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The Effect of Post-Conditioning Exposure to Morphine on the Retention of a Morphine-Induced Conditioned Taste Aversion

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JACOBS, W. J., D. A. ZELLNER, V. M. LoLORDO AND A. L. RILEY. *The effect of post-conditioning exposure to morphine on the retention of a morphine-induced conditioned taste aversion.* PHARMAC. BIOCHEM. BEHAV. 14(6) 779–785, 1981.—In the following experiment, multiple injections of morphine sulfate following the acquisition of a morphine-induced taste aversion had no effect on the retention of the previously acquired aversion. Post-conditioning injections of morphine resulted in the development of physical dependence to morphine and led to a decrement in the ability of morphine to induce a subsequent aversion to a second novel taste. This failure of post-conditioning exposures to morphine to affect a previously acquired morphine-induced taste aversion even though tolerance to morphine had occurred was discussed in the context of Rescorla's event-memory model of conditioning.

Conditioned taste aversion UCS habituation Tolerance Dependence UCS pre-exposure Blocking Morphine Naloxone

RESCORLA [24] observed that conditioned suppression evoked by a conditioned stimulus (CS) which had been paired with an electric shock unconditioned stimulus (UCS) was attenuated following post-conditioning presentations of that UCS. His interpretation of this outcome was based on two assumptions (cf., [33]). First, because first-order conditioning results from a stimulus-stimulus (S-S) association, the conditioned emotional response to a CS which has been paired with shock depends upon the current memorial representation of shock evoked by the CS and on the emotional response which occurs when that representation is evoked. Second, repeated post-conditioning presentations of the shock result in a changed representation of shock, the new representation eliciting an attenuated emotional response. Thus, when a CS previously associated with shock is presented, it evokes the changed representation of shock and elicits an attenuated conditioned emotional response.

Several investigators have asked whether conditioned taste aversions will also be weakened by post-conditioning presentations of the UCS. Riley, Jacobs, and LoLordo [28] failed to obtain an attenuation of an aversion to a saccharin solution paired with lithium chloride (LiCl) despite four post-conditioning injections of LiCl (see also [16]). Similarly, Brookshire and Brackbill [5] demonstrated that exposure to the emetic apomorphine hydrochloride following the acquisition of an apomorphine-induced taste aversion had no effect on the retention of the aversion. On the other hand, under somewhat different conditions, Colby and Smith [9] and Mikulka, Leard, and Klein [20] have obtained an attenuation of a previously established LiCl-based aversion with post-conditioning injections of LiCl.

None of these studies, however, has used a drug to which tolerance clearly occurs. Intuitively, use of such a drug would provide an especially appropriate test of Rescorla's event-memory model within a taste aversion design. In the language of Rescorla's model [24–27], the representation of a drug to which tolerance occurs should be altered by multiple post-conditioning exposures, with the new representation eliciting an attenuated unconditioned response. Rescorla's model predicts that previously conditioned responses based on the unconditioned response to the drug will be attenuated as a result of the post-conditioning injections.

Because tolerance occurs to a range of the effects produced by morphine, e.g., analgesia [14,19], body weight loss [21], and hyperthermia [36], repeated post-aversion conditioning injections of morphine should result in a change in the representation of morphine and thereby an attenuation of the conditioned aversion to the taste previously paired with morphine.

To test this prediction, in the present experiment a conditioned aversion to a novel flavor was established by pairing access of that flavor with an intraperitoneal (IP) injection of morphine. Following repeated injections of similar doses of morphine in the absence of the taste, rats were tested for the retention of the previously acquired, morphine-based conditioned taste aversion.

The development of tolerance to morphine during the post-conditioning exposures was assessed in several ways.

