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The Role of Associative Factors in Tolerance to the Hypothermic Effects of Morphine in Mice[1]

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SHAPIRO, N. R., B. C. DUDEK AND R. A. ROSELLINI. *The role of associative factors in tolerance to the hypothermic effects of morphine in mice.* PHARMACOL BIOCHEM BEHAV **19**(2) 327–333, 1983.—Associative learning theories of drug tolerance emphasize the importance of stimuli which predict drug administration. One such model holds that drug tolerance is due to the development of a conditional response (CR) which is directionally opposed to the unconditional response (UCR) to the drug. By virtue of their opposing natures, the overlapping occurrence of CR and UCR is seen as a diminished response, i.e., tolerance. The present experiments tested the predictions of this model using two doses of morphine, and included truly random controls to examine the role of excitatory and inhibitory conditioning in tolerance. Tolerance was greatest in mice administered morphine in the context of stimuli previously paired with drug administration, intermediate in random controls, and least or absent in mice administered the drug in the presence of cues paired with vehicle injections. No direct evidence of a compensatory CR which could offset morphine's hypothermic effect was obtained in placebo test sessions, nor was evidence for such a response obtained in cross-drug tests with amphetamine and apomorphine.

Conditioned tolerance Morphine tolerance Thermoregulation Pavlovian conditioning Mice

WITH repeated administration of a drug, a diminution of response is often observed. Traditionally, it had been assumed that the sufficient condition for such tolerance development was continued or repeated contact with the drug, independent of any extrinsic stimulation. However, research with a number of different drugs has underlined the role of conditioning in the acquisition of tolerance.

While there are several conditioning models of tolerance, the most prevalent [15] holds that drug tolerance is due to the development of a compensatory (drug-opposed) conditional response (CR). A CR, elicited in anticipation of drug administration, and continuing during the unconditional response (UCR), might be expected either to augment or offset the UCR. That is, the growth of the CR might be evidenced as a change in responsiveness to the drug with repeated administrations.

Considerable data support such a compensatory response conditioning model of tolerance. Central to the evidence are demonstrations that tolerance to the analgesic and hyperthermic actions of morphine is context specific. In these experiments, tolerance was observed only in the presence of cues previously associated with morphine administration, but not in the presence of novel cues or those paired with vehicle but not morphine injections [15–19]. Also supportive of the conditioning model are findings that tolerance can be modified by manipulations which influence associative learning. Tolerance to the analgesic effect of moprhine is attenuated by preexposure to the CS, subject to the decremental effects of partial reinforcement, and can be extinguished by postacquisition presentations of the CS without the UCS [17]. Similarly, tolerance to the hyperthermic [18] and the lethal effects of morphine [20] may be diminished by an extinction procedure. In addition, by administering a placebo in a drug administration context, direct evidence of a compensatory CR, for morphine-induced analgesia (a hyperalgesic CR, [15]), and hyperthermia (a hypothermic CR, [18]) has been obtained.

EXPERIMENT 1

Much of the evidence that morphine tolerance is conditioned has been obtained using rats and low (approximately 5 mg/kg) doses of morphine. Given the importance of dose generality to a model of tolerance [9], recent experiments have begun to examine the applicability of the conditioning model with an extended dose range [2, 11, 21]. In the present experiment, we used two doses which produce a pronounced hypothermia. Context specificity of morphine tolerance was assessed by administering morphine to groups of animals with equivalent amounts of drug exposure but dif-

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TABLE 1

CS ENVIRONMENT AS A FUNCTION OF DRUG AND GROUP FOR THE RECYCLING EIGHT DAY SEQUENCE

Day=	1	2	3	4	5	6	7	8
Drug*=	S	M	M	S	M	S	M	S
CS-Schedule (n's)								
(1) MOR-RS/SAL-HC (6:6)	H	R	R	H	R	H	H	R
(2) SAL-RES/MOR-HC (6:6)	R	H	H	R	H	R	R	H
(3) Random-1 (3:3)	H	R	H	R	R	H	R	H
(4) Random-2 (3:3)	R	H	R	H	H	R	H	R
(5) Saline	H	R	R	H	R	H	H	R
(6) Saline	R	H	H	R	H	R	R	H
(7) Saline	H	R	H	R	R	H	R	H
(8) Saline	R	H	R	H	H	R	H	R

*Groups 1–4 only; Groups 5–8 received only saline (n=13).
S=Saline; M=Morphine; H=Home Cage Environment; R=Restraint Environment.

ferent histories of context-drug pairings. During the tolerance test, one group of animals received the drug in the presence of cues previously associated with morphine administration, whereas another received morphine in the context of cues which had only been paired with saline. This latter group, which is often used to control for unconditional effects of drug exposure, is, however, actually conditioned to expect the absence of drug in the test environment. Thus, a truly random control group [11], for which the test context predicted neither administration nor omission of the morphine UCS, was included. It can be argued that the truly random control provides an index of nonassociative effects, whereas a group given morphine in the presence of cues predicting UCS omission reveals the influence of inhibitory conditioning. Thus, in addition to examining the dose generality of the conditioned modulation of tolerance, the present experiment examined the role of inhibitory and excitatory conditioning.

