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Opiate Withdrawal: The Result of Conditioning or Physiological Mechanisms?

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ZELLNER, D. A., R. J. DACANAY AND A. L. RILEY. *Opiate withdrawal: The result of conditioning or physiological mechanisms?* PHARMACOL BIOCHEM BEHAV **20**(2) 175–180, 1984.—Although it has been suggested that opiate withdrawal responses might be conditioned compensatory responses elicited by drug-associated stimuli, the present results do not support such a view. Withdrawal, as measured by an aversion to a saccharin solution following the termination of morphine administration, occurred independent of the presence of morphine-paired environmental or temporal cues. These results suggest that withdrawal is most likely the result of some physiological mechanism, rather than the result of conditioning.

Compensatory classical conditioning Withdrawal Aversions

IT has been known for years that stimuli paired with drugs (in particular, opiates) in a Pavlovian paradigm can elicit conditioned responses (CRs) opposite in direction to the direct effects of the drug (UCRs) (see [5] for a review). Recently, Siegel [18, 19, 20, 21, 22, 23, 24, 25] has investigated the conditioning of drug-opposite CRs which he calls compensatory classical conditioning. Most of his research concerns the role of this process in tolerance formation. Rats administered a given dose of an opiate repeatedly in one environment show an attenuation of particular drug responses (analgesia, hyperthermia) to a subsequent injection of morphine in that same environment; i.e., they show tolerance to the drug. However, similarly treated animals show no evidence of tolerance when tested in an environment distinctly different from the environment in which they were previously injected. Thus, conditioned compensatory responses might influence the development of drug tolerance.

Although most of the focus on the role of compensatory classical conditioning has been concerned with its role in tolerance, it has also been suggested that compensatory drug responses are the cause of withdrawal responses as well. This idea was first suggested by Wikler [27]. He proposed that cues associated with drug administration might come to elicit CRs opposite in direction to the drug effects. These responses, when elicited by conditioned stimuli in the absence of drug administration, would appear as withdrawal responses, which are generally opposite in direction to responses elicited by drug itself. Siegel [23] has also suggested that this might be the mechanism involved in at least some types of withdrawal responses.

If withdrawal responses are compensatory CRs elicited by drug-associated stimuli, one should see evidence of withdrawal to morphine following termination of chronic drug administration only in the presence of drug-associated stimuli following termination of drug administration. The present studies investigated this prediction.

EXPERIMENT 1

While numerous techniques have been used to assess opiate withdrawal, one recent reliable and easy method is taste aversions [16]. Taste aversions have been established with precipitated and non-precipitated withdrawal. For example, aversions occur to a preferred novel saccharin solution when this solution is given concurrent with the termination of chronic opiate administration. Although rats given a two-bottle choice between saccharin and water normally prefer saccharin, during opiate withdrawal they show a decreased preference for saccharin over water [11]. The preference measure is sensitive to the degree of withdrawal, in that the degree of the aversion produced is proportional to the degree of prior drug exposure. Aversions can also be induced by precipitating withdrawal by the administration of an opiate antagonist, such as naloxone. In this procedure, rats chronically exposed to morphine avoid consumption of a saccharin solution previously paired with a naloxone injection [6, 14, 15, 26].

Because taste aversions have been found to be a sensitive measure of non-precipiated withdrawal, it was used to test the hypothesis that withdrawal responses are drug-

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compensatory CRs. In this experiment, one environment was consistently associated with drug injections. Testing for withdrawal, i.e., formation of taste aversions, was then conducted in either the drug-associated or different environment. If withdrawal responses are conditioned responses then only animals tested in the morphine-associated environment should show a taste aversion, since only that environment should elicit conditioned drug responses.

METHOD

Subjects

The subjects were 24 experimentally naive, female rats of Long-Evans descent, approximately 90 days of age at the beginning of the experiment. They were maintained on ad lib access to food and water throughout the experiment. All animals were maintained on a 12-hr-light/12-hr-dark cycle (lights on at 0800 hr) for the duration of the experiment.