Immediately following the post-conditioning injections of morphine, rats were given a second novel solution paired with morphine. In this procedure, the post-conditioning injections functionally exposed the subjects to morphine *prior* to the subsequent conditioning to the second novel solution. Such *pre*-exposures typically attenuate subsequent conditioning, an effect often explained as the result of the development of tolerance during the drug exposure period [6,28]. Following this test, all rats were given a third novel solution paired with the morphine antagonist, naloxone hydrochloride. Naloxone is effective in inducing aversions to novel solutions in subjects who have previously received multiple exposures to morphine [6, 22, 42, 44]. Such aversions are assumed to reflect naloxone's aversive effects in morphine-dependent animals. Because of the correlation between physical dependence and tolerance [19, 21, 45], this test will provide an indirect assessment of the tolerance acquired during the multiple post-conditioning exposures to morphine.

METHOD

Subjects

The subjects were 40 experimentally naive, female rats of Long-Evans descent, approximately 90 days of age at the beginning of the experiment. All subjects were allowed free access to food but were water deprived throughout the study. Rats were maintained on a 12-hr-light/12-hr-dark cycle with all treatments administered during the light period.

Apparatus

Subjects were housed in individual wire-mesh cages. In the front of each cage were openings into which graduated Nalgene tubes were placed for the presentation of water or the flavored solutions.

Procedure

Phase I: Adaptation and conditioning. Rats were given 20-min access to water once a day for 12 consecutive days, at which point all subjects were approaching and drinking from the tube within 2 sec of its presentation. On Day 13, different treatments were administered to two groups of randomly selected rats. Group M (n=20) was given 20-min access to a novel saccharin solution (0.1% w/v, Fisher purified) followed immediately by an IP injection of morphine sulfate (80 mg/kg). Group S (n=20) was given 20-min access to saccharin followed immediately by an equivolume (≈2 cc) IP injection of physiological saline (0.9% w/v). All rats were given 20-min access to water on the following day. On the next day (Day 15), rats were given saccharin and water in a 20-min, two-bottle test of the aversion to saccharin. On Day 16, rats received a second pairing of saccharin and morphine (Group M) or physiological saline (Group S). Following a day on which they received 20-min access to water, all rats were again given 20-min access to saccharin and water in a two-bottle test of the aversion to saccharin.

Phase II: Post-conditioning injections. On the day after the second two-bottle test (Day 19), all subjects were given ad lib access to food and water. Group M, subjects given the saccharin-morphine pairings during Phase I, was divided into two groups receiving daily maintenance injections of either 80 mg/kg morphine sulfate (Group MM) or physiological saline (Group MS) at 1000 hr each day for 21 consecutive days. Group S, subjects given the saccharin-physiological saline pairings during Phase I, was also divided into two groups, receiving either morphine (Group SM) or saline (Group SS) during this phase.

On Day 36, all rats were deprived of water at 0950 hr, 10 min prior to receiving their daily maintenance injection of morphine or saline. At 1600 hr on the same day, and each day until Day 40, all subjects received 20-min access to water. Subjects continued to receive their maintenance injections during this water-deprivation procedure.

Phase III: Aversion retention test. On Day 40, 6 hr after the daily maintenance injection, all rats received 20-min access to saccharin and water in a two-bottle test of the retention of the aversion to saccharin. On the following day, the rats received 20-min access to water. As above, subjects continued to receive their maintenance injections at 1000 hr on each day of this phase.

Phase IV: Assessment of UCS pre-exposure. On Day 42, 6 hr after the daily maintenance injection of morphine or physiological saline, all rats received 20-min access to a novel saline solution (0.9% w/v) followed immediately by an IP injection of morphine sulfate (80 mg/kg). After an intervening recovery day on which there was 20-min access to water, all rats were given 20-min access to the saline solution and water in a two-bottle test of the aversion to saline. On the following recovery day, all subjects were given 20-min exposure to water. This cycle of conditioning/recovery/aversion testing/recovery was repeated on Days 46–49. As above, maintenance injections were continued on each day of this phase.

Phase V: Assessment of physical dependence. On Day 50, all rats received 20-min access to a novel apple juice solution followed immediately by an IP injection of naloxone HCl (8 mg/kg). After a day on which all subjects were given 20-min access to water (Day 52), they received 20-min exposure to apple juice and water in a two-bottle test of the aversion to apple juice. Following another day on which 20-min access to water was given (Day 54), all rats received 20-min access to apple juice in a one-bottle aversion test. As before, subjects continued to receive their maintenance injections at 1000 hr on each day of this procedure.

