.12$, $p > 0.05$. Both the TPP-lesioned, $t(7) = 2.7$, $p < 0.05$, and sham-lesioned, $t(8) = 4.3$, $p < 0.05$, groups showed significant conditioned place preferences for cocaine. There was no significant difference in the preferences of the sham and lesioned groups, $t(15) = 0.3$, $p > 0.05$. A two-way ANOVA on the times spent on the morphine paired side and the saline paired side from sham- and TPP-lesioned groups (Fig. 1) revealed a significant interaction of drug and lesion, $F(1, 15) = 8.6$, $p < 0.05$. There was a significant difference between sham- and TPP-lesioned groups in the morphine conditioning phase, $t(15) = 2.9$, $p < 0.05$. Sham animals showed significant preferences for the morphine paired environment, $t(8) = 6.9$, $p < 0.05$, whereas TPP-lesioned animals did not, $t(7) = 0.6$, $p > 0.05$. Successful TPP lesions were anatomically defined as those that destroyed the majority of TPP neurons bilaterally. A representative Nissl section from a TPP-lesioned animal (Fig. 2) showed considerable neuronal loss accompanied by gliosis in the TPP area. One animal's lesion was unilateral, and this animal was eliminated from the data analysis above. Five of the seven animals remaining had lesions that extended the full caudal to rostral extent of the TPP.

An ANOVA on the conditioned place aversions scores of previously cocaine naive animals did not reveal any effect of conditioning time, $F(3, 24) = 0.3$, $p > 0.05$ (Table 1). An analysis of each group at the postinjection time point sampled also did not reveal any effect of the conditioning time: 6 h, $t(7) = 0.3$, $p > 0.05$; 11 h, $t(7) = 0.6$, $p > 0.05$; 16 h, $t(6) = 0.5$, $p > 0.05$; and 20 h, $t(5) = 0.4$, $p > 0.05$. An ANOVA on the scores of chronically treated animals also did not reveal any significant effect of conditioning time, $F(5, 68) = 0.5$, $p > 0.05$ (first chronic drug protocol, Table 1). An analysis of each of the groups treated under the first chronic drug protocol failed to show any significant aversions: 6 h, $t(7) = 0.4$, $p > 0.05$; 11 h, $t(6) = 0.2$, $p > 0.05$; 16 h, $t(15) = 1.4$, $p > 0.05$; 20 h, $t(14) = 0.4$, $p > 0.05$; 24 h, $t(12) = 1.2$, $p > 0.05$; and 32 h, $t(14) = 0.5$, $p > 0.05$. In the second chronic drug protocol, an ANOVA, excluding the naloxone

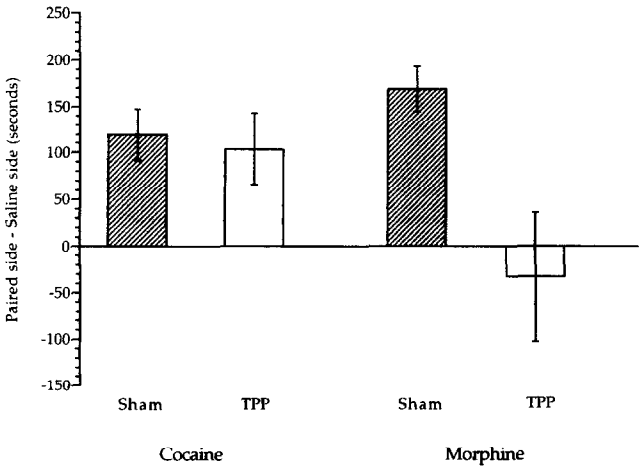

FIG. 1. Conditioned place preference scores of TPP-lesioned (n = 8) and sham-lesioned animals (n = 9) conditioned with cocaine (10 mg/kg, IP, for six pairings) and morphine (5 mg/kg, IP, for six pairings). Bars represent means ± SEM.

