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Associative and Nonassociative Tolerance: The Effects of Dose and Interdose Interval

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COX, L. S. AND S. T. TIFFANY. *Associative and nonassociative tolerance: The effects of dose and interdose interval.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 31–36, 1997.—Two experiments examined the effects of dose and interdose interval (IDI) on associative and nonassociative tolerance to morphine analgesia in rats. Associative contingencies were manipulated by administering low (5 mg/kg) or high (20 mg/kg) doses of morphine explicitly paired or unpaired with a distinctive context. Nonassociative processes were manipulated by administering morphine at a short (6-h) or long (96-h) IDI. Tolerance was assessed as shifts in morphine dose–response curves on the tail-flick test. Animals in the long IDI conditions showed considerable context-specific tolerance. Tolerance in the short IDI conditions was not influenced by contextual contingencies at the immediate test (Experiment 1) and showed no retention over a 30-day interval (Experiment 2), suggesting this tolerance was nonassociative. The impact of massed exposure to morphine and context on the disruption of learning at the short IDI is discussed. © 1997 Elsevier Science Inc.

Associative Nonassociative Tolerance Morphine Rats Dose–response curves Interdose interval

TOLERANCE,[2] which can be quantified as shifts to the right in dose–response curves, is readily produced by repeated drug administration (8,9). Although pharmacologic models generally emphasize dose magnitude and interdose interval (IDI) as the critical factors controlling adaptations responsible for tolerance development, many examples of drug tolerance appear to represent the operation of learning processes (1,10). Classical conditioning models hypothesize that certain stimuli consistently paired with drug administration can become conditioned stimuli (CSs) that produce conditioned tolerance effects (1,12,13). For example, Siegel's (13) compensatory response model states that conditioned responses (CRs) take the form of behavioral effects counterdirectional to the direct action of the drug. Over the course of conditioning, these compensatory responses grow in magnitude and counteract direct drug effects (i.e., tolerance develops). Although there is considerable evidence that conditioning factors may have a powerful influence on tolerance, Siegel's theory may not provide a complete account of all instances of tolerance development. Of particular significance to the present research, Siegel's theory cannot explain tolerance that develops in the absence of drug-predictive cues.

A number of recent theories have examined tolerance as a process that may have both associative and nonassociative aspects [e.g., (1,11,12)]. Baker and Tiffany's (1) habituation model of morphine tolerance, derived from a priming theory of general habituation (19), hypothesizes that when the drug is administered tolerance mechanisms are elicited to the extent that the drug's stimulus properties (US) are already represented or "primed" in working memory. The drug's stimulus properties can be primed nonassociatively, through a recent presentation of the drug, or associatively, through the presentation of distinctive stimuli that had been previously paired with drug administration. Tolerance is elicited as a direct function of the magnitude and duration of priming. Nonassociative tolerance develops without predictive environmental cues and represents the accumulation of nonassociative priming across drug administrations. The magnitude of nonassociative tolerance is predicted to be positively related to dose and negatively related

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[2] Pharmacologic studies typically report that morphine tolerance is characterized by parallel shifts in dose–response curves [e.g., (8,9)]. Research from this laboratory has also generally found that tolerance effects are represented by parallel shifts in DRC (2,15,17), and most examples of tolerance in this study similarly exhibited parallel DRC shifts. However, results from conditioning using the low dose at the long IDI show that the experimental groups produced DRCs with a slope greater than the control group. Such results are similar to findings from a long-IDI condition using a low conditioning dose (16); although nonparallel shifts in DRCs have not been found in this laboratory when using similar test doses with the short-IDI or high-conditioning dose [e.g., (15)]. Further exploration may be necessary to identify the factors related to this finding, which appears to be limited to low-dose, long-IDI conditions.

to IDI. Associative tolerance develops when predictive environmental cues are paired with drug administration and is expected to be positively related to dose at IDIs that are long enough to prevent the development of nonassociative tolerance.