RESULTS

Generally, data were analyzed using Rodger's method for the analysis of variance [31,32]. In each case, when the overall null hypothesis was rejected, a set of mutually orthogonal contrasts of the form $\Sigma_j c_j m_j$, where $\Sigma_j c_j = 0$ and m_j are sample means, was sought. Such a set of post-hoc contrasts consists of comparisons of weighted combinations of the means in which the coefficient c_j is the weight given to the jth mean m_j. The critical value for rejecting the null contrast was obtained from Rodger's tables of $F[E\alpha]$; $v_1 v_2$. $F[0.05]$; $v_1 v_2$ used in these analyses insured that the proportion of null contrasts rejected in error would be α when the null contrasts were true.

Phase I: Adaptation and conditioning. When saccharin replaced water during the 20-min access period on Day 13, there were no differences in the amount consumed between Groups M and S. Following the pairing of saccharin with morphine or physiological saline, when all subjects were given a two-bottle test between saccharin and water, significant differences emerged between the two groups of subjects, $F_m(3,36)=6.19$. Figure 1 presents saccharin and water consumption during this two-bottle test. Groups MM and

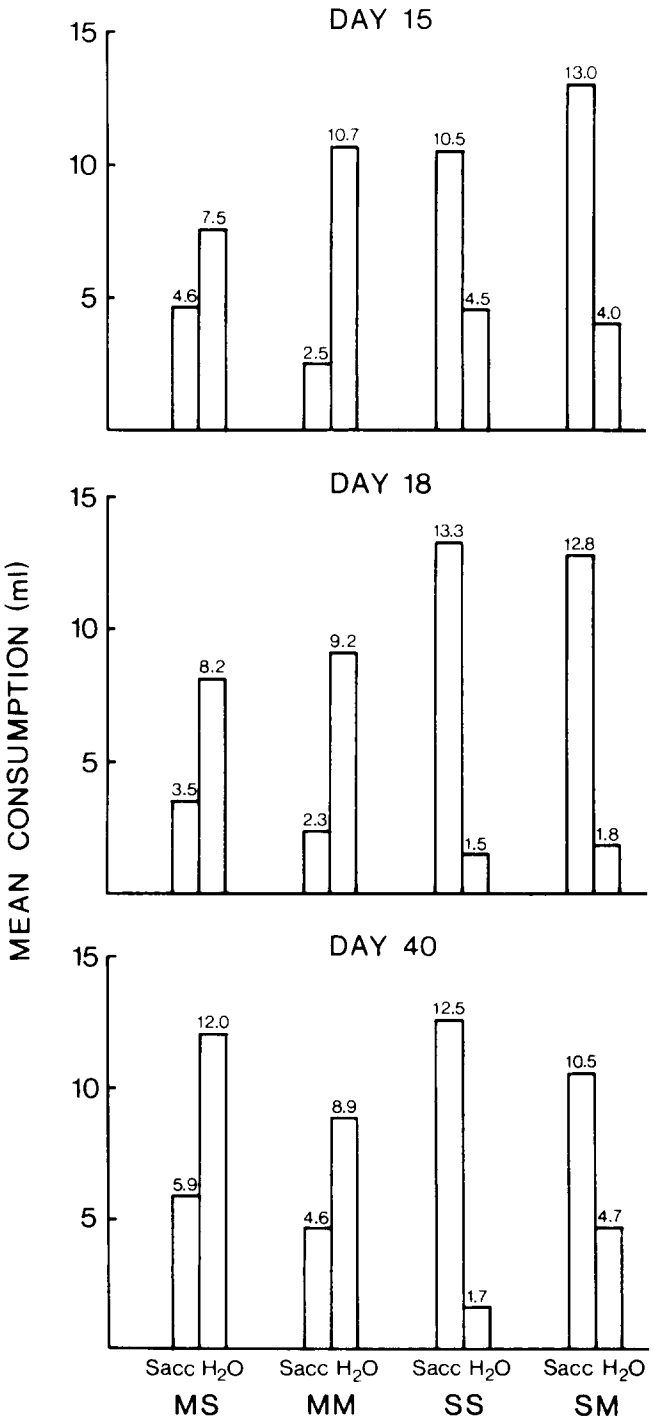

FIG. 1. Mean consumption (ml) of saccharin and water on the two-bottle tests prior to (Days 15 and 18) and following (Day 40) chronic injections of morphine or saline.

MS, subjects previously injected with morphine following saccharin consumption, drank significantly less saccharin than control subjects, Groups SM and SS, on this test, $F=5.56$ (see Fig. 1, Day 15). This difference in saccharin consumption was maintained following a second conditioning trial (see Fig. 1, Day 18).

Phase III: Aversion retention test. On Day 40, following the multiple post-conditioning exposures to morphine or saline (Phase II), there were no significant changes in saccharin consumption for any group from the amount consumed on Day 18, the last test of the aversion to saccharin prior to the post-conditioning exposures (see Fig. 1, Days 18 and 40). The pattern of saccharin consumption on Day 40 was like that of Day 18. Groups MM and MS did not differ in the amount of saccharin consumed (mean=4.6 and 5.9) or in the variability of the aversion to saccharin (SD=3.73 and 3.81). Both groups drank significantly less saccharin than Groups SM and SS, $F=8.75$, where $F_m(3,36)=9.29$, which did not differ from each other.