Apparatus. Home Environment

A subject's home environment consisted of an individual wire-mesh cage (24×18×18 cm). Purina Rat Chow was dispersed on the floor and water or water and sodium saccharin (0.1% w/v, Fisher purified) was made available via graduated Wahmann tubes, the spouts of which protruded through openings in the front of the cage. The cage was located in a quiet, windowless animal colony maintained at a constant temperature of 24–25°C.

Distinctive Environment

The distinctive environment consisted of an individual plastic holding bin (29×18.5×12.5 cm), the floor of which was lined with approximately 1 cm of wood chips. Purina Rat Chow was dispersed on the floor of the chamber, and water or water and sodium saccharin was made available via graduated Nalgene drinking tubes the spouts of which protruded through openings in a stainless steel overhead grid. The chamber was isolated in a room with windows adjacent to the animal colony. A constant noise was provided by a radio. The room was maintained at a constant temperature of 24–25°C. This same environment was used in a previous study [1] where it proved a salient stimulus in supporting conditioning with LiCl.

Procedure. Phase 1: Chronic Morphine Exposure

All manipulations were conducted at the same time each day (1000–1200 hr). On Day 1 of this phase, all subjects were weighed and immediately given an intraperitoneal injection of either 80 mg/kg morphine sulfate drawn from a 10 mg/ml solution (Group M, n=12) or the distilled water vehicle (Group W, n=12). Immediately after their respective injections, the subjects were placed in the distinctive environment for 30 min. At the end of the 30-min period, all subjects were returned to their home cages. This procedure was repeated daily for 14 consecutive days.

Throughout this phase, food and water were continuously available in the home and the distinctive environments. Water consumption was measured and the position (left or right side) of the bottles in both environments was alternated daily.

Phase 2: Assessment of Withdrawal

On Day 15, all animals were given an IP injection of distilled water at their usual injection time. Immediately following the injection, differential treatments were given to four groups of subjects. Half of the animals injected with morphine (Group ME, n=6) and half of the animals injected with distilled water (Group WE, n=6) during Phase 1 were placed in the distinctive environment following their injection. The remaining two groups of animals (Groups MH, n=6, and WH, n=6) were returned to their home cages. All subjects remained in their respective environments for 14 consecutive days during which time they had continuous access to both water and a novel saccharin solution. Consumption from both bottles was recorded every 12 hr at which point the bottles were refilled. The side of presentation of the two solutions was switched daily. Food was available ad lib in both environments during this 14 day treatment.

RESULTS

Phase 1: Chronic Morphine Exposure

Over the 14 days of injections, subjects receiving chronic injections of water, Group W, showed a slight but nonsignificant increase in water consumption (Wilcoxon matched pairs T=13.5, 52.5; $p>0.05$ from the first to the last day of Phase 1). On the other hand, subjects chronically injected with morphine, Group M, significantly decreased water consumption over injection days (T=2, 76; $p<0.05$). On the final injection day, Group M drank significantly less water than Group W (U=11.5, 132.5; $p<0.05$). While both groups showed a significant increase in body weight from the first to the last day of chronic injection (T=0, 78; $p<0.05$ for Group W; T=2.5, 75.5; $p<0.05$ for Group M), this increase was significantly greater for Group W (U=25, 119; $p<0.05$).

Phase 2: Assessment of Withdrawal

Figure 1 illustrates the daily mean percent saccharin intakes of Groups MD, MH, WD, and WH during Phase 2. While both water preexposed groups (WD and WH) showed a strong preference for the saccharin solution over the 14 test days, the two morphine groups (MD and MH) showed a strong aversion to the saccharin solution for the first 168 hr of testing. From this point on, both Groups MD and MH gradually increased their preference for the saccharin solution to the level of water-injected controls.

