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Context-Specific Sensitization to Naloxone-Precipitated Withdrawal in Hamsters: Effect of Pimozide

PAUL SCHNUR,[1] MANUEL ESPINOZA AND RYAN FLORES

University of Southern Colorado

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SCHNUR, P., M. ESPINOZA AND R. FLORES. *Context-specific sensitization to naloxone-precipitated withdrawal in hamsters: Effect of pimozide.* PHARMACOL BIOCHEM BEHAV **48**(3) 791–797, 1994.—Three experiments were conducted to investigate the development of context-specific sensitization to naloxone-precipitated withdrawal in hamsters. In Experiment 1, animals in group M/S were given morphine (15 mg/kg) injections in a distinctive environment and saline in the home cage. Animals in group S/M were given saline in the distinctive environment and morphine in the home cage, and animals in group S/S were given saline in both environments. All groups were challenged subsequently with naloxone (0.4 mg/kg) in the distinctive environment and then observed for signs of opiate withdrawal. The results showed that group M/S gave more naloxone-precipitated withdrawal signs than each of the other groups, which did not differ from one another. Experiment 2 was designed to test the effect of pimozide on context-specific sensitization to naloxone-precipitated withdrawal. The design was similar to that of Experiment 1 but group P/M/S, which received an injection of pimozide (0.5 mg/kg) 4 h prior to morphine, was added. The results indicated that context-specific sensitization developed as in Experiment 1, except among animals treated with pimozide. Experiment 3 was designed to determine whether pimozide interferes with the development or the expression of context-specific sensitization. Six groups, differing in the frequency and timing of the pimozide injection, were employed. The results indicated that pimozide interfered with context-specific sensitization, whenever it was given. It is concluded that pimozide interferes with the expression of context-specific sensitization, although a separate effect on the development of sensitization is not ruled out.

Sensitization Naloxone-precipitated withdrawal Morphine Pimozide Dopamine Conditioning Hamsters Context-specific

A PROMINENT feature of repeated opiate administration is the development of behavioral sensitization to the locomotor activating effects of low doses of opiates. Behavioral sensitization to opiates has been demonstrated following systemic administration of morphine as well as after the intracerebral administration of morphine and the opioid peptides DAMGO, DALA, and DADLE (2–4,9,19–21,23,39,42,52,53,55). Accumulating evidence indicates that behavioral sensitization to opiates is mediated by functional alterations in the mesolimbic dopamine (DA) system. For example, sensitization to morphine is correlated with an increased turnover of DA in the nucleus accumbens [NACC; (20)] and with decreased release of DA from cell bodies in the ventral tegmentum [VTA; (21, 22)]. In addition, sensitization is blocked by intra-VTA administration of naltrexone (21) and pimozide, the DA receptor antagonist (55).

Previous research has demonstrated that opiate-induced sensitization to the locomotor activating effects of systemic or intra-VTA morphine can be conditioned to environmental stimuli (24,34,54). That is, animals given repeated intra-VTA injections in a distinctive environment show sensitized locomotor activity to a morphine challenge when tested in that same environment, whereas animals given daily intra-VTA saline or intra-VTA morphine in a different environment do not (34). Evidence that the sensitized activity to morphine is a conditioned effect is provided by the increase in activity following a saline challenge in the morphine-associated environment (50,54). Furthermore, both the development and ex-

[1] Requests for reprints should be addressed to Paul Schnur, Department of Psychology, Indiana University South Bend, South Bend, IN 46634.

pression of context-specific sensitization are blocked by prior administration of pimozide (35,54).

A second feature of repeated opiate administration is the development of sensitization to the effects of the opiate antagonists, naloxone and naltrexone. For example, exposure to morphine produces a leftward shift in the dose–response curve for naloxone-induced suppression of operant responding [(1, 8,11,14,25,32,48,61,60,62); but see (10)]. Similarly, sensitization to naltrexone-induced suppression of operant responding occurs following exposure to mu opioid agonists such as levorphanol, fentanyl, and methadone, and to a lesser extent, following exposure to the kappa agonists, ethylketocyclazocine and U50,488 (1). Sensitization to naloxone-precipitated withdrawal signs such as wet dog shakes, paw tremors, teeth chattering, and yawning following morphine administration is taken as an indication of opioid dependence and has been reported in a variety of species (5,15,18,30,38,40,41,57).