Phase IV: Assessment of UCS pre-exposure. On the first exposure to the novel saline solution (Day 42) and prior to its pairing with morphine, Groups MM and SM drank significantly less saline than Groups MS and SS, $F=14.20$, where $F_m(3,36)=15.62$. Although a history of multiple post-conditioning morphine exposures apparently suppressed the subsequent consumption of the novel saline solution (Groups MM and SM), this suppression was not evident in Group MS, suggesting that the prior saccharin-morphine pairings did not contribute to the suppression seen in Group MM.

When the saline solution was presented to the subjects following the pairing of saline with morphine, there were significant differences among the four groups of subjects, $F_m(3,36)=5.10$. Figure 2 illustrates saline and water consumption for the various groups during the 20-min two-bottle aversion test on Day 44. Although all the subjects had received the saline-morphine pairing, subjects with the prior history of daily morphine injections (Groups MM and SM) drank significantly *more* saline on this test than subjects without that morphine history (Groups MS and SS), $F=4.10$ (see Fig. 2, Day 44). On the two-bottle test following the second saline-morphine pairing, Groups MS and SS further decreased saline consumption, while groups MM and SM increased consumption of saline. On this second two-bottle test, Groups MM and SM continued to drink significantly more saline that Groups MS and SS, $F=19.24$, where $F_m(3,36)=22.08$; see Fig. 2, Day 48.

Phase V: Assessment of physical dependence. On the first exposure to the novel apple juice and prior to its pairing with naloxone, Groups MM and SM drank significantly less apple juice than Groups MS and SS, $F=19.17$, where $F_m(3,36)=20.25$, a suppressive effect of morphine exposure similar to that seen on the first exposure to saline.

When apple juice was presented to the subjects following its pairing with naloxone, there were significant differences among the groups, $F_m(3,36)=6.13$. Although all subjects drank less apple juice than water, Groups MM and SM drank significantly less apple juice than Groups MS and SS, $F=5.11$. Figure 3 illustrates apple juice and water consumption for all groups during the 20-min two-bottle aversion test.