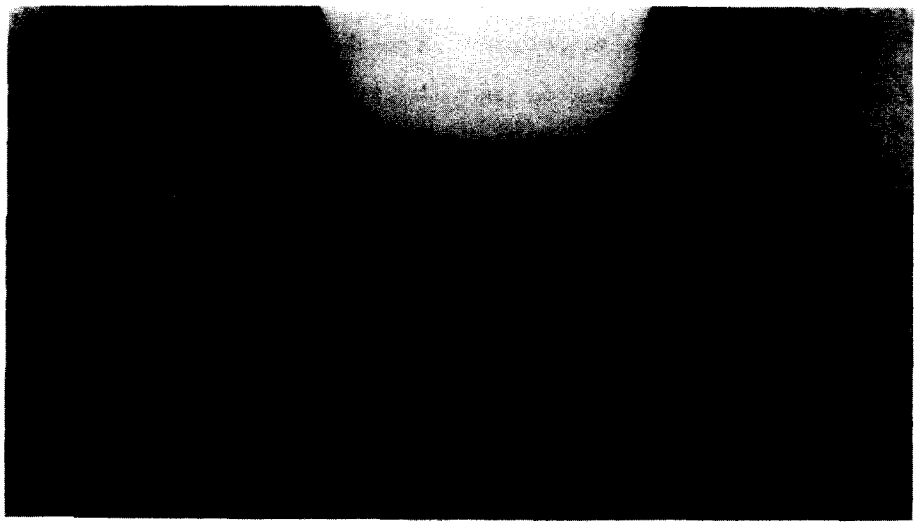

FIG. 2. A representative Nissl-stained coronal section from a TPP-lesioned animal. TPP animals were lesioned bilaterally with ibotenic acid and displayed neuronal loss and gliosis (arrows).

group, did not reveal an effect of conditioning time, $F(4, 37) = 0.3$, $p > 0.05$ (Table 1). An analysis of individual group scores did not show any significant place aversions in the second chronic drug protocol at the postinjection times sampled: 0.5 h, $t(7) = 0.2$, $p > 0.05$; 3 h, $t(7) = 1.7$, $p > 0.05$; 13 h, $t(4) = 0.2$, $p > 0.05$; 16 h, $t(13) = 0.6$, $p > 0.05$; 19 h, $t(6) = 0.1$, $p > 0.05$. The procedural control group showed a significant conditioned place aversion to the naloxone paired environment, $t(7) = 3.292$, $p < 0.05$.

TABLE 1

MOTIVATIONAL EFFECTS OF COCAINE WITHDRAWAL

Treatment Group	Paired Side-Neutral Side (s)
Naive protocol	
6 hours	16.5 ± 53.6
11 hour	−32.5 ± 58.5
16 hour	49.6 ± 92.4
20 hour	10.2 ± 23
First chronic drug protocol	
6 hour	23.2 ± 63.3
11 hour	−12.4 ± 71.4
16 hour	−51.9 ± 37
20 hour	11.9 ± 32
24 hour	−31.4 ± 26.4
32 hour	−16.9 ± 34.2
Second chronic drug protocol	
0.5 hour	−5.5 ± 33
3 hour	−61.8 ± 36.1
13 hour	−4.6 ± 29.2
16 hour	−29.6 ± 46.7
19 hour	−6.23 ± 56.4
Naloxone†	−163.8 ± 49.7

*Conditioned place aversion scores for environments paired with cocaine withdrawal at various times postinjection following a loading dose of cocaine (see the Method section for details of drug histories). Data represent means + SEM.

†A previously drug naive group treated with naloxone was included as a procedural control, and was conditioned immediately following a low dose of naloxone (1 mg/kg). The mean scores of the naloxone group represent times on the naloxone-paired sides minus the times on the neutral sides.

In the second chronic drug protocol, seven animals were lost due to convulsions. These deaths occurred in response to the 40-mg/kg injections, which were given during the week of conditioning. On the other hand, the 35-mg/kg injections given in the conditioning phase in the other two drug protocols never resulted in death. This suggests that the animals were sensitized to the convulsant property of cocaine in the second chronic drug protocol.

