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# Reinstatement of Heroin and Cocaine Self-Administration Behavior in the Rat by Intracerebral Application of Morphine in the Ventral Tegmental Area

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STEWART, J *Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of morphine in the ventral tegmental area* PHARMACOL BIOCHEM BEHAV 20(6) 917–923, 1984.—In rats trained to self-administer heroin or cocaine intravenously, non-contingent priming injections of heroin or cocaine, respectively, reinstated responding after a period of extinction. In rats similarly trained to self-administer heroin or cocaine intravenously, morphine sulphate was applied centrally to sites in the ventral tegmental area (VTA), the periventricular grey (PVG) and the caudate nucleus following a period of extinction Self-administration behavior was reinstated by morphine application to sites in the region of the VTA, but not to other sites, in both heroin and cocaine-trained animals. This priming effect of morphine was blocked or attenuated by prior administration of naltrexone, given intraperitoneally Morphine in the VTA is known to activate mesolimbic dopamine neurons, suggesting that dopamine activity in this system may underlie the priming effects of both opiates and stimulants Furthermore, the fact that the mesolimbic system is implicated in the positive motivational actions of both drug groups, suggests that morphine reinstates drug-taking behavior in these animals by activating appetitive motivational systems of the brain

Morphine Ventral tegmental area Reinstatement of drug-taking Priming Heroin Cocaine

STUDIES from this laboratory have shown that in animals previously trained to self-administer heroin intravenously, noncontingent intravenous "priming" injections of heroin (or morphine) reinstate responding after a period of extinction [12]. Similarly, in cocaine-trained animals, intravenous priming injections of cocaine reinstate the previously reinforced behavior [11]. We have proposed that these priming injections of the drug activate appetitive motivational states that are involved in the reinitiation and maintenance of drug-seeking behavior. One question that arises from the intravenous priming experiments is, can we specify which actions of the drugs are responsible for the priming effects, and can we delineate the specific neural systems of the brain involved? The idea that priming injections reinstate behavior by activating appetitive motivational states, suggests that these stimulant and opiate drugs might have their priming effects via their actions on the mesolimbic dopamine pathways. It is known, for example, that the positive reinforcing properties of the stimulants, cocaine and amphetamine, depend on the integrity of the neurons of the mesolimbic dopamine system where they act to release dopamine from terminals or to block the mechanisms of transmitter inactivation [10, 13, 23, 32, 42] In addition, animals will self-administer amphetamine to the terminal regions of these neurons in the nucleus accumbens [26]. Recent evidence suggests that the reinforcing effects of opiates derive from their actions on these same dopamine neurons. Rats will self-administer morphine directly into the ventral tegmental area (VTA) of the brain, the cell body region of these mesolimbic dopamine neurons [4], and will display an increased preference for a place associated with central injections to the area [5,29]. Thus the appetitive motivational, or positive incentive, properties of opiates, like those of stimulants, appear to be mediated via the mesolimbic dopamine pathway. Opiates appear to excite one subpopulation of these neurons by acting on opiate receptors in the cell body region [18,24]. Bilateral application of morphine to the region elicits forward locomotion and exploration of the environment [22,40], behavior normally elicited by positive incentive stimuli [2, 3, 9, 25]. In light of these observations we have approached the problem of specifying the neural substrate involved in the priming effect by examining the effects of application of morphine to VTA and other sites in animals previously trained to self-administer either heroin or cocaine intravenously.

## EXPERIMENTS IN HEROIN-TRAINED ANIMALS

### METHOD

Twenty-one Sprague-Dawley rats from Canadian Breeding Farms, St. Constant, Quebec, weighing 300–350 g upon arrival were used in these experiments. The animals were