If exposure to opiates produces correlated changes in several response systems, one might expect that sensitization to naloxone-precipitated withdrawal, like sensitization to locomotor hyperactivity, could be conditioned to environmental stimuli and that such conditioning would be blocked by pimozide. Previous research has demonstrated that withdrawal responses can be conditioned to morphine associated environments (13,17,26,36,45). Conditioned withdrawal responses occur when animals are challenged with saline in a morphine-associated environment. Such conditioned withdrawal responses, if elicited in a morphine-associated environment, could be expected to summate with any withdrawal responses elicited by naloxone to yield context-specific sensitization. Kelsey and his colleagues (13,26) demonstrated that rats given morphine in a specific environment show sensitized withdrawal responses to naltrexone (6 mg/kg) when tested in the morphine-associated environment. Falls and Kelsey (13) found that more wet dog shakes were elicited by naltrexone in a morphine paired than in a morphine unpaired environment. In a subsequent study, Kelsey et al. (26) examined sensitized responses to naltrexone following either 1 or 5 days of morphine abstinence in paired and unpaired rats. After 5 days of abstinence, there were no differences between paired and unpaired rats in their withdrawal responses to naltrexone. After one day of abstinence, however, paired rats circled, reared, and jumped more than did unpaired rats, but there were no differences on other withdrawal measures such as wet dog shakes. It is not clear why wet dog shakes (a prototypical withdrawal response) showed context-specific sensitization in one study but not in another using similar procedures. Moreover, since circling, jumping, and rearing are indicative of increased activity, Kelsey et al. (1990) acknowledged that these results might be interpreted as revealing conditioned activity rather than conditioned withdrawal.

In light of such interpretive difficulties, a replication seemed warranted. Because previous work in our laboratory has documented the development of opiate dependence and the conditioning of naloxone-precipitated withdrawal in hamsters (40,41,43), the present work used hamsters as subjects. To minimize the possible contamination of conditioned withdrawal by conditioned activity, we utilized measures of withdrawal (wet dog shakes, paw tremors, and yawning, etc.) that are distinct from measures of activity (31,57). Thus, Experiment 1 was designed to investigate whether animals given morphine daily in a distinctive environment would show sensitized withdrawal when challenged with naloxone in that environment compared to opiate-naive animals and to animals given daily morphine in an environment different from the one where they would be challenged with naloxone. In our previous work (41), context-specific withdrawal was demonstrated in hamsters by pairing naloxone-precipitated withdrawal with distinctive environmental cues and then challenging animals with saline on a test day in the presence of those cues. Here, in Experiment 1, animals were given morphine daily in the presence of distinctive environmental cues and then challenged with naloxone in the presence of those cues, a protocol similar to that used by Kelsey and colleagues (13,26).

EXPERIMENT 1

Method

Subjects. The subjects were 16 female and 8 male golden Syrian hamsters, weighing approximately 110 g. They were housed individually in stainless steel hanging cages in a temperature-controlled vivarium under a 12 : 12 reversed lighting cycle (lights off at 0800) with free access to water and Purina lab chow. All experiments were conducted during the dark phase of the hamster's circadian cycle and in accordance with NIH guidelines for the use and care of laboratory animals.

Apparatus and materials. The hamsters were observed for symptoms of withdrawal in a transparent polycarbonate cage (45.7 × 24.1 × 20.3 cm). Morphine sulfate (15 mg/kg), naloxone hydrochloride (0.4 mg/kg), and 0.9% saline were administered intraperitoneally (IP) in 1 ml/kg volumes. Doses of morphine and naloxone refer to the salt.