These observations are supported by statistical analysis. The data for each 12-hr preference measure was analyzed by partitioning the chi-square for the Kruskal-Wallis test into three orthogonal contrasts [9]. Here, the contrasts between the two morphine groups, the two water groups, and the morphine vs. the water groups each become chi-square variables with one degree of freedom. The total of the three chi-square values is the value of Kruskal-Wallis H that would occur were all four groups compared simultaneously. Since three contrasts were performed, the proper criterial significance level is (conservatively, using the Bonferroni inequality) (0.05/3), or 0.017, for each test. For each contrast, the chi-square value was computed and its significance level was found from the Biometrika Tables [11]. Figure 2 graphs the significance level for each contrast over the 14-day period. The 0.017 level is indicated by a horizontal line. Notice that the significance levels on the ordinate are spaced logarithmically.

As shown in Fig. 2, the preference for saccharin in the morphine-pretreated groups (Groups MD and MH) differed significantly from that in the water-pretreated controls (Groups WD and WH) from the 36th to the 168th hr following the final injection in Phase 1. This difference in saccharin

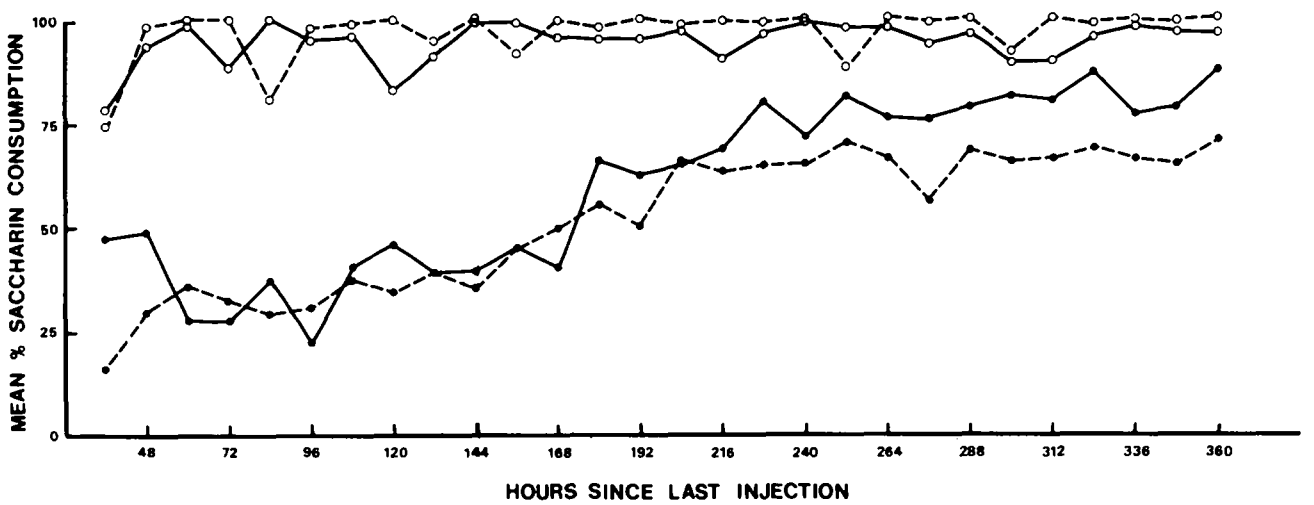

FIG. 1. 12-hr % saccharin consumption during the two-bottle preference test of Phase 2, Experiment 1, for Groups WD (○—○), WH (○ — — ○), MD (●—●), and MH (● — — ●).

preference between the morphine vs. water groups vacillated between significance and nonsignificance from the 180th and 264th hr. It was no longer significant after the 276th hr post-injection.

While there was a significant difference between the morphine and water-pretreated groups, no difference was found between the two morphine-pretreated groups tested in the distinctive and home cage environments, i.e., although only Group MD was tested in the environment associated with morphine, the two chronically injected morphine groups did not differ in their aversion to the saccharin solution at any point during testing. Similarly, no difference in the saccharin preference was found between the two water-pretreated groups tested in the distinctive and home cage environments.