housed in a temperature and humidity controlled environment under a 12 hr light-dark cycle. Food and water were continuously available from the time of surgery. Prior to surgery all animals were placed on a 23-hr food deprivation schedule for a period of approximately one week. During this time they were handled daily and trained to bar-press for food in a chamber used exclusively for this purpose. At the time of surgery, animals had IV catheters implanted into the left jugular vein while under pentobarbital anesthesia. Catheters were constructed from silastic tubing (0.064 cm inner diameter, 0.119 cm outer diameter). The catheter was secured to the vein with surgical thread and passed SC to the top of the head where it exited into a connector mounted on the skull. A stainless steel screw was also mounted in dental cement with 0.6 cm of the threaded end exposed. A cap was placed over the open end of the connector when the infusion system was not in use. Catheters were flushed daily with heparinized (5 IU/ml) physiological saline for the first week after catheterization to protect against the formation of emboliems in the vein. When catheter failure occurred due to blockage or leakage during the course of the experiment, animals were recatheterized using the right vein.

Animals were also implanted stereotaxically with intracerebral guide cannulae directed at the regions of the ventral tegmental area (VTA), the periventricular grey (PVG), or the caudate nucleus (CAUD). Each animal had cannulae placed in two of the regions All placements made into the VTA and PVG region ranged from 2 2 to 4.2 mm posterior from bregma. Cannulae were lowered vertically, 0.6 mm lateral from the midline, or at a 16 degree angle, 3.3 mm lateral from the midline. The guide cannulae, cut from 22-gauge stainless steel tubing, were lowered to a range of depths (Fig 2). The coordinates for the caudate guide cannulae were 2.1 mm anterior from bregma, 3.0 mm lateral from the midline, and 5.0 mm ventral from the dura. Drug could be delivered to a brain site in crystalline form via 28-gauge stainless steel inner applicator tubes that were lowered 1 0 mm beyond the tip of the guide cannulae. "Dummy" inner tubes with caps were kept in place between drug applications Following completion of the experiment, animals were perfused with physiological saline and 10% formalin with the applicator tubes in place. Brains were sliced in frozen section and stained to allow for localization of the injector tips.

Animals were trained to self-administer heroin in operant chambers equipped for self-administration of fluids [11,12]. Boxes were equipped with one or two bars raised to a height of 9 0 cm above the floor to prevent accidental activation by the animal Each bar press during self-administration periods led to an infusion rate of 0.01 ml/sec. Bar presses during the 9–13 sec infusion were counted, but did not lead to further infusions. The heroin solution (diacetylmorphine HCl, Health and Welfare, Canada) was made up weekly with physiological saline in a concentration of 400 μg/ml with 5 IU/ml heparin added. Daily training sessions of 2 to 3 hr were run until responding was stable and reliable (usually 7 to 10 days) Following training, each animal was submitted to a series of tests over a period of several weeks An attempt was made to test every animal twice on each of the tests, but this was not always possible.

## THE TESTS

### *Reinstatement by an IV "Priming" Injection of Heroin*

All test sessions consisted of a 1- to 2-hr period of self-administration followed by extinction conditions for the rest of the session. Extinction conditions were introduced by replacing the drug solution in the syringe with physiological saline. Rats administered 3 to 5 100 μg/kg heroin infusions/hr under these conditions. When extinction conditions were introduced, response rate initially increased and was then reduced to zero. When a period of 30 min with no responses had passed the animal was picked up and given a 1 0 ml/kg IP injection physiological saline. Thirty min later an IV infusion of 0.3 ml saline was delivered by the experimenter and 30 min after that an IV infusion of 100 μg/kg heroin was delivered by the experimenter. It is important to note that the animals in these experiments were habituated to being picked up and manipulated while in the self-administration chambers. This was done to ensure that any changes in responding that occurred following the experimental manipulation were not due merely to disturbing the animal Control injections of saline, IV or IP, were given appropriately, and removal and reinsertion of dummy intracerebral applicators was also done. Behavior was normally monitored for 3 hr following a "priming" drug manipulation

### *Naltrexone Challenge of the IV Priming Injection of Heroin*

This test session was identical to Test 1 except that a 2.0 mg/kg IP injection of the long-acting opiate antagonist naltrexone HCl (Endo Laboratories Inc., Garden City, NY) was substituted for the IP injection of saline.