METHOD

Subjects

Forty-nine male CD-1 mice (Charles River Breeding Laboratories, Wilmington, MA) served as subjects. Mice were approximately 100 days of age at the start of the experiment. All were individually housed in white translucent cages on a pine shaving bedding under a 16/8 hr light/dark cycle.

Apparatus

Rectal temperatures were assessed using a telethermometer and a thermistor probe (Models 43TD and 402 respectively, Yellow Springs Instrument Co., Yellow Springs, OH). The output of the telethermometer was attached to a millivolt recorder, calibrated to permit temperature readings to the nearest 0.07°C.

Temperatures were assessed in a partial restraint apparatus [6]. Five six-compartment partial restraint boxes were constructed of Plexiglas. Each compartment, 17.46× 9.52×17.46 cm, had a hardware cloth floor to permit urine to escape, and was left uncovered for ventilation. A 1.27 cm diameter hole in the front wall of each compartment permitted access to the mouse's tail and anus. Restraint was accomplished by taping the tail to a stainless steel rod extending outside the chamber. Underneath the elevated chambers was a tray of a 1:2 part mix of Litter Green (McFadden Co., Oakland, CA) and Beta Chips (Northeastern Products Corp., Warrensburg, NY) which had a scent distinctive from the home cage litter.

Procedure

In order to minimize the reliability of injection cues a discriminative conditioning procedure was used. Twenty acquisition trials were given, one per day, during the light portion of the light cycle. One half of the trials took place in the home cage, and the other half in a partial restraint environment where the animal was restrained by the tail, but free to posture, groom, and make lateral and vertical movements. Each environment was maintained at 22°C. Temperature assessments took place only in the restraint environment, by inserting a thermistor probe, lubricated with petroleum jelly, 2.5 cm past the anal sphincter, and allowing 30 sec for stabilization.

On home cage trials animals were weighed, and food and water removed. Ninety minutes later mice were injected and returned to the home cage; food and water were returned 2 hr postinjection. Temperatures were assessed during restraint trials only, following 30 and 90 min of restraint, and every 30 min for two hours. Following the 90 min assessment, animals were removed from the chambers for approximately one minute, during which time they were injected.

Mice in the morphine groups received 10 subcutaneous injections of morphine at either 8 or 40 mg/kg, and 10 injections of the saline vehicle, according to a recycling eight day schedule shown in Table 1. Only the first four days of the schedule were repeated on the third cycle to yield a 20 day training regimen. All of the morphine-treated groups received the same daily schedule of drug administration. The saline-treated groups received only saline injections during training.

Discriminative conditioning groups were defined by the schedule of CS environments—RES (restraint chamber) or HC (home cage)—in relation to the drug administration schedule. Group MOR-RES/SAL-HC received all its morphine injections in the restraint chamber, and saline injec-

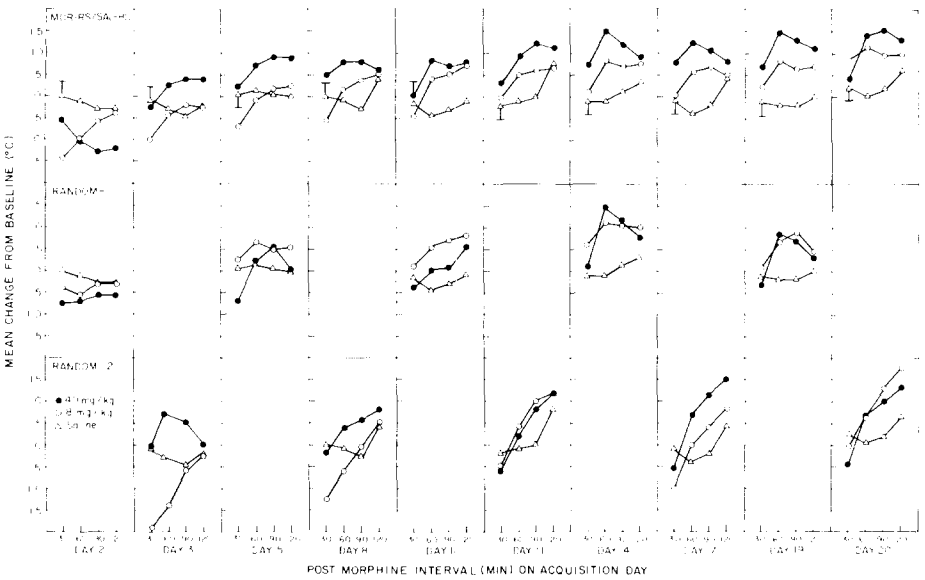

FIG. 1. Mean change from baseline temperature (measured just prior to injection) following morphine injection (or saline for saline controls) as a function of postinjection interval and acquisition day for groups receiving morphine in the restraint environment. Vertical bars represent the generalized standard error, computed from the ANOVA error term reflecting pooled within cell variance.