In addition to the saccharin preference measure, we also looked for differences between the groups in total consumption (saccharin plus water). There was a significant difference in this measure from the 36th to the 72nd hour following the final injection of morphine. This difference then vacillated between significance and nonsignificance from the 84th hour to the end of testing (Kruskall-Wallis test, from $H=0.17$, $p>0.05$ to $H=16.78$, $p<0.05$). This effect was due primarily to the water-injected groups drinking large amounts of saccharin in excess of their fluid requirement [e.g., mean=20.33 ml total (mean=17.17 ml saccharin) and mean=26.04 ml total (mean=20.88 ml saccharin) for Groups WH and WD respectively, and mean=10.00 ml total (mean =2.5 ml saccharin) and mean=7.67 ml total (mean=1.88 ml saccharin) for Groups MH and MD respectively for the 36 hour measure].

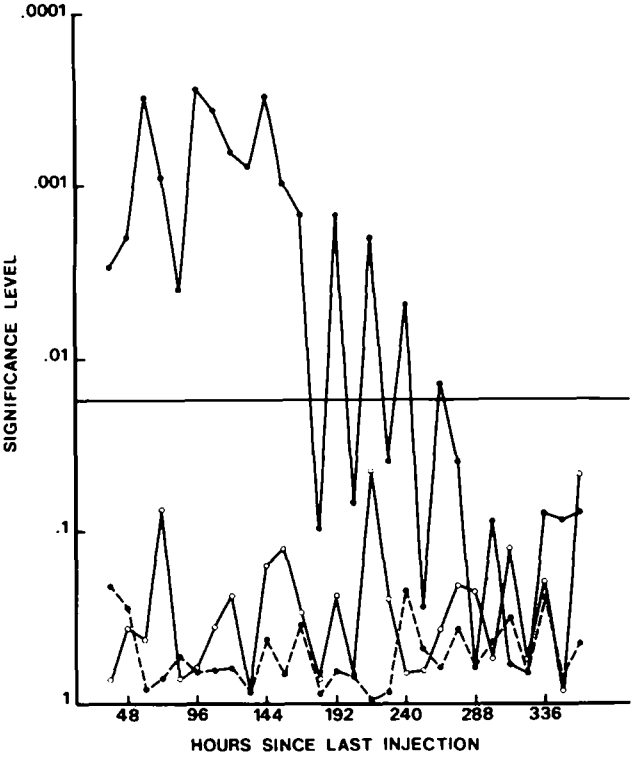

FIG. 2. Significance levels of contrasts comparing % saccharin consumption in: morphine (MD and MH) and water (WD and WH) groups (●—●); home cage (MH) and distinctive environment (MN) morphine groups (● — — ●); home cage (WH) and distinctive environment (WD) water groups (○—○).

DISCUSSION

In agreement with previous findings [11], animals previously injected with morphine avoided the saccharin solution. Testing environment, however, had no effect on saccharin preference. Since there was no difference in saccharin aversion between morphine-injected animals tested in the morphine-associated environment vs. the home cage, these data appear incompatible with the idea that withdrawal responses are drug-compensatory responses elicited by the drug-associated stimuli. In the very least, withdrawal responses were not dependent on the presence of the environmental CS paired with morphine.

However, it is possible that other stimuli present during the conditioning and testing of both morphine-injected groups became associated with the morphine, eliciting drug-compensatory withdrawal responses. Experiment 2 examined this possibility.

EXPERIMENT 2

Although Siegel [22] has shown that environmental stimuli do become associated with morphine and elicit the compensatory response of hypothermia, no effect of test environment was seen in the preceding study. It is possible that other cues predictive of morphine, which were present in both morphine-injected groups, elicited the withdrawal state as measured by the taste aversion procedure in that study. Two cues that were present during conditioning and testing that might have become associated with morphine were temporal and injection cues. That other stimuli might be associated with morphine and result in compensatory classical conditioning is supported in recent work by Eikelboom and Stewart [4]. They demonstrated that temporal cues associated with a morphine injection produce hypothermia, a conditioned response opposite in direction to the morphine-induced hyperthermia.

