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Facilitation of Sexual Behaviors in the Male Rat in the Presence of Stimuli Previously Paired With Systemic Injections of Morphine

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MITCHELL, J. B. AND J. STEWART. *Facilitation of sexual behaviors in the male rat in the presence of stimuli previously paired with systemic injections of morphine*. PHARMACOL BIOCHEM BEHAV **35**(2) 367–372, 1990.—Male rats were tested for sexual behaviors in an environment previously associated with injections of morphine. Both gonadally intact and castrated males displayed more frequent female-directed behavior, such as pursuit of the female, anogenital exploration, and partial mounts, and gonadally intact animals had shorter latencies to initiate copulation when tested for sexual behaviors in the environment previously associated with morphine. These results suggest that a conditioned state induced by stimuli previously paired with the positive incentive effects of an opiate drug can facilitate or modulate behaviors under the control of other primary positive incentives.

Morphine Sexual arousal Sexual behavior in male rats Conditioned drug effects

EVIDENCE that stimuli paired with systemic administration of morphine or heroin can acquire positive incentive properties comes largely from studies of conditioned place preference. In these studies, following repeated experience with the drug in the presence of one set of stimuli, and absence of drug in the presence of another, animals show a shift in preference for the stimuli previously paired with morphine (5, 7, 19, 28, 31, 34, 35, 37, 38). In the conditioned place preference paradigm, the positive incentive effects of drugs are inferred from the increased time that the animal spends in the presence of the conditioned stimuli, and in some cases from the increased activity seen in the presence of such conditioned stimuli [see (37)]. In addition to these behavioral changes, it might be expected that such conditioned drug effects could have general modulatory influences over ongoing behaviors, facilitating behaviors under the control of other positive incentives and inhibiting those controlled by aversive events.

Evidence from a variety of sources suggests that common neural mechanisms may underlie at least some aspects of all appetitively motivated behaviors (33). Exploration, feeding, drinking, copulation and predation can be elicited by electrical stimulation within the medial forebrain bundle (12), and there is considerable evidence that the appetitive properties of drugs of abuse are mediated by components within the same system (39). We were interested, therefore, in determining whether the conditioned incentive effects induced by a drug such as morphine might manifest themselves in the expression of behaviors directed toward a different but primary incentive object, the estrous female. In the experiments reported here, therefore, we tested for the facilitatory effects of conditioned stimuli previously associated with morphine injections on sexual behavior in the male rat.

EXPERIMENT 1

METHOD

Subjects

Male Long-Evans rats used in this and the subsequent experiment were selected from a larger population on the basis of a single test of copulatory behavior; only those males that mounted within 20 min and ejaculated within 30 min of the first intromission were included as subjects.

Target females were ovariectomized under a methoxyflurane anesthesia (Metofane, Pitman-Moore Ltd./M.T.C. Pharmaceuticals, Mississauga, Canada). Sexual receptivity was induced by injections of 10 μg estradiol benzoate, SC (Sigma, St. Louis, MO) in 0.1 ml peanut oil 72 and 24 hr before use, and 0.5 mg

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progesterone (Sigma) in 0.2 ml peanut oil 4 to 6 hr before use. Female sexual receptivity was verified by placing a female with a vigorous copulator just prior to use with an experimental male.

All animals were housed in standard wire mesh cages with Purina Rat Chow and water available ad lib. The animal colony was maintained on a 12-hr light:12-hr dark reverse light cycle with lights off at 0930 hr. All testing occurred during the animals dark cycle, between 1200 and 1700 hr.

Apparatus

Subjects were screened for sexual behavior in semi-circular boxes, 61 cm diameter × 36 cm deep, in a room dimly lit by four, 40-watt red light bulbs. Tests for sexual behavior were conducted in wooden boxes, 36 × 50 × 28 cm, with Plexiglas front walls. Each box was lit by a 7-w red light bulb. A red-light sensitive camera (Panasonic CCTV camera, model WV-1460), and a video cassette recorder (Sony Betamax VCR, model SLO-420 or SL-HFR30) were used to record the sessions for future scoring.