tions in the home cage. Conversely, Group SAL-RES/MOR-HC received only saline injections in the restraint chamber, and morphine injections in the home cage. Thus, the restraint environment represents a CS+ and a CS− for these two groups respectively. The random control animals received an equal number of saline and morphine injections in each environment, and thus the restraint environment was not a reliable predictor of drug administration. Two random control groups were included to counterbalance for order of CS presentation, since it has been demonstrated that substantial conditioning may occur during early chance pairings of a CS and UCS [1].

To examine the development of conditional responses, on Days 13 and 22, all mice were injected with saline vehicle in the restraint environment. Day 13 was interposed into the 8 day CS-UCS recycling schedule, thus, the last day of acquisition was Day 21. On Day 23, morphine-pretreated mice were injected with their usual morphine dose, and saline-pretreated mice were assigned randomly to the low and high dose conditions, all mice being injected in the restraint environment. Following this test and a one day test and drug free day, all animals were injected with the 8 mg/kg morphine dose in the restraint environment (Day 24).

RESULTS AND DISCUSSION

Data from the preinjection periods of the acquisition phase failed to support the conditioning model's prediction of the development of anticipatory responses to morphine administration. There were no differences in temperature change as a function of time since CS onset (and thus the time until UCS delivery). There was also no indication of a reliable overall difference (collapsed across the preinjection intervals) between morphine-treated and saline-treated animals.

Postinjection difference scores as a function of conditioning schedule, dose, and day of acquisition are presented in Fig. 1. During acquisition, the degree of morphine-induced hypothermia diminished while morphine-induced hyperthermia became more prominent, a finding consistent with work by others (see [5,6]). As can be seen in Fig. 1, Schedule MOR-RS/SAL-HC demonstrates this transition most dramatically.

Conditioning was assessed in the absence of drug on Days 13 and 22 by administering saline to all animals in the restraint environment. There were no consistent temperature differences between the various conditioning groups and the saline controls. Thus, the data from these two tests do not provide evidence for either excitatory or inhibitory conditioning. Similarly, analysis of preinjection temperatures on these days or on the subsequent morphine test day failed to reveal evidence of conditioning.

In contrast, following morphine injection on Day 23, differences were evident among the conditioning groups, as summarized in Fig. 2. Morphine administration initially resulted in a dose-dependent hypothermic response in the morphine-naive saline control group, and this response reversed to hyperthermia by the end of the session. The response of Group SAL-RES/MOR-HC appears quite similar, indicating a lack of tolerance in these animals, F's<1 for the contrast between Group SAL-RS/MOR-HC and the saline controls, and for the interactions with this contrast, morphine dose (8 vs. 40 mg/kg), and assessment period. On the other hand, the response of mice of Schedule MOR-RES/SAL-HC was exclusively hyperthermic, and differed significantly from the saline controls, $F(1,39)=8.08$, $p<0.01$. The significant tolerance observed in mice of Schedule MOR-RS/SAL-HC but not SAL-RS/MOR-HC demonstrates context-specific tolerance, in support of the conditioning model's prediction. Moreover, these results were consistent across the two doses.

Comparison of the acquisition curves with the Day 23 test data (see Figs. 1 and 2) suggests that both Random-1 and Random-2 mice acquired tolerance to morphine. However,

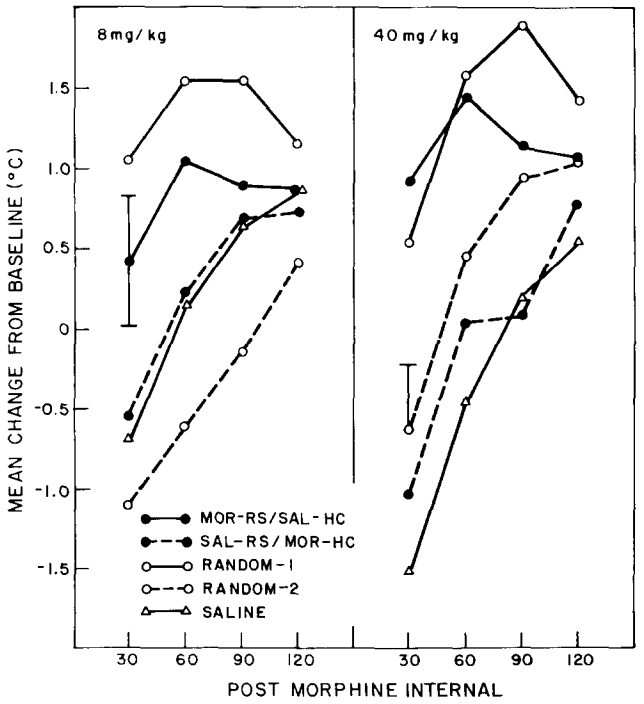

FIG. 2. Mean change from baseline temperature following morphine injection in the restraint environment over 30 min intervals for all groups on Day 23. Vertical bars indicate the generalized standard error.