Procedure. Animals were assigned randomly to one of three groups (n = 8) for the training phase of the experiment. Male and female hamsters were distributed as equally as possible among the three groups. On each of 7 days, animals in group M/S (morphine/saline) were injected with morphine prior to being placed in a transparent plastic cage for 50 min. Three hours later, they were injected with saline in the home cage. In group S/M (saline/morphine), animals were injected with saline prior to being placed in the plastic cage for 50 min. Three hours later, they were injected with morphine in the home cage. In group S/S (saline/saline), animals were injected with saline prior to being placed in the plastic cage for 50 min and injected with saline in the home cage 3 h later. On the eighth day, animals were tested: following a naloxone challenge, animals were placed in the transparent plastic cage and observed for 40 min for signs of withdrawal.

Behavioral measures. In all experiments, animals were tested individually by an observer who was blind with respect to the hypothesis under test. Behavior was sampled continuously during the 40-min observation period and signs of withdrawal, including paw tremors, wet dog shakes, abdominal writhing, teeth chattering, and yawning, were counted. Paw tremors refer to vigorous shaking of the front or rear paws that is unrelated to grooming or scratching. Wet dog shakes refer to torsional shakes involving the head and shoulders. Abdominal writhing was noted when the animal rotated its torso while pressing its abdomen to the floor, typically accompanied by arching of the back. Teeth chattering refers to tremors in the jaw muscles that produce visible movements of the mouth and muscles of the face, often accompanied by audible knocking of the teeth. Yawning needs no explanation. These responses were selected for study because they have been used commonly to define opiate withdrawal in the rat (6,31,56,57) and because we have found them to be reliably scored indices of opiate dependence in the hamster that are readily distinguished from general activity (40,41).

Data analysis. Since the frequency of occurrence of some

withdrawal responses (e.g., yawning, writhing) was too low for analysis, a composite withdrawal score (the sum of paw tremors, wet dog shakes, abdominal writhing, teeth chattering, yawning) was calculated for each animal in this and subsequent experiments. In all experiments, data were analyzed using analysis of variance (ANOVA) and Newman-Keuls post hoc tests where appropriate. A significance level of $p < 0.05$ was adopted throughout.

Results and Discussion

Figure 1 shows the mean composite withdrawal score for all groups on the test day. It can be seen that group M/S gave more withdrawal responses in the transparent test cage than either group S/M or group S/S. A one-way ANOVA indicated that the effect of groups was significant, $F(2, 21) = 9.82$. A Newman-Keuls test indicated that group M/S had a higher withdrawal score than either group S/M or group S/S, which did not differ from one another.

These results indicate that morphine-induced sensitization to naloxone-precipitated withdrawal can be conditioned to environmental stimuli in the hamster. These results extend our previous findings in the hamster that withdrawal can be conditioned to contextual cues when naloxone-precipitated withdrawal occurs daily in a distinctive environment (42). In the present experiment, naloxone was not given during training and, thus, precipitated withdrawal did not occur in the distinctive environment. Moreover, previous work using a similar protocol in our laboratory (43) suggests that little spontaneous withdrawal would have occurred in the distinctive environment. Thus, in the present experiment, as in the work by Kelsey and his colleagues using rats (13,26), exposure to morphine in a distinctive environment is sufficient to produce a sensitized withdrawal response to naloxone in that environment. These results are consistent with the hypothesis that morphine administration elicits compensatory responses that may be conditioned to environmental cues (44–47). Moreover, the present experiment demonstrated a robust effect using commonly employed measures of opiate withdrawal [e.g., (6)] that are readily distinguished from general activity.

The present results are consistent also with the hypothesis that exposure to opiates produces correlated changes in several response systems. That is, exposure to opiates produces context specific sensitization to naloxone-precipitated withdrawal [present results; (13,26)] as well as context-specific sensitization to locomotor hyperactivity (24,34,54). Because context-specific sensitization to locomotor activity is blocked by pimozide (35,54), it is plausible to ask whether context-specific sensitization of naloxone-precipitated withdrawal similarly is blocked by pimozide.

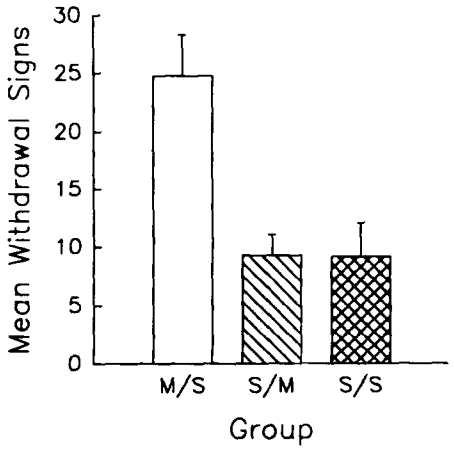

FIG. 1. Mean withdrawal signs on the test day for each group in Experiment 1. Error bars indicate the standard error of the mean.