### *Reinstatement by Intracerebral Priming With Morphine*

As in Tests 1 and 2, following at least 30 min without responding under extinction conditions, the animal was picked up and the inner dummy tube of one of the intracerebral cannulae was removed and replaced by an empty applicator. Thirty min later the empty applicator was replaced by one containing crystalline morphine sulphate (BDH Chemicals, Toronto) and was left in place for the 3-hr test. Each brain site was tested in a similar manner on different days. Morphine was tapped into the 28-gauge applicator by making 10 taps on a thin layer of crystals placed on a glass surface. The amount of morphine inserted into the applicator by this method was found to be constant at approximately 18 μg The applicators were checked under a microscope before and after tapping. Used applicators were cleaned in a sonifyer containing 70% ethanol

### *Naltrexone Challenge of Intracerebral Priming With Morphine*

These tests were identical to Test 3 except that, 30 min prior to the insertion of the empty applicator, the animals were given an IP injection of 2.0 mg/kg naltrexone.

## RESULTS

The results of Test 1 verified that in these animals, as in animals in our previous experiments [12], non-contingent intravenous priming injections of heroin reinstate heroin-reinforced responding after a period of extinction The mean number of responses made in each 15-min period of the first hour after the priming infusion in 19 tests made in 11 animals was 5.9, 15 3, 0.8 and 0.3. When the IV priming infusions of heroin was given following the IP injection of naltrexone in Test 2 (14 tests in 11 animals) none of the animals responded during the period following the infusion

The results obtained when the application of morphine to

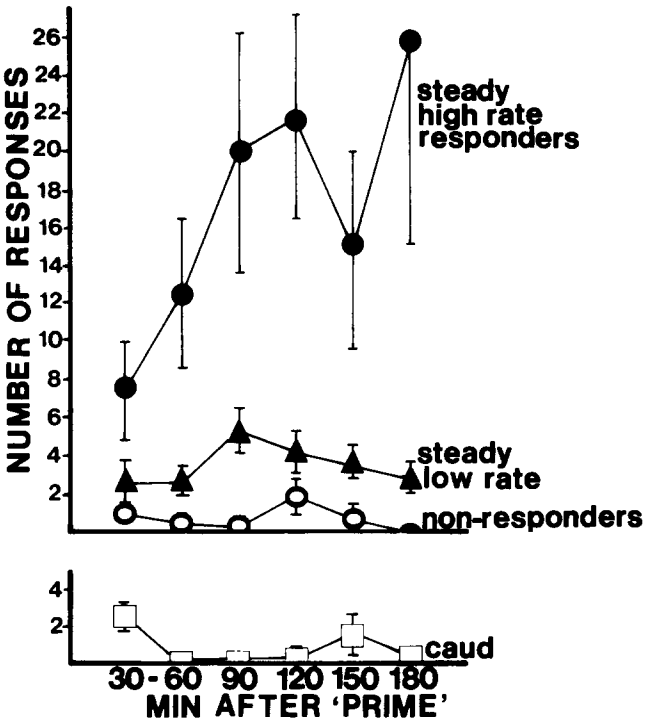


FIG 1 Mean (±SEM) number of responses made under extinction conditions by *heroin-trained* animals following the "priming" application of morphine to sites in the region of the VTA and PVG (upper part of figure) and the caudate nucleus (CAUD) Filled symbols represent data from animals that responded (see text) Cannula placements for these animals are indicated in Fig 2 by the same symbols