It is possible, based on this work by Eikelboom and Stewart [4], that the reason withdrawal occurred in both morphine-injected groups in Experiment 1 was that for both groups, temporal cues (or injection cues), rather than environmental cues, became associated with morphine. Despite the fact that morphine-injected rats were tested in environments differentially paired with morphine, perhaps these drug-associated temporal cues elicited compensatory conditioned responses during the termination of drug administration. Withdrawal for both groups may then have been sufficient to produce an aversion to the saccharin solution. If the temporal cues did elicit the withdrawal responses seen in Experiment 1, they should induce a taste aversion when they are the only cues predictive of morphine.

Also, removing the predictive relation between these temporal cues and morphine should allow the environment to become associated with morphine. We should then see withdrawal only in the presence of the drug-associated environment. In addition, no withdrawal response should be elicited when no stimulus is associated with the drug.

As in Experiment 1, rats in the present study were repeatedly injected with morphine and placed in a distinctive environment. For half of these subjects, the morphine injection occurred at a fixed time each day; for the other half, this injection occurred at random temporal intervals. An additional water injection was administered to all animals in order to make injection cues irrelevant. By this procedure the associability of these respective cues and the conditionability of withdrawal was assessed.

METHOD

Subjects

The subjects were 24 experimentally naive, female rats of Long-Evans descent, approximately 90 days of age at the beginning of the experiment. They were maintained as in Experiment 1.

Apparatus

The home and distinctive experimental environments were identical to those in Experiment 1.

Procedure. Phase 1: Chronic Morphine Exposure

Prior to this phase, subjects were divided into two groups, Group F (n=12) and Group R (n=12). On Day 1, Group F was weighed and given an IP injection of 80 mg/kg morphine sulfate at 1030 hr. Group R, on the other hand, was weighed and given an IP injection of 80 mg/kg morphine sulfate between the hours of 0830–1730, with the specific time randomly chosen from this temporal interval. Immediately following the morphine injection, subjects in both groups were placed into the novel experimental environment for 30 min, during which time tap water was present. Following the 30-min period, the animals were returned to their home cages. This procedure was repeated daily for 14 consecutive days.

In addition to these fixed-time and random-time morphine injections, subjects in each group also received a daily injection of distilled water, administered at a random time, to control for injection cues. This injection was given between 0830–1730 hr, with the specific time randomly chosen from this temporal interval. As above, animals were weighed prior to each injection, but following the control injection they were returned to their home cage rather than to the distinctive experimental environment.

As in Experiment 1, water was continuously available in the home cage and the novel environmental chamber during this morphine exposure phase. Water consumption was measured and the position of the bottles in both environments was alternated daily.

Phase 2: Assessment of Withdrawal

On Day 15, *all* animals were given an IP injection of distilled water at 1030 hr, the time at which Group F had previously been given its daily morphine injection. Differential treatments were then administered to four groups of animals. During this phase, half of the animals previously injected with morphine at the fixed time each day (Group FD, n=6) and half of the animals previously injected with morphine at the random time each day (Group RD, n=6) were placed in the distinctive environment immediately following this water injection. The remaining two groups of animals (Groups FH, n=6, and RH, n=6) were injected and placed back in their home cages. At this point, all animals were given free access to tap water and sodium saccharin in a two-bottle preference test during withdrawal. All animals remained in their respective environments with continuous access to the two solutions for seven consecutive days. Consumption from all bottles was recorded and each bottle was refilled every 12 hr. The side of presentation of the two solutions was switched daily.

RESULTS

Phase 1: Chronic Morphine Exposure

Over the 14 injection days, subjects receiving morphine injections at random times (Group R) and at fixed times (Group F) each day significantly decreased water consumption ($T=0$, 125; $p<0.05$ for Group R, and $T=2$, 117; $p<0.05$ for Group F). On the final injection day, there was no significant difference in water consumption between Groups R and F ($U=65$, 79; $p>0.05$). Although there was no significant difference in body weight between Groups R and F on either the first or the last day of drug injection ($U=57.5$, 86.5; $p>0.05$ and $U=63$, 81; $p>0.05$ for the first and last days, respectively), Group R showed a significant increase in body weight over the course of chronic morphine administration, whereas Group F did not ($T=6.5$, 71.5; $p<0.05$ for Group R, and $T=22$, 56; $p>0.05$ for Group F).