EXPERIMENT 2

The purpose of Experiment 2 was to replicate the results of Experiment 1 and to determine whether context-specific sensitization to naloxone-precipitated withdrawal is blocked by pimozide. Based on the finding that pimozide blocks the development and the expression of context-specific sensitization to morphine-induced locomotor hyperactivity (35,54), it was predicted that pimozide similarly would block context-specific sensitization to naloxone-precipitated withdrawal.

Method

Subjects. Sixteen male hamsters weighing approximately 120 g were used. Conditions of housing and maintenance were the same as those in Experiment 1.

Apparatus and materials. As in Experiment 1, hamsters were observed for symptoms of withdrawal in a transparent polycarbonate cage. Morphine sulfate (15 mg/kg), naloxone hydrochloride (0.4 mg/kg) and saline, as well as pimozide (0.5 mg/kg) and its 3% tartaric acid (TTA) vehicle were administered intraperitoneally (IP) in 1 ml/kg volumes. Doses of morphine and naloxone refer to the salt.

Procedure. Animals were assigned randomly to one of four treatment groups ($n = 4$) for seven training days. In group P/M/S (pimozide/morphine/saline), animals were injected with pimozide in the home cage 4 h prior to an injection of morphine. Immediately after the morphine injection, they were placed in the plastic cage for 50 min. Three hours later, they were injected with saline in the home cage. Similarly, animals in group T/M/S (tartaric acid/morphine/saline) were injected with TTA vehicle 4 h prior to an injection of morphine, then placed in the plastic cage for 50 min and injected with saline 3 h later in the home cage. In group S/M (saline/morphine), animals were injected with saline prior to being placed in the plastic cage for 50 min and then injected with morphine 3 h later in the home cage. In group S/S (saline/saline), animals were injected with saline prior to being placed in the plastic cage for 50 min and then injected with saline in the home cage 3 h later. Following the seventh training day, animals remained undisturbed in the home cage for 2 days. On day 10, they were tested: after a naloxone challenge, animals were placed in the transparent plastic cage and observed for 40 min for signs of withdrawal. Three cycles of training and testing were completed. The second and third training cycles began on the day following the preceding test days.

Results and Discussion

Figure 2 shows the mean composite withdrawal score for all groups on each test day. It is evident that differences among groups were small on the first 2 test days. On the third test day, however, group T/M/S gave more withdrawal responses than any of the other groups. Moreover, group P/M/S and group S/M gave more withdrawal responses than group S/S. A 4 (groups) × 3 (test days) mixed factorial ANOVA indicated that the effect of groups, $F(3, 12) = 21.42$, the effect of test days, $F(2, 24) = 10.57$, and the inter-

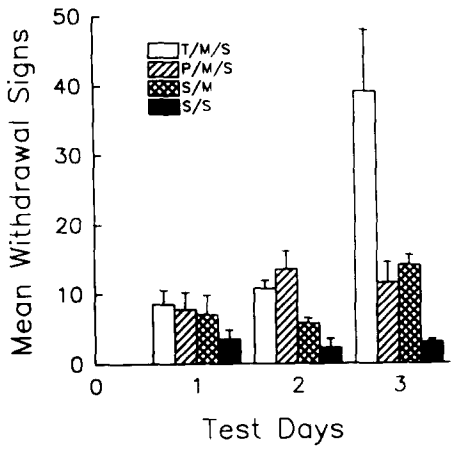

FIG. 2. Mean withdrawal signs on each test day for each group in Experiment 2. Error bars indicate the standard error of the mean.

action between groups and test days, $F(6, 24) = 5.63$, all were significant. Post hoc comparisons using Newman-Keuls tests indicated that group T/M/S gave more withdrawal responses following the naloxone challenge than each of the other groups. In addition, group P/M/S and group S/M each gave more withdrawal responses than group S/S, but the former two groups did not differ from each other. On the third test day, group T/M/S gave more withdrawal responses than each of the other groups.