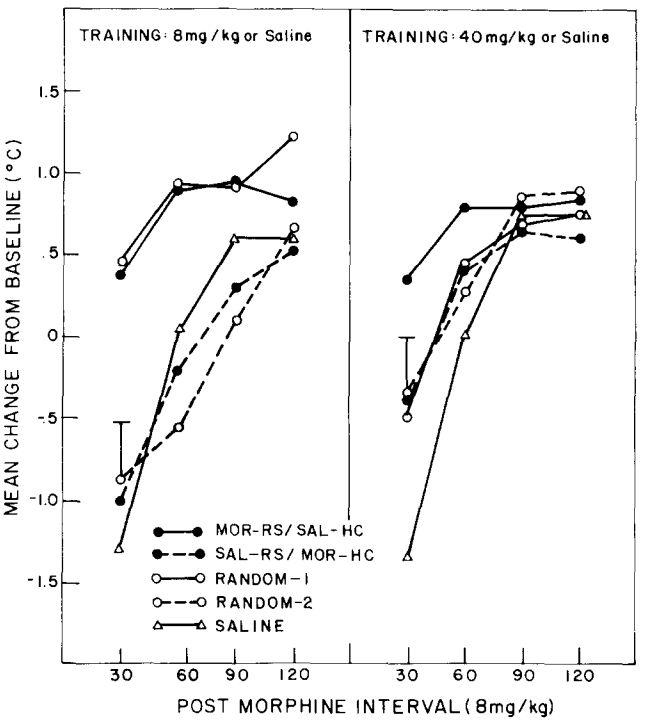

FIG. 3. Mean change from baseline temperature following an 8 mg/kg morphine injection in the restraint environment for all groups on Day 24. Vertical bars represent the generalized standard error.

only Schedule Random-1 mice were consistently more tolerant than the saline controls, $F(1,39)=14.90$, $p<0.001$. Whereas the high dose group of Schedule Random-2 appears to be more tolerant than the saline controls, the low dose group appears less tolerant, $F(1,39)=4.26$, $p<0.05$. It is not possible, however, to determine whether the difference between the mice of the two random schedules was due to variance in initial sensitivity, or to the CS presentation order which distinguished the two schedules, since the initial response to morphine for Schedule Random-2 was not assessed. Unfortunately, the differences between the two random schedules also limits any conclusions regarding the role of inhibitory and excitatory conditioning in tolerance.

Given the finding of context-specific tolerance to morphine just described, it it important to reconsider the results of the saline test session, in which compensatory conditioned responses were not readily apparent. On such a test, the animal may quickly detect the absence of intrinsic stimulus properties of the UCS. Since the probability of a CR should increase as the stimulus properties of the test injection become more similar to the training dose, a test in which animals in both dosage groups receive an 8 mg/kg dose might reveal a compensatory response in the 40 mg/kg CS+ groups. In contrast to the saline test, this dose should provide a stimulus which is similar to the training dose for the 40 mg/kg groups, while like saline, is less potent in inducing hypothermia. If compensatory hyperthermic mechanisms are engaged in expectation of the usual hypothermia inducing dose, and a lower dose is delivered, overcompensation might result. Such a finding would be predicted by the compensatory response model in the present case, since the UCR to the original 40 mg/kg dose, is presumably being offset by a CR of greater magnitude (resulting in a hyperthermic response).

The results of this test, given on Day 24, failed to reveal overcompensation for any of the 40 mg/kg training groups, despite the delivery of a less potent UCS (Fig. 3). In fact, while the data from the 8 mg/kg trained groups appear similar to those in Fig. 2, the 40 mg/kg groups were less well differentiated by the 8 mg/kg dose. Thus, these data question the compensatory response interpretation of the morphine induced hyperthermia seen in Groups Random-1 and MOR-RES/SAL-HC on the prior morphine test day. If those data were the result of summation of morphine's hypothermic effect and a conditioned hyperthermic response, more rather than less hyperthermia should have been shown by these groups on this latter test.