A subsequent one-bottle test of the aversion to apple juice (Day 54) supported the two-bottle data. Figure 4 illustrates apple juice consumption on this one-bottle test and on the first exposure to apple juice (Day 50). While animals without a history of post-conditioning morphine injections increased consumption of apple juice following its pairing with

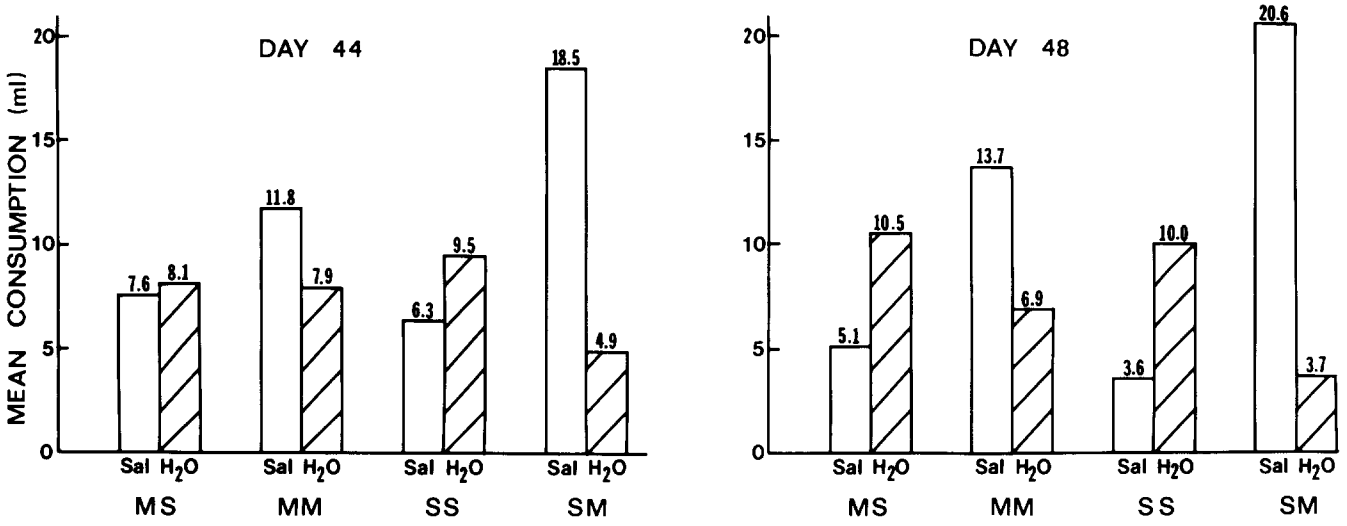

FIG. 2. Mean consumption (ml) of saline and water on the two-bottle tests on Days 44 and 48 following pairings of saline with an injection of morphine.

naloxone, $F_m(1,19)=10.91$ (see Fig. 4, Groups MS and SS on Days 50 and 54), morphine-exposed subjects significantly decreased consumption of apple juice following its pairing with naloxone, $F_m(1,19)=10.11$ (see Groups MM and SM, Days 50 and 54).

Administration of naloxone on Day 50 also had differential effects on the weights of rats which had extensive prior exposure to morphine and of those which had received control injections. Rats in Groups MM and SM lost a mean of 25.5 g in the 24 hr following the naloxone injection (range 14–32 g), whereas rats in Groups MS and SS lost a mean of 5.3 g in the same interval (range 0–9 g). Whereas the rats did not differ in body weights on Day 50 before the naloxone injection, Groups SS and MS weighed more than Groups SM and MM on Day 51, $F=2.42$, where $F_m(3,36)=2.83$.

DISCUSSION

It is clear from the data that unlike the effects of post-conditioning exposures to shock or loud noise (see [24,25]), the multiple post-conditioning exposures to morphine sulfate had no effect on a previously acquired association, i.e., animals that had received the 21 daily injections of morphine continued to avoid the saccharin solution previously paired with morphine.