The present results replicate the findings of Experiment 1 that morphine-induced sensitization to naloxone-precipitated withdrawal can be conditioned to environmental stimuli in the hamster. In Experiment 1, context-specific sensitization was evident on the first test day after 7 days of training. In Experiment 2, where 2 rest days intervened between training and testing in each cycle, context-specific sensitization was not evident until the third test day. The fact that environmental control of naloxone-precipitated withdrawal can be demonstrated 2 days removed from the training episodes is consistent with an interpretation based upon conditioning processes. Perhaps the conditioned response is labile during the initial training periods and, thus, not detectable after a 2-day rest period; but, with further training, it grows in strength and can be detected, therefore, on the third test day.

The procedures used in Experiment 2 are very similar to procedures reported to result in context-specific sensitization of morphine-elicited locomotor activation (54). Moreover, the results of Experiment 2 indicate that the DA receptor antagonist pimozide blocked context-specific sensitization of naloxone-precipitated withdrawal. That is, animals given pimozide prior to the daily morphine injection did not show context-specific sensitization of withdrawal (group P/M/S), whereas those given the TTA vehicle prior to morphine did (group T/M/S). It is possible, of course, that TTA alone enhanced withdrawal in this experiment. In our view, this hypothesis is unlikely, but it is tested in Experiment 3 by the inclusion of control groups that receive TTA (T/S/M and T/S/S). The present experiment is silent with regard to the locus of pimozide's effect. It may have acted during training to interfere with the development of context-specific sensitization or it might have acted at the time of test to interfere with the expression of context-specific sensitization. Although 2 test days intervened between the last pimozide injection and the test day, perhaps enough pimozide remained in the brain from that last injection to suppress withdrawal directly at the time of test.

EXPERIMENT 3

Experiment 3 was designed to determine whether pimozide must be given before the morphine injection to block context-specific sensitization or whether pimozide after the morphine injection is sufficient. Thus, one group of morphine-treated animals received daily pimozide injections 3 h after their removal from the distinctive cage. Experiment 3 also investigated whether a single pimozide injection is sufficient to block the expression of sensitization. Thus, another group of morphine-treated animals received a single pimozide injection 48 h prior to the test. Finally, by giving TTA vehicle to all control groups, Experiment 3 assessed whether TTA might contribute to an enhanced withdrawal response to naloxone.

Method

Subjects. Forty-eight hamsters (41 males, 7 females), weighing approximately 122 g, were used. Conditions of housing and maintenance were the same as those in Experiment 1.

Apparatus and materials. As in the first two experiments, hamsters were observed for symptoms of withdrawal in a transparent polycarbonate cage. The drugs and their doses were the same as those in Experiment 2.

Procedure. Animals were assigned randomly to one of six treatment groups ($n = 8$) for 7 training days. In group P/M/S (pimozide/morphine/saline), animals were injected with pimozide in the home cage 4 h prior to an injection of morphine. Immediately after the morphine injection, they were placed in the plastic cage for 50 min. Three hours later, they were injected with saline in the home cage. Similarly, animals in group T/M/S (tartaric acid/morphine/saline) were injected with TTA vehicle 4 h prior to an injection of morphine, then placed in the plastic cage for 50 min and injected with saline 3 h later in the home cage. These two groups, then, replicate groups used in Experiment 2. In group T/S/M (tartaric acid/saline/morphine), animals were injected with TTA vehicle 4 h prior to an injection of saline, then placed in the plastic cage for 50 min and then injected with morphine 3 h later in the home cage. In group T/S/S (tartaric acid/saline/saline), animals were injected with TTA vehicle 4 h prior to an injection of saline, then placed in the plastic cage for 50 min and then injected with saline in the home cage 3 h later. These two groups, then, replicate the control groups used in Experiment 2, but include the TTA vehicle injection. In group T/M/P (tartaric acid/morphine/pimozide), animals were injected with TTA vehicle 4 h prior to an injection of morphine, then placed in the plastic cage for 50 min and injected with pimozide 3 h later in the home cage. This group was designed to determine whether pimozide would block context-specific sensitization if it were given each day after the morphine injection in the distinctive environment; that is, after the animal has had time to associate morphine with the distinctive environment. Finally, animals in group 1P were treated exactly like those in group T/M/S except that, on the seventh training day, a single pimozide injection was given in the home cage in place of the usual saline injection. Following the seventh training day, animals remained undisturbed in the home cage for 2 days. On day 10, they were tested: after a naloxone challenge, animals were placed in the transparent plastic cage and observed for 40 min for signs of withdrawal. Three cycles of training and testing were completed. The second and third