EXPERIMENT 2

While context-specific tolerance was observed in Experiment 1, using two different test procedures there was no evidence for the conditioned compensatory response mechanism which has been proposed as its basis. However, it is possible that temperature assessment intervals of 30 min are too long to detect the conditioned compensatory response in mice. Experiment 2 was designed to examine this possibility, by measuring temperatures every five minutes in the restraint environment. Furthermore, Experiment 2 examined whether such conditional responses might interact with unconditional responses to drugs other than the training drug. That is, a conditional hyperthermic response developed to stimuli associated with a morphine UCS may exacerbate a hyperthermic response induced by a different drug (e.g.,

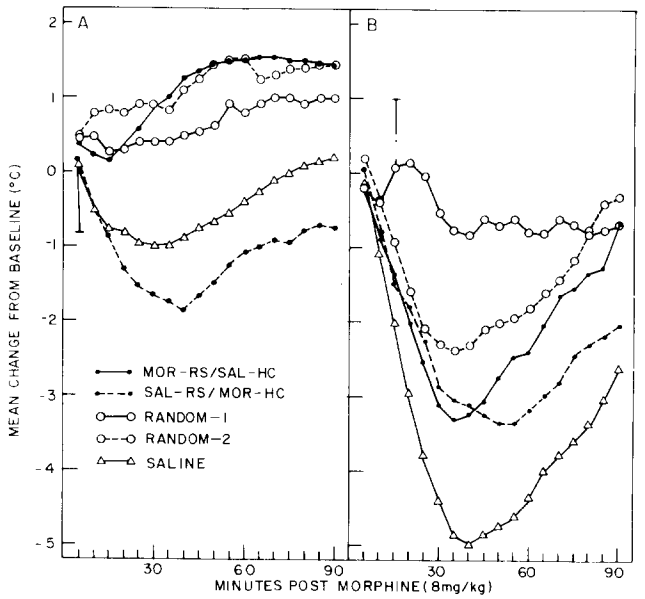

FIG. 4. Mean change from baseline temperature over 5-min intervals following an 8 mg/kg morphine injection in the restraint environment during the Day 22 tolerance test. Panels A and B represent the data of Replications 1 and 2 combined, and Replication 3, respectively. It should be cautioned that two of the curves involving the random groups—Random-2 in Panel A and Random-1 in Panel B—represent data from only one subject.

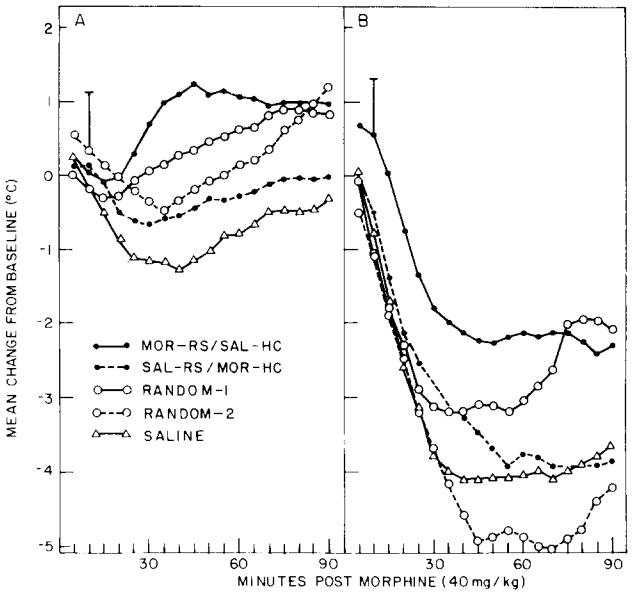

FIG. 5. Mean change from baseline temperature over 5-min intervals following a 40 mg/kg morphine injection in the restraint environment during the Day 22 tolerance test. Panels A and B represent the data of Replications 1 and 2 combined, and Replication 3, respectively. It should be cautioned that two of the curves in the figure involving the random groups—Random-2 in Panel A and Random-1 in Panel B—represent data from only one subject.

amphetamine), or may act to offset a hypothermic response to another drug (e.g., apomorphine).

METHOD

Subjects

A total of 153 male CD-1 mice (Charles River Breeding Laboratories, Wilmington, MA, and Kingston, NY) were received and tested in three replications. Mice were randomly assigned to the four conditioning schedules: MOR-RS/SAL-HC (n=37), SAL-RS/MOR-HC (n=37), Random-1 (n=19), and Random-2 (n=17). Approximately half of the mice in each of these conditions were assigned to the 8 mg/kg pretreatment group, and half to the 40 mg/kg group. Mice were further divided (approximately equally) on the Day 22 morphine and cross-drug test into three subgroups defined by the drug administered on this day—morphine (each mouse received its usual dose), amphetamine (15 mg/kg), or apomorphine (0.625 mg/kg). A group of control animals, counterbalanced across CS schedule, were given saline throughout training and on Day 21 (n=44), and divided among the four drug conditions for the Day 22 test. Age and breeding colony origin varied across replication due to supply problems; mice of the first and second replications, from the Wilmington colony, were approximately 100 days of age at the time of testing, whereas mice of Replication 3 were approximately 70 days old, and from the Kingston colony. Animal husbandry was identical to that of Experiment 1.