It could be argued that this experiment provided no evidence that the aversion to saccharin in Group M was conditioned, i.e., resulted from the pairings of access to a saccharin solution and an injection of morphine and not from the nonassociative effects of morphine administration [11]. However, in a subsequent experiment, a group which re-

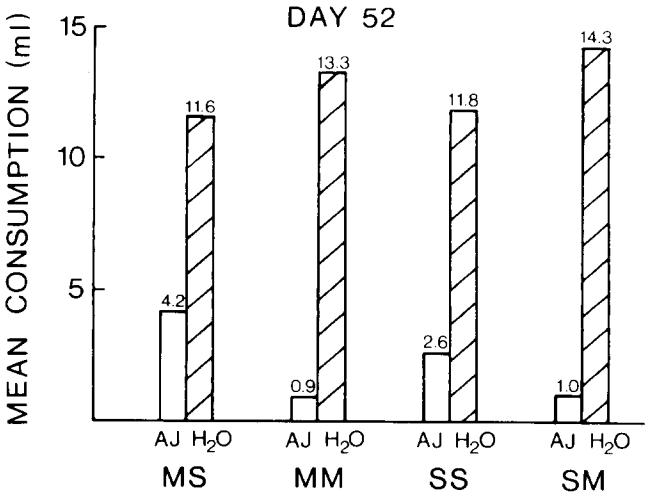

FIG. 3. Mean consumption (ml) of apple juice and water on the two-bottle test (Day 52) which followed the pairing of apple juice and naloxone.

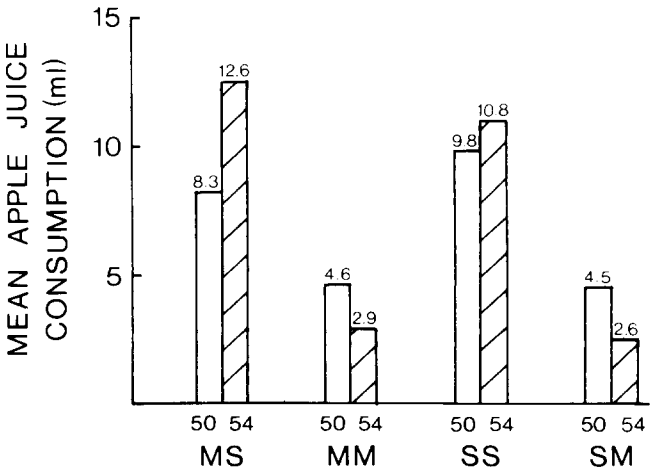

FIG. 4. Mean consumption (ml) of apple juice prior to (Day 50) and following (Day 54) the pairing of apple juice and naloxone.

ceived two trials on which access to saccharin was followed 7 hr later by an injection of morphine was added to an exact replication of Phase I of the present experiment. Only the group which received morphine immediately after access to saccharin developed an aversion to saccharin, i.e., Group M consumed less saccharin on a subsequent two-bottle test than Group S or the group receiving the delayed morphine injection, which did not differ from each other. The aversion to saccharin in the present experiment, therefore, appears to be a conditioned aversion and not simply a nonassociative reaction to morphine.

It has been argued that an extinction procedure provides a more sensitive test of the effects of post-conditioning exposures to a UCS than does a single test trial [24]. Studies which have used such a procedure with drug UCSs, however, have generated conflicting data [5, 9, 16]. For example, Brookshire and Brackbill [5] found that an aversion to saccharin extinguished at the same rate in a group of rats which had been exposed to apomorphine following saccharin-apomorphine pairings and in a control group which had received no exposure to apomorphine following conditioning. In our own laboratory, in a replication of the first three phases of the present experiment, Groups MM and MS showed similar patterns of saccharin consumption over four extinction trials.

That post-conditioning exposures to morphine do not attenuate previously acquired, morphine-induced taste aversions is in apparent contradiction to Rescorla's event-memory model [24–27]. Given that tolerance develops to morphine [19, 21, 36], it was expected that the post exposures would result in a change in the representation of morphine and thereby in an attenuated conditioned aversion. Although tolerance, as indexed by the attenuation of subsequent conditioning and by the efficacy of naloxone in inducing an aversion, appeared to develop during the post-conditioning exposures in the present experiment, it is possible that these two indices do not reflect a diminution in the components of the morphine reaction which initially induced the avoidance response. If there were no changes in the unconditioned responses elicited by morphine which were responsible for inducing the conditioned aversion, the post-conditioning exposures would not be expected to attenuate the previously acquired aversion.