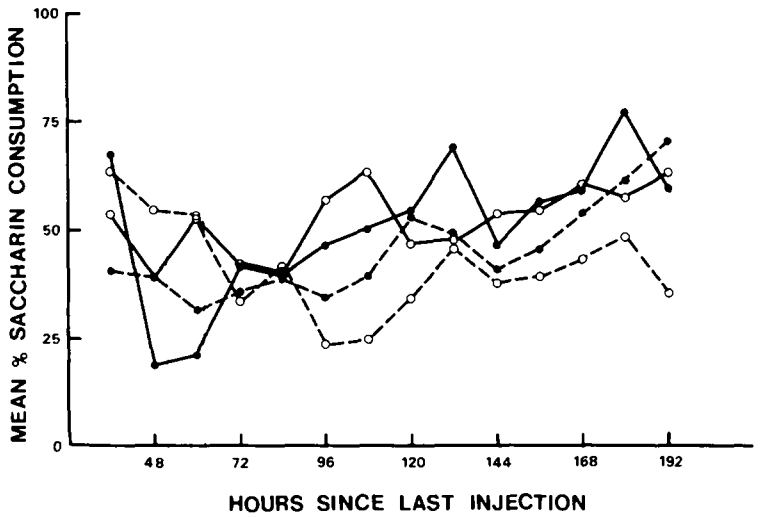

FIG. 3. 12-hr % saccharin consumption during the two-bottle preference test of Phase 2, Experiment 2, for Groups RD (○—○), RH (○ — — ○), FD (●—●), and FH (● — — ●).

Phase 2: Assessment of Withdrawal

When subjects were given access to water and saccharin in a two-bottle test following the termination of chronic morphine injections, all groups (Groups RD, RH, FD, and FH) showed a low preference for the saccharin solution. While all groups initially avoided the saccharin solution, they gradually increased consumption of this solution over test days (see Fig. 3). The degree of saccharin aversion was independent of either morphine-associated temporal or environmental cues, with equal aversions occurring in all groups. Even Group RH which had no cues predictive of morphine showed an aversion equal to the other groups.

Kruskal-Wallis tests performed on percent saccharin consumption showed no difference between any of the four groups (RH, RD, FH, FD) on any 12 hr period ($H=0.77$ to 3.23, $p>0.05$). In addition, a Kendall coefficient of concordance performed on the sum of the ranks of the groups over all of the 12 hr periods indicated no consistency in ranking of the groups, $\chi^2(3)=3.11$, $p>0.05$.

Again we checked for an effect on total fluid consumption. Kruskal-Wallis tests revealed significant differences in total fluid consumption between groups at the 48th hr ($H=8.81$, $p<0.05$) and 120th hr measures ($H=8.50$, $p<0.05$); however, the ranking of the groups on total fluid consumption on these two measures were different, suggesting that these differences were not due to any effect of conditioning.

DISCUSSION

In this experiment, the degree of aversion to the saccharin solution, and therefore the degree of withdrawal, was independent of the presence of any morphine-associated stimulus. There was no evidence of temporal conditioning, and when temporal cues were made irrelevant, there was no evidence of environmental conditioning. It therefore appears that the failure to obtain differences in aversions in the two morphine-injected groups in Experiment 1 was not due to overshadowing of the drug-associated environmental cues by other morphine-predictive stimuli such as temporal or injection cues. This conclusion is most strongly supported by the fact that an aversion occurred even in Group RH, which had no stimuli paired with morphine. Moreover, this group experienced withdrawal with an intensity equal to that of the other groups for which stimuli were present that were predictive of morphine. These results do not support the idea that compensatory classical conditioning results in withdrawal following the termination of chronic opiate administration in rats.