training cycles began on the day following the preceding test days.

Results and Discussion

Figure 3 shows the mean composite withdrawal score for all groups on each test day. It can be seen that group T/M/S gave more withdrawal responses on each test day than any of the other groups, although on the first test day, the difference between group T/M/S and group T/S/M was small. It is evident also that pimozide blocked context-specific sensitization whenever it was given. That is, giving pimozide before or after the daily morphine injection (groups P/M/S and T/M/P, respectively) or only once 48 h before each test day (group 1P) was sufficient to prevent sensitization. Finally, it is evident that TTA itself contributes little or nothing to sensitized responding. That is, group T/S/S gave few withdrawal signs compared with group T/M/S.

A 6 (groups) × 3 (test days) mixed factorial ANOVA indicated that the effect of groups was significant, $F(5, 42) = 4.46$, but that neither the effect of test days nor the interaction between groups and test days was significant. Post hoc comparisons using Newman-Keuls tests indicated that group T/M/S gave more withdrawal responses than each of the other groups, except group T/S/M. None of the other pair-wise comparisons was significant.

The results of Experiment 3 indicate that animals given morphine in the home cage environment (group T/S/M) were sensitized to naloxone-precipitated withdrawal in the test cage and that there was no statistically significant difference between group T/M/S and group T/S/M across the three test days. In Experiments 1 and 2, by contrast, the difference between the analogous groups was significant. Because the comparison between these two groups is critical to the demonstration of context-specific sensitization, it is important to understand that the failure to achieve statistical significance in Experiment 3 probably reflects a Type II statistical error which can be attributed to the performance of a single animal in group T/S/M that gave very high levels of withdrawal on each test day. This deviant pattern increased the mean withdrawal performance of group T/S/M and it increased within group variance, as well. To gauge the impact of this one animal, consider that the mean withdrawal score of group T/M/S was 17.13, whereas that of group T/S/M was 13.29. When the groups are compared in terms of medians, however, the withdrawal score of group T/M/S was 16.17, whereas that of group T/S/M was 8.33, a statistically significant difference using the Mann-Whitney *U*-test ($p < 0.02$).

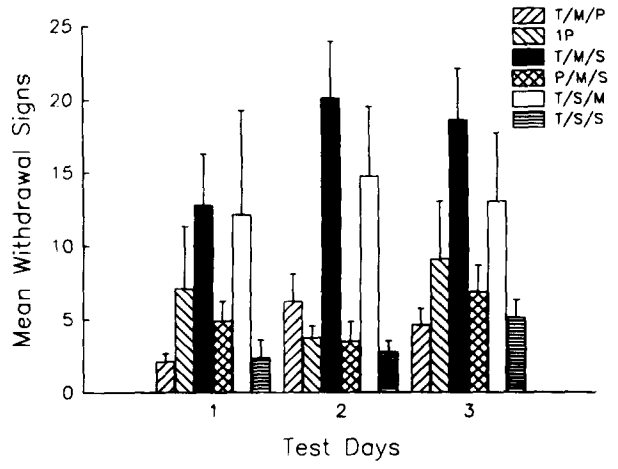

FIG. 3. Mean withdrawal signs on each test day for each group in Experiment 3. Error bars indicate the standard error of the mean.