Apparatus and Procedure

The apparatus and procedure were similar to that of Experiment 1, with the following changes incorporated to minimize variability due to probe insertion and removal, and to accommodate decreased interassessment intervals: (a) a different probe was used for each animal in a particular session, and electronic switching was used to monitor temperatures rather than manually moving the probe, as in Experiment 1; (b) sessions were shortened to 150 min—animals were injected following 60 min of restraint, and remained in the test chamber for 90 min postinjection; (c) animals were injected without being removed from the restraint chambers by lifting the neckskin with a pair of padded forceps.

RESULTS AND DISCUSSION

As in the previous experiment, analysis of preinjection temperatures during acquisition (or the subsequent test days) failed to reveal anticipatory conditional responses. Again, there were no consistent differences in overall preinjection temperatures as a function of conditioning schedule. Moreover, mice of the two replication groupings showed similar preinjection temperatures.

There were, however, marked differences in response to morphine among mice from the two CD-1 colonies—that is, between mice of Replications 3 and those of Replications 1 and 2, which showed comparable responses. For example, 30 min after the first morphine injection, mice of Replication 3 showed a mean temperature decrease of 4.25 and 4.26°C to the 8 and 40 mg/kg doses respectively, whereas mice of Replications 1 and 2 showed mean decreases of 1.58 and 2.51°C. Thus, all analyses included replication as a factor, with Replications 1 and 2 combined. Mice of the two replication groupings appeared quite similar following saline injection, temperatures decreasing less than 1°C during the 90 min postinjection interval.

During the Day 21 saline test, temperatures were elevated for all groups during the first 10 min postinjection, probably as a result of the stress of the injection procedure. However, there was no evidence for a conditional hyperthermic response, since none of the groups displayed significantly greater hyperthermia than the Saline groups. There did appear to be a tendency for morphine-treated mice to have lower body temperatures in later periods following injection. Significantly lower temperatures in morphine versus saline-treated groups were, however, evident in the later periods of the session only for Schedule MOR-RS/SAL-HC, as indicated by a significant interaction of this group contrast with Periods-linear, $F(1,135)=4.44$, $p<0.05$. No other contrasts with saline-treated animals approached significance. Thus, with the one exception noted above, the morphine-treated groups' responses to saline injection were indistinguishable from the saline groups.

The results of the Day 22 morphine test are presented in Figs. 4 and 5. Context-specific tolerance was again evident. Relative to the saline controls, Groups MOR-RS/SAL-HC appear tolerant to morphine-induced hypothermia, whereas evidence of tolerance in the SAL-RS/MOR-HC animals appears inconsistent. That is, they appear less tolerant than saline controls in the Replication 1 and 2 (combined) low dose animals (Fig. 4, Panel A), and show less tolerance, if any at all, in the high dose condition (Fig. 5). An analysis of these data revealed a significant difference between the two replication groupings, $F(1,47)=30.70$, $p<0.001$, due to the greater overall hypothermic response to morphine of Replication 3 animals. However, the interactions of replication with the various group contrasts did not approach significance. Significant tolerance was demonstrated for Schedules MOR-RS/SAL-HC and Random-1, as evidenced by significant interactions of Periods-quadratic with separate contrasts comparing each of these groups to the saline control, F's$(1,47)=4.41$ and 5.09, p's<0.05, respectively. However, neither the overall contrasts (across periods) of Schedule SAL-RS/MOR-HC or Schedule Random-2 with Saline animals, nor the interactions of these contrasts with Periods-linear or Periods-quadratic approached significance, suggesting that these animals were no more or less tolerant to morphine than were mice in the Saline control groups. Thus, data from this test day appear to demonstrate stimulus-specific tolerance to morphine, as was observed in Experiment 1.

Data from the Day 22, cross-drug tests with amphetamine and apomorphine failed to distinguish the conditioning groups. Amphetamine administration resulted in marked hyperthermia, but contrary to predictions based on the conditioning model, there were no consistent differences in response attributable to morphine administration context. Similarly, while apomorphine administration resulted in a marked hypothermic response, there was no evidence of context-specific cross-tolerance to apomorphine. Taken together, morphine-pretreated groups appeared to show some evidence of cross-tolerance to apomorphine. Statistical comparison of morphine and saline pretreated animals closely approached significance, $F(1,37)=3.29$, $p\leq 0.077$. In fact, it is possible that with a lower apomorphine dose, the morphine and saline groups (as well as the various conditioning schedules) may have diverged, since the marked hypothermic effect of apomorphine may have represented a response ceiling. At very least, these data may be taken as suggestive that chronic morphine treatment can reduce sensitivity to apomorphine's hypothermic effects. Thus they are consistent with previous reports using other dopaminergic transmission inhibitors prior to apomorphine treatment (see [12]).