Procedure

The experiment included an initial conditioning phase followed by tests for sexual behavior. During the conditioning phase of the experiment, injections of 10 mg/kg (1 ml/kg) of morphine sulfate were given to the group PAIRED (n = 9) immediately before they were placed in the mating arenas, and to the UNPAIRED group (n = 9) in the animal colony. Conversely, the PAIRED group received saline injections in the animal colony, and the UNPAIRED group received saline injections prior to placement in the mating arenas. The third group (CONTROL) received injections of saline in both environments. In this and the subsequent experiment, animals were placed in the mating arenas, with no female present, for 1 hr every other day, and received their animal colony injections on the intervening days. In this, and the subsequent experiment, a total of four conditioning trials and four animal colony injections were administered.

Two days after the last injection of morphine, each animal received an injection of saline, was placed in a mating arena, and 5 min later a sexually receptive female was introduced. The test for sexual behavior lasted 30 min. Two weeks later, a second test for sexual behavior was given.

Tests for sexual behaviors. Males were placed individually in the mating arenas, and 5 min later a sexually receptive female was introduced. Tests lasted 30 min from the time of the introduction of the female.

After the female had been placed in the mating arena, sexual behaviors were scored using the following categories (31): *Mounts:* Identified by the male mounting the female from the rear and displaying a number of rapid, shallow pelvic thrusts. *Intromissions:* Similar to a mount, but included a long, deep thrust after the rapid shallow thrusts, a rapid kick with one hindleg, and a rapid short-stepped withdrawal from the female. *Ejaculatory pattern:* Identified by a final pelvic thrust that was slower and deeper than of an intromission, lateral removal of the forelimbs from the female that was held momentarily at the apex, and an absence of back-stepping before genital grooming. Where appropriate, six other measures were taken. These included: *Mount latency:* The latency from the introduction of the female to the first mount. *Intromission latency:* The latency from the introduction of the female to the first intromission. *Ejaculation latency:* The length of time from the first intromission to the first ejaculation. *Postejaculatory interval:* the time between ejaculation and the first intromission of the next copulatory series. *Interintromission interval:* the average number of intromissions per min to the first ejaculation. *Intromission ratio:* the ratio of intromissions to mounts plus intromissions.

The videotapes were scored for female-directed behavior using a time sampling procedure. Female-directed behavior was defined as activities directed toward the female that commonly precede and accompany copulation. These included: anogenital exploration, pursuing, sniffing, grooming, and climbing over the female, and manipulating the female's flanks (15,20). During the 30-min test, each male was observed for 2–3 sec every 30 sec and the predominant behavior noted, providing 60 observations per animal in each test. An animal's overall score was expressed as the percent of observations in which female-directed behavior occurred.

Measures of sexual behavior were analysed by analysis of variance, and subsequent post hoc comparisons were made using Tukey's HSD. The proportion of animals in each group mounting, intromitting, or displaying the ejaculatory pattern were analysed by χ^2 tests.

RESULTS

The mean percent of observations in which female-directed behaviors were observed for the three groups on both tests is shown in Fig. 1. An analysis of variance (group × time × test) of these scores yielded a significant group effect, $F(2,24) = 13.85$, $p<0.001$. Overall, the PAIRED group differed from both the CONTROL and UNPAIRED groups (p's<0.01), whereas the CONTROL and UNPAIRED groups did not differ from each other ($p>0.1$).The differences between the PAIRED group and the CONTROL and UNPAIRED groups were greater after the initial 10 min during both tests. Post hoc comparisons of scores from the first test showed that by 30 min the PAIRED group displayed significantly more female-directed behavior than either the CONTROL ($p<0.01$) or the UNPAIRED ($p<0.05$) groups. During the second test, the PAIRED group displayed significantly more frequent female-directed behavior than either the CONTROL or UNPAIRED groups at 20 min (p's<0.05) and more than the CONTROL group at 30 min ($p<0.01$). Overall, female-directed behavior was less frequent on the second test than on the first, $F(1,24) = 4.48$, $p<0.05$, but the differences between the first and second test for individual groups were not significant (p's>0.1). Finally, the frequency of female-directed behavior decreased during the test session for all groups, $F(2,28) = 82.49$, $p<0.001$.

The measures of copulation are shown in Table 1. Because not all animals copulated on both tests, each test was analysed separately. The analysis of variance of mount latencies yielded significant group effects for the first, $F(2,20) = 5.25$, $p<0.05$, and second tests, $F(2,24) = 4.30$, $p<0.05$, of sexual behavior. It can be seen in Fig. 2 that the PAIRED group initiated mounting more quickly than either the CONTROL or UNPAIRED groups during both tests (p's<0.05). The mean intromission latency of the PAIRED group in the first test was considerably shorter than either of the other two groups, but due to highly variable scores, the group effect was not significant ($p>0.1$). During the second test, however, there was a significant group effect, $F(2,23) = 3.64$, $p<0.05$, and post hoc comparisons showed that the PAIRED group intromitted more quickly than the UNPAIRED group ($p<0.05$).