GENERAL DISCUSSION

If withdrawal, as indexed by taste aversions, is a compensatory drug response, it should be evident only in the presence of drug-associated cues (environmental or temporal). However, its occurrence was independent of the presence of such cues and only dependent on previous opiate administration. These results lead us to suggest that withdrawal responses are not compensatory conditioned responses elicited by drug-associated cues. More likely, they are the result of some physiological mechanism.

This is not to say that conditioning has no effect upon opiate withdrawal. It probably plays a role in modulating the severity of withdrawal responses, rather than being the cause of their occurrence. Evidence does exist for this function of conditioning where the CRs are similar to the responses elicited by the UCSs. Withdrawal-like responses have been shown to stimuli previously associated with withdrawal itself (see [7] for a review). For example, Goldberg and Schuster [8] found that morphine-dependent monkeys trained to press a lever for food reinforcement showed conditioned suppression of responding, bradycardia, emesis, and excessive salivation (i.e., withdrawal symptoms) upon presentation of a tone previously paired with an injection of nalorphine, an opiate antagonist.

Stimuli associated with morphine injections have also been shown to alleviate withdrawal symptoms. For example, exposure to a bell previously associated with morphine injections resulted in a reversal of withdrawal hypothermia in dependent rats placed into withdrawal [2, 3, 17]. Other with-

drawal responses have also been alleviated by stimuli associated with morphine injections, such as "wet dog" shakes and aggression (see [9] for a review).

The above evidence does argue for some role of UCR-similar conditioning in opiate withdrawal; however, the present study gives no evidence that compensatory classical conditioning is responsible for or modulates withdrawal. It is possible that compensatory conditioned responses can modulate withdrawal, but that in the present studies the withdrawal caused by physiological responses was so strong as to make it impossible for any conditioning to make it any stronger, i.e., a ceiling effect. One reason for this occurring in the present set of experiments is that the dose of morphine used during the conditioning phase was much larger than that used in most conditioning studies with rats, i.e., 80 mg/kg in the present experiments vs. 5 mg/kg in most others including Siegel's. It could also be the case that our measure, i.e., taste aversions, was more sensitive in detecting any degree of withdrawal than other measures, mostly physiological, reported in other studies [15].

The evidence from the present studies suggest that withdrawal responses are not compensatory classical conditioned responses as Wikler [27] suggests since they occur independently of morphine-associated cues. Instead, withdrawal is most likely the result of some physiological mechanism (e.g., [13]) with any modulatory effect of compensatory classical conditioning being weak and secondary to the physiological component.