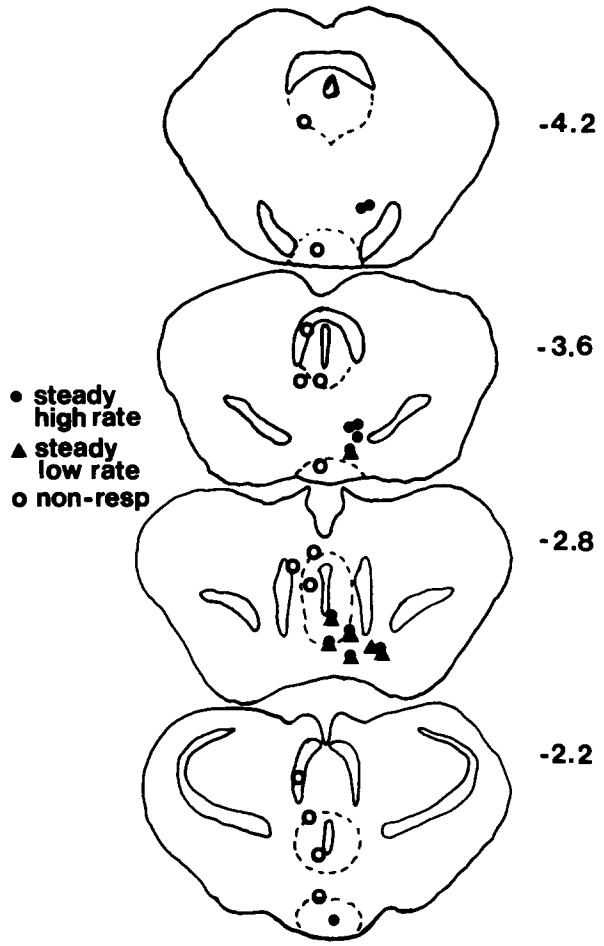


FIG 2. Location of cannulae tips in regions of the VTA and PVG in *heroin-trained* animals. Filled symbols represent placements where the "priming" administration of morphine led to reinstatement of responding (see Fig. 1). Sections were drawn after Pellegrino, Pellegrino and Cushman (L J Pellegrino, A S. Pellegrino and A. J. Cushman *A Stereotaxic Atlas of the Rat Brain* New York Plenum, 1979). Numbers at the right indicate mm from bregma.

the brain was used as the priming event (Test 3) can be seen in Figs. 1 and 2. The filled circles in Fig. 1 represent the results from 12 tests in 6 animals that displayed steady high levels of responding throughout the 3-hr period when morphine was applied, often making more than 20 responses in 30 min. It can be seen from Fig. 2 that the placement of the cannula tips of these animals (filled circles) was in or near the VTA. The filled triangles in Fig. 1 represent the results form 15 tests in 8 animals that also responded reliably throughout the 3-hr period, but at much lower rates, only occasionally making more than 10 responses in 30 min and never as many as 20. The cannula tips of these animals (filled triangles, Fig. 2) tended with one exception to be more distant from the VTA region than were those of the first group. Only occasional or no responding was obtained from 24 tests in 12 animals represented by the open circles. These placements were most often in the PVG region and clearly outside of the VTA Animals rarely responded when morphine was applied to the caudate nucleus. The results of 22 tests in 12 animals are shown by the open squares in the lower portion of Fig 1.

Figure 3 presents the results from six animals that showed reinstatement of responding by morphine (13 tests) and that were tested with morphine on other occasions following the injection of naltrexone (11 tests). It can be seen that naltrexone severely attenuated the priming effect of intracerebral morphine especially during the first two hours of the 3-hr session.

## EXPERIMENTS IN COCAINE-TRAINED ANIMALS

### METHOD

Twenty Sprague-Dawley rats from the same source served as subjects in these experiments Treatment, housing and surgery were the same as in the heroin experiments except that animals were trained to self-administer a 1.0 mg/kg cocaine solution delivered at an infusion rate of 0.01 ml/sec. The solution of cocaine HCl (BDH Chemicals, Toronto) was made up with physiological saline in a concentration of 4.0 mg/ml with 5 IU/ml heparin added. Following training, 11 of the animals were submitted to the same series of 4 tests as were the heroin-trained animals (IV priming, but with cocaine; naltrexone challenge of IV priming, intracerebral priming with morphine; and naltrexone challenge) The second group of 9 animals was submitted only to Tests 3 and 4, intracerebral priming with morphine and naltrexone challenge. The results for all the animals given intracerebral priming with morphine were combined for presentation. Two