The results of Experiment 3 are unequivocal in demonstrating that pimozide interferes with the expression of context-specific sensitization. Context-specific sensitization was not evident under any condition of pimozide administration. In particular, the fact that a single injection of pimozide was sufficient to disrupt sensitization when administered 48 h prior to the naloxone challenge, is consistent with the hypothesis that pimozide remains in the brain to suppress withdrawal directly at the time of test. It is possible, of course, that pimozide also acts during training to disrupt the development of context-specific sensitization (35,54). The present results also indicate that TTA does not enhance withdrawal. Group T/S/S showed no sensitized responding to naloxone and, thus, we gain confidence in the conclusions of Experiment 2, where the control groups (groups S/S and S/M) responded less on the test day than group T/M/S.

An important question concerning context-specific sensitization is what responses are being conditioned. Although we did not test for the presence of conditioned withdrawal responses, numerous other investigators (see above) have demonstrated that conditioned withdrawal responses are elicited by a saline challenge in morphine-associated environments. To the extent that conditioned withdrawal responses occur in the morphine-associated environment, context-specific sensitization could be accounted for in terms of a summation between withdrawal responses precipitated by naloxone in opiate-dependent animals and conditioned withdrawal responses elicited by conditioned stimuli. Judging by the present results, the role of conditioning in accounting for the total number of withdrawal responses is considerable. In Experiment 1, for example, there was no difference in naloxone-precipitated withdrawal between morphine-treated animals in group S/M and morphine naive animals in group S/S, whereas the number of naloxone-precipitated withdrawal responses elicited in group M/S was significantly greater than in each of the other groups. Thus, in Experiment 1, all of the sensitized responding was attributable to responses elicited by conditioned stimuli. In Experiment 2, the number of withdrawal responses elicited in groups P/M/S and S/M was greater than in group S/S. Yet, the number of withdrawal responses in group T/M/S was many times greater than in the other two morphine-treated groups, indicating a prominent contribution of conditioning processes to the total number of responses. In Experiment 3, the median number of withdrawal responses in group T/M/S was double that in group T/S/M.

If the very same procedures lead to context-specific sensitization of diverse responses, it is reasonable to hypothesize that common neural elements mediate these effects. That is, repeated presentation of morphine in a distinctive environment leads to context-specific sensitization of locomotor activation when animals are challenged with a low dose of morphine (54) and to context-specific sensitization of precipitated withdrawal when animals are challenged with naloxone (Experiments 1-3, above). Because the challenge dose is not administered until after the system has been sensitized, it follows that some of the same neural elements may subserve context-specific sensitization of the two response systems. As discussed above, there is considerable evidence indicating that context-specific sensitization of locomotor activation is mediated by the mesolimbic DA system. The present finding that

pimozide antagonizes context-specific sensitization of naloxone-precipitated withdrawal is consistent with the common elements hypothesis. The present results, therefore, are congruent with recent demonstrations that both positive and negative incentive effects of opiates can be elicited from the same neural structures [(27,29); cf., (7)].

Context-specific sensitization of locomotor activity has been interpreted to reflect the operation of a behavioral facilitatory system localized to the mesolimbic DA system (49,59). According to this formulation, activity in the mesolimbic DA pathway promotes locomotion or approach behavior and increases the efficacy of positive incentives, such as stimulant and opiate drugs. Moreover, conditioned stimuli are presumed to have neural access to this system and, thus, to enhance the effectiveness of a range of postitive incentives. For example, it has been shown that stimuli associated with morphine can facilitate male sexual behavior in the presence of a sexually receptive female (33). The present results, however, suggest that context-specific sensitization gives environmental stimuli access to a neural system underlying negative incentives, as well. It is possible that the same neural system subserves both positive and negative incentive effects of drugs (28) or that correlated changes occur in complementary neural systems. That is, perhaps exposure to opiates sensitizes neural structures subserving the direct effects of the drug, as well as structures subserving the homeostatic or compensatory adjustments that follow drug absorption (12,16,37,44,46,47,58,61).

Finally, if context-specific sensitization of naloxone-precipitated withdrawal reflects the involvement of a system mediating the effects of negative incentives, then a number of predictions follow. First, stimuli associated with opiate withdrawal should have aversive properties and should increase the effectiveness of negative incentives. Second, such stimuli should promote locomotor withdrawal and avoidance behavior. Third, such stimuli should attenuate the effectiveness of positive incentives.

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