It could be argued, for example, that the UCS pre-exposure effect does not reflect a diminution in the effects of morphine during post-conditioning exposures, but instead results from an associative mechanism (cf. [23] for a review of this issue). One associative account, based on a phenomenon called blocking [18,43], maintains that the repeated injections of morphine resulted in the conditioning of a response to contextual cues, e.g., cues arising from the morphine injections, and that conditioning to the context subsequently blocked conditioning to a novel taste paired with morphine when this conditioning was attempted in the presence of the previously conditioned contextual cues. In support of this account, Batson and Best [2] demonstrated that conditioned taste aversions were significantly weaker in subjects for whom aversion training was done in the presence of environmental stimuli previously paired with LiCl (see also [8,47]). On the other hand, in an explicit test of the blocking hypothesis, Zellner and Riley [48] found no evidence of blocking in the UCS pre-exposure effect induced by two drugs of abuse, methadone and methylphenidate (see also [7]).

Recently, Siegel [35,36] has proposed a second associative mechanism which could account for the UCS pre-exposure effect in the present experiment. According to this mechanism, the attenuation of morphine-induced taste aversion by morphine pre-exposure does not reflect an actual diminution in morphine's effects but results from the summation of the unconditioned response to morphine with the compensatory responses conditioned to stimuli which preceded morphine administration, a summation which minimized morphine's effects during aversion conditioning (see also [2, 4, 21, 34, 35, 37]). The single assessment of this model with *morphine* within a UCS pre-exposure design, however, has not supported the position that the UCS pre-exposure effect with morphine is a result of the classical conditioning of compensatory responses [41].

That morphine-exposed rats acquired an aversion to apple juice following its pairing with naloxone does not necessarily indicate that these subjects were tolerant to morphine. Although the naloxone-induced aversions suggest that the animals were dependent on morphine [6, 22, 42, 44] and although dependence and tolerance are correlated [19,21], tolerance to the various effects of specific drugs occurs at different rates [3, 13, 17, 21]. It is quite possible that tolerance did not occur to the specific effects of morphine responsible for the conditioning of the original aversion to the saccharin solution paired with morphine. If no tolerance occurred to these effects, it would not be expected that the previously acquired conditioned aversion would be attenuated (see [24]). Although the present report does not directly examine tolerance to any specific response, one morphine-induced response which has been suggested as a mediator of conditioned aversions, i.e., ACTH release [1, 4, 28–30, 46], has been reported to decrease with repeated exposures to morphine [38,39].

If Rescorla's event-memory model is to predict the effects of post-conditioning exposure to the UCS, it must assume that the UCS is somehow identified as the same event throughout post-conditioning exposures, i.e., in order for the conditioned response to be attenuated, the UCS evoked by the CS must be perceived as similar to the UCS now eliciting an altered unconditioned response. It could be argued that morphine may be perceived as a different event when the rat has become tolerant to or physically dependent on the drug, e.g., because some salient stimulus property of the drug has changed. However, in order for the above argument to account for the failure of post-exposure to morphine to affect previously acquired aversions, it must also explain why UCSs like shock and loud noise which do affect previously acquired associations are recognized as the same event throughout exposures. Moreover, this argument is not supported by the recent research on state dependency in which drugs are used as discriminative stimuli for operant responding. In such designs, although tolerance may occur to morphine, its efficacy as a discriminative stimulus is not altered with the repeated drug exposures. Although these reports do not determine what stimuli the animals are using as the discriminative cue, they do suggest that some component of the narcotic cue is maintained intact despite the occurrence of tolerance [10].

Although tolerance was only indirectly assessed in the present experiment, e.g., by the UCS pre-exposure effect and naloxone-induced aversions, together these indices of tolerance suggest that the impact of morphine did change during chronic post-exposures. Because this exposure had no effect on the previously acquired aversion, however, these data question the generality of the event-memory model [24].

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