The interintromission and postejaculatory intervals both appeared to be shorter in the PAIRED group, especially during the first test, but the differences were small and not statistically significant (p's>0.1). Groups did not differ significantly on any other measure in either test (p's>0.1), nor did groups differ significantly in the number of animals that mounted, intromitted, or ejaculated during each test (p's>0.05).

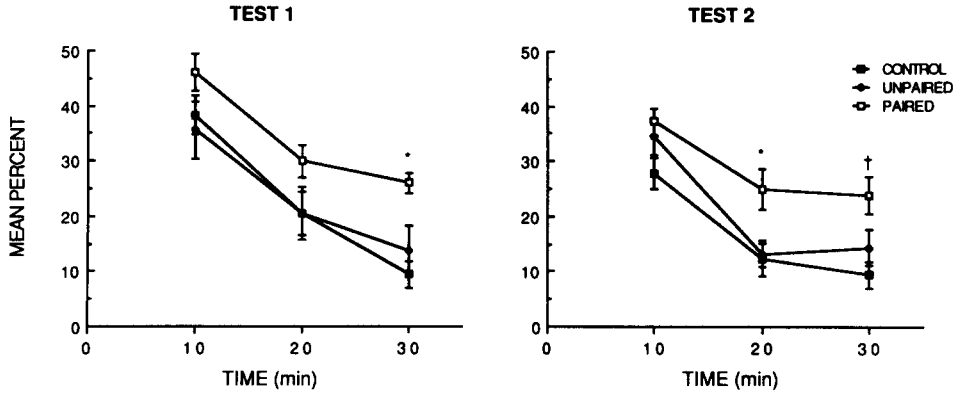

FIG. 1. Mean (±1 S.E.M.) percent of observations during which female-directed behavior was observed for animals that had previously received morphine paired with the mating arena (PAIRED), morphine in the animal colony (UNPAIRED), or had previously received saline injections in both locations (CONTROL). *Significantly different from CONTROL and UNPAIRED groups ($p<0.05$), †significantly different from CONTROL ($p<0.05$).

DISCUSSION

In this experiment, female-directed behavior increased and latencies to initiate copulation decreased in an environment previously paired with injection of morphine. These data suggest that the elicitation of the conditioned drug effect was able to facilitate sexual arousal when animals were presented with a sexually receptive female in that environment. Facilitation of sexual arousal has been shown to occur in spontaneously noncopulating male rats (8,22) or in recently castrated males (6) when animals are given mild tail or flank shock in the presence of a receptive female. In addition, it has been reported that in animals previously unwilling to initiate copulation, the presentation of a conditioned stimulus previously associated with peripheral shock, will also facilitate sexual behavior (10). Tail shock-induced facilitation of copulation is impaired by a variety of dopamine (DA) receptor blockers (2), suggesting dopaminergic mediation of the effect and a role for DA systems in sexual arousability.

Because castration has been reported to affect DA concentrations, and DA metabolism in the nucleus accumbens, a terminal field of the mesolimbic DA system (1,27), it was decided to test castrated male rats for sexual behaviors in an environment previously associated with morphine at a time after castration when both mesolimbic DA levels and sexual behaviors would be decreased. Because the unpaired and saline control groups in Experiment 1 did not differ from each other on any measure, only the unpaired control groups were included.

EXPERIMENT 2

METHOD

Male rats, screened for sexual activity, were bilaterally cas-

TABLE 1

MEAN BEHAVIORAL SCORES OF SUBJECTS AFTER REPEATED INJECTIONS OF MORPHINE IN THE MATING ARENA (PAIRED), OR THE ANIMAL COLONY (UNPAIRED), OR INJECTIONS OF SALINE IN BOTH ENVIRONMENTS (CONTROL)

Group	M*	I	E	ML	IL	EL	PEI	NM	NI	III	I ratio
Test 1											
CONTROL	7	6	5	140.6	183.5	475.2	322.2	23.3	14.7	1.43	0.351
UNPAIRED	8	6	5	121.2	236.0	558.1	322.2	19.1	16.2	1.18	0.410
PAIRED	8	7	6	41.6†‡	84.7	766.2	309.5	24.3	14.6	0.96	0.347
Test 2											
CONTROL	9	9	5	47.7	76.7	639.2	307.2	30.2	18.9	1.26	0.382
UNPAIRED	9	8	6	54.6	195.5	634.1	325.5	35.8	17.4	1.27	0.382
PAIRED	9	9	8	17.0†‡	47.2‡	550.6	276.9	40.2	19.0	1.32	0.338