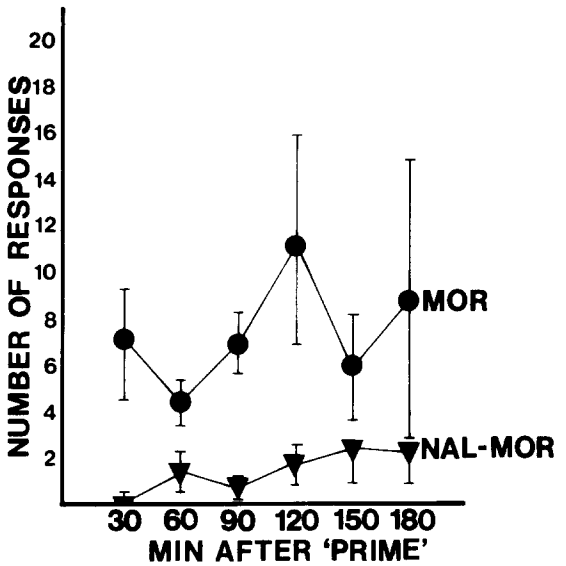


FIG 3 Mean (±SEM) number of responses made under extinction conditions by *heroin-trained* animals that responded to the "priming" applications of morphine and that were subsequently retested following naltrexone pretreatment

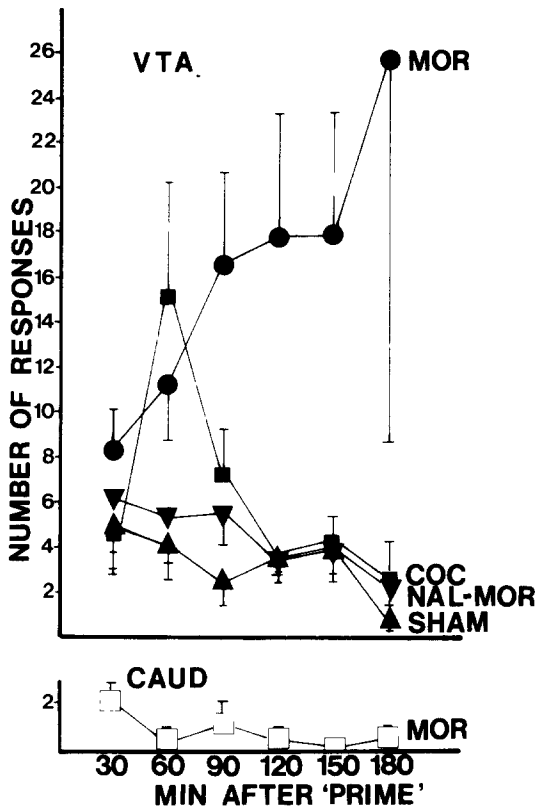


FIG 4 Mean (±SEM) number of responses made under extinction conditions by *cocaine-trained* animals following "priming" administrations The filled circles in the upper part of the figure represent the data from animals that responded to "priming" applications of morphine to sites in the VTA (see Fig 5). Data from animals in this group following naltrexone pretreatment (inverted triangles), sham cannula placement (upright triangles) and cocaine application (filled squares) are also shown Responses to morphine applications in the caudate nucleus (CAUD) are shown in the lower part of the figure

additional intracerebral priming tests were carried out in animals from the second group Either cocaine or an empty cannula was applied in the same way as morphine was applied in Test 3

## RESULTS

The results of Test 1 again verified our previous finding that non-contingent intravenous priming injection of cocaine reinstate cocaine-reinforced responding after a period of extinction [11]. The mean number of responses made in each 15-min period of the first hour after the priming infusion in 15 tests made in 7 animals was 0.8, 15.4, 3.3 and 1.3 When the IV priming infusion of cocaine was given following the IP injection of naltrexone on 14 tests made in these same 7 animals the mean number of responses in each 15-min period was 2.2, 8.1, 3.5 and 1 7 An analysis of variance done for pretreatment condition over the 4 15-min time blocks showed that the effectiveness of the cocaine priming infusions was not significantly affected by naltrexone pretreatment ($F>1.0$).