Thus, as in Experiment 1, a compensatory hyperthermic response, hypothesized to offset the hypothermic effect of morphine, was not evident following saline injection, nor was there sufficient evidence that such a response was interacting with the temperature-altering effects of apomorphine or amphetamine. Nonetheless, data from the Day 22 morphine test replicate the findings of Experiment 1, in which mice of Schedule MOR-RS/SAL-HC but not Schedule SAL-RS/MOR-HC were tolerant to the hypothermic effects of morphine.

GENERAL DISCUSSION

The present experiments demonstrated context-specific tolerance to the hypothermic effect of morphine. Due to the variability in initial response to morphine observed across experiments and across replication of Experiment 2, UCR magnitude varied. While the degree of stimulus control of morphine tolerance varied across experiments, and thus across UCR size, morphine-treated animals consistently displayed greater tolerance in the presence of cues previously paired with morphine administration. Thus, these findings extend the evidence for conditioned modulation of morphine tolerance to mice and a dose range initially producing hypothermia.

The present experiments did not, however, adequately answer questions regarding inhibitory or excitatory control of tolerance. In order to make such inferences, Random control groups were included. However, data from these groups appeared affected by the order of CS presentation, since the two random control schedules, which differed on this dimension, showed differential acquisition of tolerance. Mice of both random schedules did acquire tolerance, and this may indicate that investigators using explicitly unpaired control groups may be overestimating the magnitude of excitatory conditioning effects on morphine tolerance, since the control is receiving inhibitory conditioning. On the other hand, tolerance development in the random controls in the present experiment may be the result of excitatory conditioning, since it is not known whether these animals received sufficient training to overcome conditioning which may occur as a result of pairings in early trials [1].

While context-specific tolerance was observed, there was no evidence for a compensatory thermic response following saline injection, in contrast to work using rats and hyperthermic doses of morphine [18], and hypothermic doses of ethanol (e.g., [7,10]). Conditional compensatory responses were also not observed during the preinjection interval, a period during which anticipatory responses should be evident, and yet have not been reported.

These data thus question the generality of interpretations of conditioned tolerance based on an additive relationship between CR and UCR. It is of course possible that a reconceptualization of the unconditional response to morphine might lead one to look for a CR of a markedly different nature. For example, it has been suggested (cf. [6,13]) that morphine renders mice poikilothermic, and that given this decrease in the ability to thermoregulate as a UCR to the drug, one might expect to see an increased ability to thermoregulate as the CR. If this were the case then, the CR might not appear during the test, since no thermic challenge was presented. However, mice so conditioned did not show

evidence of increased thermoregulation when challenged with amphetamine or apomorphine in Experiment 2. Furthermore, the hyperthermic response to morphine administration cannot be described as an increased ability to thermoregulate.

There are, of course, other mechanisms by which conditioning may modulate drug tolerance. For example, Wagner's [22] stimulus priming model of short-term memory can account for findings of context-specific tolerance without postulating the occurrence of a conditioned compensatory response. This model holds that a CS which has previously been paired with a US for a number of trials may lessen the surprise of the US, and thus weaken its effect. However, this model, like the conditioned compensatory response model, would predict context-specific cross-tolerance between drugs with similar effects, and context-specific cross-sensitization between drugs with opposite effects. In the present work (Experiment 2), no evidence for either cross-tolerance nor cross-sensitization was obtained. In contrast, there are several recent reports in support of these predictions. For example, in a taste aversion paradigm [3], rats pretreated with amphetamine showed context-specific tolerance to aversions induced by morphine as well as amphetamine. In more recent work [4], context-specific cross-tolerance to the hypothermic effect of ethanol in rats trained with a hypothermic dose of pentobarbital was demonstrated. Conversely, potentiation of cocaine-induced stimulation when animals were administered the drug in an environment previously paired with pentobarbital administration has been demonstrated [8]. In this latter study, administration of saline in conjunction with the CS+ failed to elicit a compensatory response, specifically, excitation to compensate for the training UCR, pentobarbital-induced sedation. The findings were interpreted as suggesting that, at least with some response systems, there may be an inertia which must be overcome by the use of a challenge drug. With respect to the present data, this interpretation of the lack of conditional responses during the saline test is not supported by data from the cross-drug tests, despite the excitation induced by amphetamine.

In sum, the present work does lend support to the conceptualization of tolerance development in Pavlovian conditioning terms. The data suggest that such a conceptualization should not be considered to be limited to low dose effects of morphine, nor to rats. In making conclusions regarding the role of conditioning in tolerance we emphasized the importance of including the truly random control condition to assess for nonassociative effects; however, in light of the data presented here, this design may not be optimal for such controls. It is hoped that future investigations of the Pavlovian modulation of tolerance will take such factors into consideration, since the model, which appears to account for many instances of tolerance, sensitization, cross-tolerance, and cross-sensitization to drugs, has important implications for the understanding and treatment of drug tolerance and addiction.