*Abbreviations: M: the number of animals that mounted; I: the number of animals that intromitted; E: the number of animals that ejaculated; ML: mean mount latency (sec); IL: mean intromission latency (sec); EL: mean ejaculation latency (sec); PEI: postejaculatory interval (sec); NM: mean number of mounts; NI: mean number of intromissions; III: mean interintromission interval (NI/min); I ratio: mean intromission ratio [NI/(NI + NM)].

n = 9 for all groups.

†Significantly different from CONTROL, $p<0.05$.

‡Significantly different from UNPAIRED, $p<0.05$.

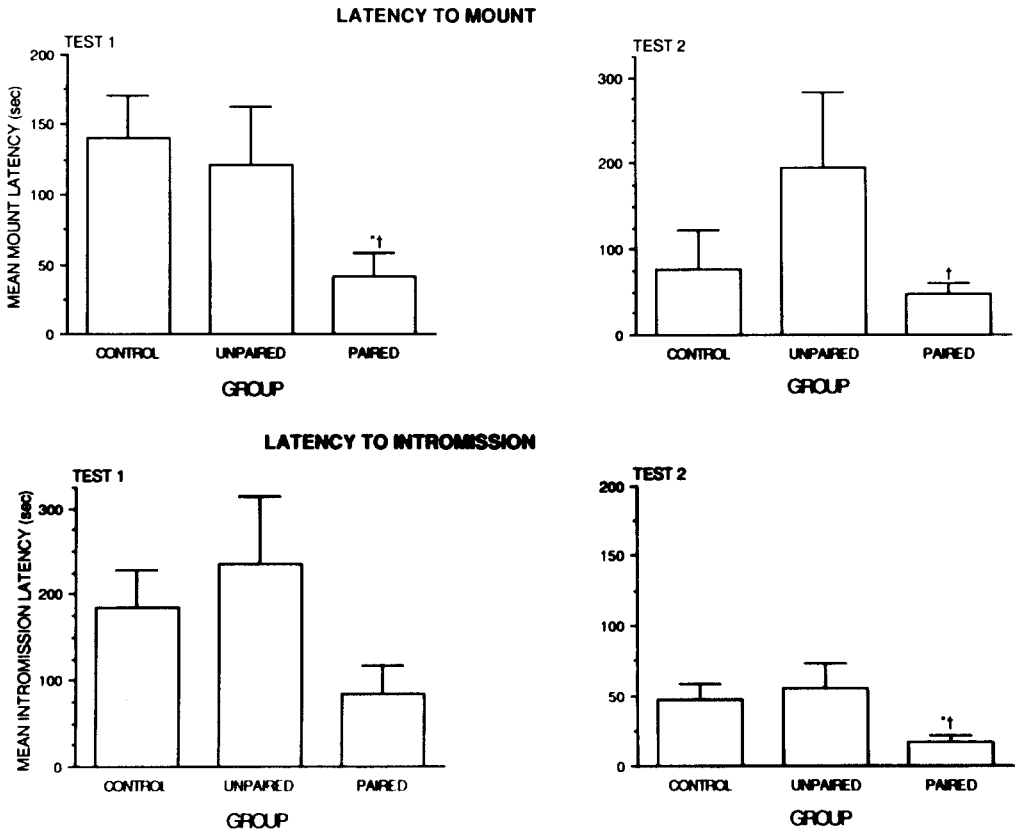

FIG. 2. Mean (± 1 S.E.M.) mount and intromission latencies of animals that had previously received morphine paired with the mating arena (PAIRED), morphine in the animal colony (UNPAIRED), or had previously received saline injections in both locations (CONTROL) in the two tests for male sexual behavior. *Significantly different from Control, $p<0.05$; †significantly different from UNPAIRED, $p<0.05$.

trated via a single incision along the midline of the scrotum. Sham-castrates received the scrotal incision, and the testes were left undisturbed. Surgery was performed under methoxyflurane anesthetic. Beginning 20 days after bilateral castration, one group of castrates (CAST-PAIRED), and a gonadally intact group (SHAM-PAIRED) received injections or 10 mg/kg morphine sulfate immediately before being placed in empty mating arenas, and injections of saline in the animal colony. Another group of castrates (CAST-UNPAIRED) and sham-castrates (SHAM-UNPAIRED) received 10 mg/kg injections of morphine sulfate in the animal colony and saline injections prior to being placed in the mating arenas. Two and 16 days after the last conditioning trial (28 and 42 days after surgery) animals received injections of saline and were given 30 min tests for sexual behavior in the mating arenas.