Figures 4 and 5 show the results obtained following intracerebral application of drug as the priming event in these cocaine-training animals. The filled circles in Fig. 4 show the results from 23 tests made in 11 animals that responded to the application of morphine to the brain. The placement of the cannula tips of these animals was in or near the VTA (see Fig. 5, filled circles). The open circles in Fig 5 represent the cannulae placements in 14 animals that in a total of 25 tests did not respond to the morphine application; although some of these animals had cannula tips in or near the VTA region, many had them outside the region and most often in the PVG. The results of 12 tests made in 9 animals with cannulae place in the caudate nucleus are shown by the open squares in Fig. 4.

The upper part of Fig. 4 also shows the results of the naltrexone challenge of the priming administration of morphine carried out in 5 animals (9 tests) that had previously responded to morphine in the VTA region (inverted triangles). It can be seen that these animals responded at about the same level as animals tested with the sham, empty cannulae in the same region (upright triangles, 11 tests in 7 animals). Finally, it can be seen that when cocaine was applied to the same region in 5 of these animals (9 tests), it caused a brief increase in responding during the second 30-min period (filled squares)

## GENERAL DISCUSSION

### INTRAVENOUS PRIMING INFUSIONS AND NALTREXONE CHALLENGE

In both sets of experiments reported here, the effects of intravenous priming infusions of the respective training drugs, heroin and cocaine, were challenged by pretreatment with naltrexone The results of these tests have relevance for two issues. The first concerns the specificity of naltrexone's

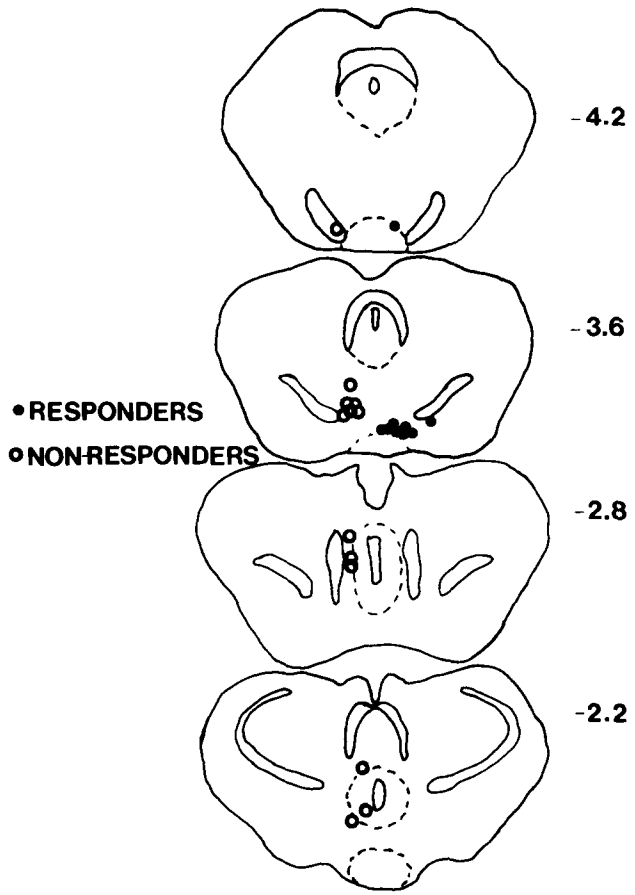


FIG 5 Location of cannulae tips in region of the VTA and PVG in *cocaine-trained* animals. Filled circles represent placements where the "priming" administration of morphine led to reinstatement of responding Open symbols represent placements where morphine led to only occasional or no responding

actions in this situation. It will be recalled that, as expected, naltrexone pretreatment blocked the priming effect of intravenous heroin in heroin-trained animals, but did not block the priming effect of intravenous cocaine in cocaine-trained animals. Thus, naltrexone appeared to be acting as a specific opiate antagonist to reduce the effectiveness of the intravenous heroin priming and not as a non-specific agent to reduce behavior in general.