REFERENCES

1. Benedict, J. O. and J. J. B. Ayres. Factors affecting conditioning in the truly random control procedure in the rat. *J Comp Physiol Psychol* **78:** 323–330, 1972.
2. Cappell, H. and C. X. Poulos. Associative factors in tolerance to morphine: Dose response determination. Paper presented in the program of Division 28, American Psychological Association, Toronto, 1978.
3. Cappell, H. and C. X. Poulos. Associative factors in drug pretreatment effects on gustatory conditioning: cross drug effects. *Psychopharmacology (Berlin)* **64:** 209–213, 1979.
4. Cappell, H., C. Roach and C. X. Poulos. Pavlovian control of cross-tolerance between pentobarbital and ethanol. *Psychopharmacology (Berlin)* **74:** 54–57, 1981.
5. Clark, W. G. and Y. L. C. Clark. Changes in body temperature after administration of acetylcholine histamine, morphine, and related agents. *Neurosci Biobehav Rev* **4:** 175–240, 1980.
6. Cochin, J., C. Rosow and J. Miller. Ambient temperature and morphine action. In: *Factors Affecting the Action of Narcotics*, edited by M. L. Adler, L. Manara and R. Saminin. New York: Raven Press, 1978.
7. Crowell, C. R., R. E. Hinson and S. Siegel. The role of conditional drug responses in tolerance to the hyperthermic effects of ethanol. *Psychopharmacology (Berlin)* **73:** 51–54, 1981.
8. Hinson, R. E., C. X. Poulos and H. Cappell. Effects of pentobarbital and cocaine in rats expecting pentobarbital. *Pharmacol Biochem Behav* **16:** 661–666, 1982.
9. Kalant, H., A. E. LeBlanc and R. J. Gibbons. Tolerance to, and dependence on, some non-opiate psychotropic drugs. *Pharmacol Rev* **23:** 135–191, 1971.
10. Mansfield, J. and C. Cunningham. Conditioning and extinction of tolerance to the hypothermic effect of ethanol. *J Comp Physiol Psychol* **94:** 962–969, 1980.
11. Mucha, R. F., C. Volkovskis and H. Kalant. Conditioned increases in locomotor activity produced with morphine as an unconditioned stimulus, and the relation of conditioning to acute morphine effect and tolerance. *J Comp Physiol Psychol* **95:** 351–362, 1981.
12. Rescorla, R. A. Pavlovian conditioning and its proper control procedures. *Psychol Rev* **74:** 71–80, 1967.
13. Rosow, C. E., J. M. Miller, E. W. Pelikan and J. Cochin. Opiates and thermoregulation in mice: I. Agonists. *J Pharmacol Exp Ther* **213:** 273–283, 1980.
14. Schwartz, J. C., J. Costentin, M. P. Martres, P. Protais and M. Baudry. Modulation of receptor mechanisms in the CNS: Hyper- and hyposensitivity to catecholamines. *Neuropharmacology* **17:** 665–685, 1978.
15. Siegel, S. Evidence from rats that morphine tolerance is a learned response. *J Comp Physiol Psychol* **89:** 498–506, 1975.
16. Siegel, S. Morphine analgesic tolerance: Its situation specificity supports a Pavlovian conditioning model. *Science* **193:** 323–325, 1976.
17. Siegel, S. Morphine tolerance acquisition as an associative process. *J Exp Psychol* **3:** 1–13, 1977.
18. Siegel, S. Tolerance to the hyperthermic effect of morphine in the rat is a learned response. *J Comp Physiol Psychol* **92:** 1137–1149, 1978.
19. Siegel, S., R. E. Hinson and M. D. Krank. The role of predrug signals in morphine analgesic tolerance: Support for a Pavlovian conditioning model of tolerance. *J Exp Psychol: Anim Behav Proc* **4:** 188–196, 1978.
20. Siegel, S., R. E. Hinson and M. D. Krank. Modulation of tolerance to the lethal effect of morphine by extinction. *Behav Neurol Biol* **25:** 257–262, 1979.
21. Tiffany, S. T. and T. B. Baker. Morphine tolerance in rats: Congruence with a Pavlovian paradigm. *J Comp Physiol Psychol* **95:** 747–762, 1981.
22. Wagner, A. R. Priming in STM: An information processing mechanism for self generated or retrieval generated depression of performance. In: *Habituation: Perspectives for Child Development, Animal Behavior, and Neurophysiology*, edited by T. J. Tighe and R. J. Leaton. Hillsdale, NJ: Erlbaum, 1976.