RESULTS

An overall analysis of variance (conditioning × castration × time × test) of the number of observations during which female-directed behavior occurred yielded a significant effect of conditioning, $F(1,32)=65.72, p<0.001$, and, more importantly, significant conditioning × castration, $F(1,32)=7.08$, $p<0.05$, and conditioning × time, $F(2,64)=12.99$, $p<0.001$, interactions. Figure 3 presents the mean percent of observations during which female-directed behavior occurred for each group during each test. During the first test, the PAIRED groups tended to display more frequent female-directed behavior than the UNPAIRED groups after the first 10 min, but at 20 min only the difference between the CAST-PAIRED and CAST-UNPAIRED groups was significant ($p<0.05$). At 30 min, however, both PAIRED groups differed from their respective controls (p's<0.05). These differences were even more pronounced during the second test; at both 20 and at 30 min, each PAIRED group differed from its UNPAIRED control group (p's<0.05). At 30 min in the second test, the difference between the SHAM-UNPAIRED and CAST-UNPAIRED groups was significant ($p<0.05$).

Groups differed significantly in the proportion of animals that mounted, $\chi^2(3)=26.19$, $p<0.001$, intromitted, $\chi^2(3)=23.84$, $p<0.001$, or showed the ejaculatory pattern, $\chi^2(3)=11.88$, $p<0.01$, during the first test. Groups also differed on these measures during the second test; mount, $\chi^2(3)=19.06$, $p<0.001$, intromissions, $\chi^2(3)=19.54$, $p<0.001$, and the ejaculatory pattern, $\chi^2(3)=24.0$, $p<0.001$. The group differences in these copulatory behaviors were due primarily to the lower incidence in castrated animals. The only exception was, perhaps surprisingly, that previous experience with morphine in the mating arena increased the proportion of SHAM animals that ejaculated during the first test from 0.22 to 0.56.

The analyses of copulation measures were done only for the gonadally intact groups; too few castrated animals copulated to be included in the analyses. Because significant heterogeneity of variance was found for the mount latency scores ($p<0.05$, Cochran's test for homogeneity of variance), these scores were analysed using Mann-Whitney U-tests. The SHAM-PAIRED group initiated mounting more quickly than the UNPAIRED group, although the difference was not statistically significant for the first

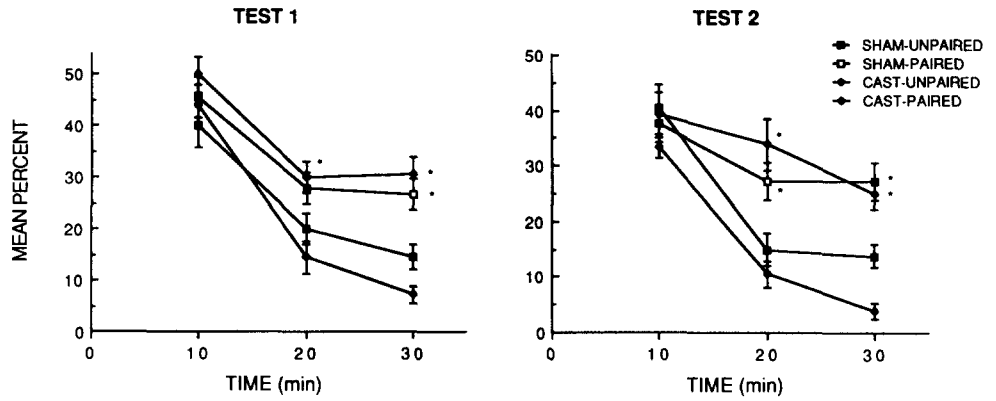

FIG. 3. Mean (±1 S.E.M.) percent of observations during which female-directed behavior was observed for animals that had previously received morphine paired with the mating arena (PAIRED), or in the animal colony (UNPAIRED), and been castrated (CAST) or sham-castrated (SHAM). *Significantly different from the respective UNPAIRED group ($p<0.05$).

test ($0.05<p<0.1$), it was for the second test, $U(8,8)=58$, $p<0.05$. None of the other comparisons made between the SHAM-PAIRED and SHAM-UNPAIRED groups were significant (*t*-tests for independent groups, two-tailed).