DISCUSSION

Both sham- and TPP-lesioned animals showed conditioned preferences for environments previously paired with cocaine, whereas only the TPP-lesioned animals failed to later show morphine place preferences. The failure of TPP-lesioned animals to acquire morphine conditioned place preferences has been found in the past (4,6), and thus verifies the behavioral phenotype of the lesion. Histological analysis also confirmed that the TPP was lesioned bilaterally. Sensory and learning deficits are not likely responsible for the lesion-induced impairment seen in morphine place conditioning, because in the same paradigm the animals were able to respond to the rewarding action of cocaine. It has been previously reported that the TPP does not mediate the reinforcing effects of drugs given to dependent and drug-withdrawn animals (4). Perhaps our cocaine place conditioning doses resulted in an aversive motivational state postinjection, at the time we conditioned. An aversive motivational state at the time of conditioning thus would explain our failure to find an effect of TPP lesions. However, the present data indicate that an aversiveness of cocaine withdrawal in place conditioning was not present even with doses and histories of cocaine exposure much greater than that used with the TPP-lesioned animals. Thus, it appears that in animals with little drug exposure the motivational substrates of morphine and cocaine are dissociable. Moreover, given the TPP's involvement in the naive or nondeprived re-

warding action of such agents as food (4), amphetamine (6), morphine (3,6), and heroin (23), cocaine appears to act via a different neurobiological substrate with respect to the TPP nucleus.

Neither drug-naive nor chronically cocaine-treated groups showed any significant aversions to an environment conditioned at any of several time intervals following cocaine administration. Place conditioning has been successful in detecting the aversiveness of morphine withdrawal at 16 h postinjection (3) and heroin withdrawal at 21 h postinjection (23). It is possible that we simply missed the cocaine withdrawal period that has been reported in other paradigms. Markou and Koob (19) have suggested that elevations in intracranial self-stimulation measures (16,19) detect the anhedonic facet of cocaine withdrawal, whereas others suggest that a neophobia assay has captured the anxiety component of cocaine administration (40). Measures of elevations in ICSS thresholds have detected changes following cocaine administration (40 mg/kg, IP) 24 h earlier (16,19). If animals are allowed to intravenously self-administer cocaine to a cumulative dose of 35 mg/kg, elevations in ICSS thresholds occur 1 h later and last 5 h (19). Work using the neophobic reactions of animals have found changes as early as 20 min postcocaine, with a pretreatment drug history similar to the second chronic drug protocol reported here. Animals chronically treated with cocaine at high doses for a period of 10 days (first chronic drug protocol) prior to conditioning and sampled at six time points postinjection did not reveal any conditioned place aversions. The second chronic drug protocol also attempted to sample time points as early as 0.5 h and up to 19 h postinjection, but again revealed no indication of place aversions. A group of animals run concurrently with cocaine withdrawal conditioning groups in the second chronic drug protocol received a low dose of naloxone in one environment, and later showed robust conditioned aversions to the naloxone paired environments. The naloxone group acted as a procedural control, verifying the sensitivity of the paradigm used in this study to conditioned place aversions. The second chronic drug protocol involved enough by way of daily cocaine exposure that animals became sensitized to the convulsant properties of cocaine, resulting in several deaths. A similar dose in the other two protocols never resulted in death. This is an indication that the second chronic drug protocol was a realistic attempt to give the animals as much cocaine as possible, in an effort to detect any rebound withdrawal motivational effects. Cocaine withdrawal does not appear to have aversive motivational effects in place conditioning, using drug protocols that have been successful in producing withdrawal signs in accordance with the measures of other paradigms.