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REFERENCES

1. Dacanay, R. and A. Riley. The UCS preexposure effect in taste aversion learning:Tolerance and blocking are drug specific. *Anim Learn Behav* **10:** 91–96, 1982.
2. Drawbaugh, R. and H. Lal. Reversal by narcotic antagonist of a narcotic action elicited by a conditional stimulus. *Nature* **247:** 65–67, 1974.
3. Drawbaugh, R. and H. Lal. Effect of pharmacological interference with various neuropathways on blockade of morphine-withdrawal hypothermia by morphine and by conditioned stimulus. *Neuropharmacology* **15:** 375–378, 1976.
4. Eikelboom, R. and J. Stewart. Temporal and environmental cues in conditioned hypothermia and hyperthermia associated with morphine. *Psychopharmacology (Berlin)* **72:** 147–153, 1981.
5. Eikelboom, R. and J. Stewart. Conditioning of drug-induced physiological responses. *Psychol Rev* **89:** 507–528, 1982.
6. Frumkin, K. Differential potency of taste and audiovisual stimuli in the conditioning of morphine withdrawal in rats. *Psychopharmacologia* **46:** 245–248, 1976.
7. Goldberg, S. Relapse to opioid dependence: The role of conditioning. In: *Drug Dependence*, edited by R. Harris, W. McIsaac and C. Schuster, Jr. Austin, TX: University of Texas Press, 1970.
8. Goldberg, S. and C. Schuster. Conditioned suppression by a stimulus associated with nalorphine in morphine-dependent monkeys. *J Exp Anal Behav* **10:** 235–242, 1967.
9. Lal, H., S. Miksic, R. Drawbaugh, R. Numan and N. Smith. Alleviation of narcotic withdrawal syndrome by conditional stimuli. *Pavl J Biol Sci* **11:** 251–262, 1976.
10. Marascuilo, L. and M. McSweeney. *Nonparametric and Distribution-Free Methods for the Social Sciences*. Monterey, CA: Brooks/Cole Publishing Company, 1977.
11. Parker, L. and B. Radow. Morphine-like physical dependence: A pharmacologic method for drug assessment using the rat. *Pharmacol Biochem Behav* **2:** 613–618, 1974.
12. Pearson, E. and H. Hartley. *Biometrika Tables for Statisticians*, vol 1. Cambridge: Cambridge University Press, 1966.
13. Pert, C. Type 1 and type 2 opiate receptor distribution in brain--What does it tell us? In: *Neurosecretion and Brain Peptides*, edited by J. Martin, S. Reichlin and K. Bick. New York: Raven Press, 1981.
14. Pilcher, C. and I. Stolerman. Conditioned flavor aversions for assessing precipitated morphine abstinence in rats. *Pharmacol Biochem Behav* **4:** 159–163, 1976.
15. Pilcher, C. and I. Stolerman. Recent approaches to assessing opiate dependence in rats. In: *Opiates and Endogenous Opioid Peptides*, edited by H. Kosterlitz. Amsterdam: Elsevier/North-Holland Biomedical Press, 1976.
16. Riley, A. and C. Clarke. Conditioned taste aversions: A bibliography. In: *Learning Mechanisms in Food Selection*, edited by L. Barker, M. Best and M. Domjan. Waco: Baylor University Press, 1977.
17. Roffman, M., C. Reddy and H. Lal. Control of morphine-withdrawal hypothermia by conditional stimuli. *Psychopharmacologia* **29:** 197–201, 1973.
18. Siegel, S. Evidence from rats that morphine tolerance is a learned response. *J Comp Physiol Psychol* **89:** 498–506, 1975.
19. Siegel, S. Morphine analgesic tolerance: Its situation specificity supports a Pavlovian conditioning model. *Science* **193:** 323–325, 1976.
20. Siegel, S. Morphine tolerance acquisition as an associative process. *J Exp Psychol (Anim Behav)* **3:** 1–13, 1977.
21. Siegel, S. A. Pavlovian. Conditioning analysis of morphine tolerance. In: *Behavioral Tolerance: Research and Treatment Implications*, edited by N. Krasnegor. (National Institute on Drug Abuse Research Monograph No. 18, U.S. Department of Health, Education, and Welfare Publication No. [ADM] 78-551).Washington, DC: U.S. Government Printing Office, 1978.
22. Siegel, S. Tolerance to the hyperthermic effect of morphine in the rat is a learned response. *J Comp Physiol Psychol* **92:** 1137–1149, 1978.
23. Siegel, S. Classical conditioning, drug tolerance, and drug dependence. In: *Research Advances in Alcohol and Drug Problems*, vol 7, edited by Y. Israel, F. B. Glaser, H. Kalant, R. E. Popham, W. Schmidt and R. G. Smart. New York: Plenum, 1983.
24. Siegel, S., R. Hinson and M. Krank. The role of predrug signals in morphine analgesic tolerance: Support for a Pavlovian conditioning model of tolerance. *J Exp Psychol (Anim Behav)* **4:** 188–196, 1978.
25. Siegel, S., R. Hinson and M. Krank. Modulation of tolerance to the lethal effect of morphine by extinction. *Behav Neural Biol* **25:** 257–262, 1979.
26. Ternes, J. Conditioned aversion to morphine with naloxone. *Bull Psychonom Soc* **5:** 292–294, 1975.
27. Wikler, A. Conditioning of successive adaptive responses to the initial effects of drugs. *Conditional Reflex* **8:** 193–210, 1973.