DISCUSSION

In Experiment 2, gonadally intact animals from group PAIRED tested for sexual behavior in the conditioning environment showed more frequent female-directed behaviors and shorter latencies to mount than did the SHAM-UNPAIRED animals. These finding replicate those of Experiment 1. More interesting, however, was the finding that males from the CAST-PAIRED group that were tested for sexual behaviors in the conditioning environment displayed consistently higher frequencies of female-directed behaviors than CAST-UNPAIRED males. These animals continued to pursue, sniff, and climb on the female despite the fact that they engaged in virtually no copulation. The elicitation of the conditioned drug effect in the environment previously paired with morphine appeared to enhance the effectiveness of the sexually relevant stimuli. It would be tempting to speculate that this effect might have been mediated by enhanced activity within the mesolimbic dopamine system. Indeed, conditioned changes in dopamine turnover have been found in animals repeatedly exposed to morphine in a specific environment (32).

GENERAL DISCUSSION

In these experiments, when male rats were tested for sexual behavior in an environment where they had previously been exposed to repeated injections of morphine, they displayed more frequent female-directed behavior, and, if they were gonadally intact, lower latencies to initiate copulation. It is important to note that the conditioned stimuli did not affect the performance of copulation itself; rather, it was approach to a sexually receptive female and the time to initiate sexual behaviors that were facilitated. Such findings suggest that conditioned stimuli previously paired with injections of the morphine induce conditioned changes in brain systems mediating appetitive behaviors in general. Systemic injections of low doses of morphine have excitatory effects on locomotion in the rat, whereas higher doses of morphine lead initially to behavioral depression followed by excitation and increased locomotion. With repeated injections, however, the depression is replaced by behavioral activation, and it is this response that comes to be elicited by conditioned stimuli paired with the injections (36). Systemic injections of morphine cause increased firing in mesolimbic DA neurons (23) and increased release of DA from terminals in the nucleus accumbens (11). Locomotion and exploration is induced by infusions of morphine and other endogenous opioid substances into the VTA (17,18) and it has been shown that this increased locomotion is elicited by conditioned environmental stimuli repeatedly paired with such injections (36,37). It has been reported that a conditioned stimulus previously paired with morphine will cause hyperthermia (16), and reverse morphine-withdrawal hypothermia, thus mimicking the effects of opiate administration (9). These findings suggest that stimuli associated with morphine administration may act by releasing endogenous opioids and that it is the release of endogenous opioids that facilitates sexual behaviors in the male. We have reported that infusions of morphine into the region of the VTA facilitate male sexual responding in the presence of a sexually receptive female (26). Feeding is facilitated by infusions of morphine into the VTA if food is present (13,14), and as mentioned above, if neither food nor a female is present, increased locomotion is found (17, 18, 36). Thus, activation of VTA cells elicits approach behavior appropriate to the stimuli present. It is interesting that the facilitating effects of tail-shock on appetitive behaviors are also found to be appropriate to the stimuli present. As mentioned earlier male sexual behavior is increased by tail-pinch in the presence of receptive females, as is feeding in the presence of food (2–4, 30).Tail-shock induced feeding appears to be an opiate mediated effect on the DA system shown to be attenuated by both naloxone and the DA receptor blocker pimozide. Recently, we have found in this laboratory that tail-pinch induced copulation in castrated male rats is similarly attenuated by naloxone (21).

Consistent with these findings are those from a series of experiments by Leiblich *et al.* (20) and Miller and Baum (25) concerned with the possible role of endogenous opioids in the control of male sexual behavior. They found that naloxone, given two to three weeks following castration, further reduced ejaculation and mounting in rats and significantly inhibited the resumption of mating in sexually exhausted intact males. These results suggested to them that endogenous opioids act to facilitate sexual behavior by enhancing the positive incentive properties of the female.

The experiments reported in this paper show that conditioned stimuli previously paired with one set of positive incentive stimuli

can act to facilitate behaviors appropriate to other incentive stimuli. The motivational significance of conditioned stimuli, and thus the neural processes activated, may prove to be better assessed by testing their effects on behaviors elicited in the presence of primary incentive stimuli having similar or opposite valence.

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