It has been argued that cocaine may have two rewarding aspects, one of which is a central effect and the other its local anaesthetic action (31). Procaine, a local anaesthetic given peripherally at doses that did not stimulate locomotor activity, was rewarding in a place preference paradigm (31). The authors hypothesized that the local anaesthetic properties of cocaine were rewarding. A subsequent attempt to minimize the local anaesthetic properties by giving cocaine intracerebroventricularily has shown that this rewarding action can be blocked by neuroleptics, but that neuroleptics do not block the rewarding action of intraperitoneal cocaine (20). These data appear to support the hypothesis that the local anaesthetic property of cocaine can be rewarding. Applying this interpretation, TPP lesions may have blocked one central reward system mediating cocaine's reinforcing effects, but lesioned animals still showed preferences under cocaine due to local anaesthetic effects. There are several problems with this interpretation. First, not all local anaesthetics maintain drug self-administration (37), suggesting that the local anaesthetic properties of drugs are not necessarily rewarding. Second, given that procaine has dopaminergic activity (14), procaine may be rewarding centrally in addition to its local anaesthetic properties. Third, although the doses used in the procaine place conditioning by Spyraki et al. (31) did not stimulate locomotor activity, this is only an indirect argument against a dopaminergic rewarding action of this drug at the doses tested. Fourth, Spyraki et al. (31) and Morency and Benninger (20) did not counterbalance their conditioning within groups, consistently pairing the drug with the least preferred side. This complicates interpretation of the results because the anaesthetic could be producing place preferences by virtue of its anxiety-reducing properties when the animal is placed in an unpreferred environment. Fifth, in an unbiased, counterbalanced place conditioning paradigm it has been found that an analogue of cocaine (cocaine-methiodide), which cannot pass the blood-brain barrier, gave place preferences when administered to animals intracerebroventricularily, but not when it was administered peripherally (13). Sixth, in the same study (13) it was also found that peripheral administration of procaine failed to give place preferences. The findings that some local anaesthetics fail to maintain self-administration, whereas both procaine and the blood-brain barrier impermeable analogue of cocaine fail to produce conditioned place preferences when given peripherally, argue strongly against a rewarding role for the anaesthetic property of cocaine.

Dopamine is the most popular candidate substrate for cocaine's rewarding effects (17). However, in the place conditioning paradigm it has been found that neuroleptics did not block the rewarding effects of cocaine given systemically (18,20,31). Morency and Beninger (20) suggested that neuroleptics do block the rewarding action of cocaine when cocaine is given intracerebroventricularly, thus bypassing the local anaesthetic properties that the authors believed were rewarding. Nevertheless, for the reasons outlined above, it is difficult to accept the data of Morency and Beninger (20) or Spyraki et al. (31) given that their place preference paradigms were biased and the conditioning of the animals in their groups was not counterbalanced. Studies using the cocaine self-administration paradigm found that dopamine depletion resulted in reduced response rates (27) whereas the use of neuroleptics resulted in elevated response rates, suggesting that the rewarding action of cocaine was attenuated (8,35). It may be that the place preference literature fails to find an effect of neuroleptic treatment on cocaine reward because the paradigm has been used only with previously drug naive animals. In contrast, cocaine self-administration involves animals that have been chronically exposed to the drug. Perhaps animals chronically treated with cocaine and then used in a place conditioning paradigm would produce place preferences that could be blocked by neuroleptics. Such a test might reconcile the differences with studies of cocaine self-administration.

Cocaine appears to be novel reinforcer. Its rewarding properties involve a neurobiological substrate that is separate from the TPP substrate of other rewarding stimuli. Because TPP-lesioned animals acquired and displayed cocaine conditioned place preferences, this nucleus does not play a role in either the acquisition or expression of cocaine place preferences. Unlike morphine or heroin, there also does not appear to be any cocaine withdrawal in the form of a aversive motivational state during drug abstinence. This finding calls into question the prediction of opponent process theory (30) that rebound

motivational effects develop after repeated exposure to a rewarding stimulus. Although there are no direct aversive consequences of cocaine drug abstinence, our results do not preclude other changes in animals' responses to novel stimuli or in the reinforcing strength of intracranial self-stimulation. It would be interesting to see whether place conditioning with another stimulant like amphetamine would also fail to demonstrate the aversiveness of drug withdrawal. Perhaps aversive motivational states are not a characteristic of drug abstinence from stimulants.

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