The second issue these results address is the motivational basis of drug-taking behavior in opiate-trained animals. The fact that intravenous priming injections of heroin led to a resumption of heroin-taking behavior is consistent with the view that the *presence* of the drug in the body, not its absence, promotes drug-taking behavior [12]. The demonstration here that naltrexone treatment did not facilitate drug-taking behavior, but rather blocked the priming effect of the heroin infusion, provides confirming evidence that it is the appetitive motivational properties of opiates, and not the aversive withdrawal state associated with their absence, that is primarily, if not solely, responsible for the initiation and maintenance of drug-taking behavior (see also [7, 36, 41]).

PRIMING BY INTRACEREBRAL APPLICATION OF MORPHINE

As mentioned in the introduction, we [11] have proposed that priming injections of opiates and stimulants have their effects by activating appetitive motivational states involved in the initiation and maintenance of drug-taking behavior. In the present experiments it has been shown that priming by the application of the opiate, morphine, to sites in the VTA was a sufficient condition for the reinstatement of drug-taking behavior in both heroin-trained and cocaine-trained animals. This finding allows us to relate priming effects of both opiates and stimulants to their actions on a system of the brain implicated in the mediation of their positive reinforcing, incentive motivational, effects. As noted, activation of the mesolimbic dopamine system directly, as in these experiments, by application of opiates to the cell body region of the VTA, or indirectly, by dopamine release and reuptake blockade by stimulants such as cocaine, has been shown to underlie the positive reinforcing properties of these drugs [4,26]. Lesions of the system [33,35] and pharmacological blockade [6, 13, 32, 34] have been found, with few exceptions [16,28] to reduce the reinforcing effectiveness of these drugs, suggesting that common neural mechanisms underlie their reinforcing effects.

Priming is a phenomenon common to other reinforcers or incentive events. It is thought by many investigators to result from a changed incentive motivational state that is created by the presentation of a positive incentive event [1, 14, 15, 21, 38]. The incentive motivational state leads to increased locomotion and exploration of the environment [2, 3, 9, 25], and to enhancement or resumption of learned behaviors in the presence of stimuli previously associated with the incentive event. In a recent review Panksepp [27] has linked the motivational effects of incentives to the activation of what he calls the foraging-expectancy system of the brain, that same system activated by rewarding brain stimulation in the medial forebrain bundle. It should not be surprising, therefore, that self-administered drugs that have strong appetitive motivational effects often induce increased locomotion and exploration of the environment. It has been noted in the case of the psychomotor stimulants that this behavior is directed preferentially to aspects of the environment previously associated with reinforcers, i e , to conditioned stimuli [19,31]. Repeated injections of cocaine [20,30] lead to progressive increased in activity that are seen only in the environment associated with the injections Similarly, the increased activity elicited when opiates are applied to the VTA [8, 22, 37] also shows progressive enhancement, specific to the environmental cues repeatedly associated with the drug experience [40]. These findings, and those showing that the mesolimbic-mesocortical dopamine neurons are necessary for normal exploratory behavior in rats [17], all point to the intimate relation between forward locomotion, exploration, positive incentive motivation and the priming effects of reinforcers.

These observations bear on a concern sometimes expressed about the reinstatement of drug-taking behavior by priming administrations of drugs. It is suggested that the increases in responding observed might reflect changes in general activity and not in "motivated" behavior specifically directed toward stimuli previously associated with drug. We have taken a number of steps to eliminate this possible explanation. The bars have been elevated to prevent accidental contacts; a second inactivated bar has been introduced to determine specificity of responding; and video-recordings

have been taken to monitor the mode and pattern of responding that occurs. There is no evidence that "primed" animals accidentally bump into bars while moving about the box. Normally animals limit most of their responding to the activated bar. Sometimes, however, they do develop complex patterns of behavior when two identical bars are available in the box, animals may press both bars in succession for each infusion while self-administering drug, or rapidly press the inactive bar before initiating a response on the activated bar. Whatever the animal does, however, the behavior appears to be deliberate and to be directed towards stimuli and objects previously associated with the drug. As has been noted [39], increased activity elicited by drugs during self-administration is more likely to be directed toward stimuli associated with drug delivery. Thus, the activity effects of self-administered drugs, rather than raising a problem for the interpretation of reinstatement by priming, appear to point to the processes underlying the phenomenon.

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