The habituation model (1) predicts that morphine administered at a long IDI should allow for the development of associative tolerance, whereas morphine delivered at a short IDI should allow for the development of nonassociative tolerance and disrupt the acquisition of associative tolerance. This prediction arises from the assumption that residual nonassociative priming from previous conditioning trials persisting into a current conditioning trial will diminish the effectiveness of the drug-unconditioned stimulus in the formation of associations between drug administration and environmental cues (19). Central to the habituation model is the unique prediction of an interaction between associative and nonassociative tolerance processes. Some research shows that conditions supporting the development of associative tolerance are not conducive to the development of nonassociative tolerance (15–17). More important, there is evidence that conditions that support the development of nonassociative tolerance appear to interfere with the development of associative tolerance (6,7,15,16).

The best example of this effect was provided recently by Tiffany et al. (15), who manipulated associative processes by administering a series of moderately high morphine doses either explicitly paired or unpaired with a distinctive context and nonassociative processes by using either a short (6-h) or a long (96-h) IDI during conditioning. The results showed that tolerance that developed at the long IDI was primarily associative; it was context specific and evident over a 30-day retention interval. In contrast, tolerance at the short IDI was primarily nonassociative in nature; it was unaffected by contextual contingencies and showed no retention after 30 days. The two major goals of the present study were to replicate the general findings of Tiffany et al. (15) and to examine the extent to which the pattern of effects found in that study also pertain to the use of a low conditioning dose.

EXPERIMENT 1

This experiment examined the influence of environmental contingencies on tolerance development when high and low doses of morphine were explicitly paired or unpaired with a distinctive environmental context at a short or long IDI. Some of the conditions of this study duplicated conditions of previous studies [e.g., (15)]; therefore, those conditions were expected to provide exact replications of data earlier obtained in this laboratory. For example, it was expected results from the use of high-dose conditions would demonstrate that associative tolerance develops at the long but not at the short IDI (15). Furthermore, tolerance should develop at the short IDI with high doses, but it should not be influenced by contextual contingencies. That is, it should be nonassociative in nature (15). Associative tolerance should also be evident in the low-dose conditions at the long IDI [e.g., (14,18)], although the magnitude of such an associative effect should be less than that obtained with the high dose at the long IDI (16). Results from animals given a low dose at the short IDI allowed for an examination of the extent to which massed exposures to low doses supported the development of nonassociative tolerance. Finally, data from these animals should also reveal whether the development of nonassociative tolerance with low doses was accompanied by a corresponding decline in the acquisition of learned tolerance effects.

Methods

Subjects. The subjects were 360 experimentally naive male Holtzman rats (Madison, WI), approximately 100 days old on the tolerance test session. Subjects were housed individually in wire-mesh cages in a colony room, maintained on a 12 L:12 D cycle, and given food and water ad lib throughout the experiment. Subjects were randomly assigned to one of 10 testing conditions and were run in eight cohorts of approximately equal size.

Drugs. Injections of morphine sulfate (expressed as the salt) given during the tolerance development phase of the study were 5 mg/kg in the low-dose conditions and 20 mg/kg in the high-dose conditions. The morphine was dissolved in saline with NaCl concentrations adjusted so that each dose was isotonic with physiologic saline. All injections were 1.25 ml/kg administered intraperitoneally (IP).

Analgesia Assessment. Analgesia was assessed by the tail-flick method, which measures the latency for the rat to move its tail from a radiant heat source generated by projector bulb. The test procedures were identical to those used in recent studies in this laboratory [e.g., (17)]. The experimenter gently held each rat on a flat surface, and the rat's tail was placed in a grooved acrylic plate under the heat source. When the rat moved its tail from the light beam, a photosensitive cell tripped a timer that automatically recorded tail-flick latency. Each assessment consisted of the average of three consecutive trials. The heat intensity was adjusted such that nondrugged animals would flick at approximately 5 s, and a 15-s limit was used for each trial.

Habituation. All animals were weighed once daily for 3 days, weighed twice daily for 3 days, and then weighed and injected with physiologic saline twice daily for 8 days before the start of conditioning. These injections occurred at approximately 0900 and 1600 h.

Tolerance Development. Each rat was given eight injections paired with a distinctive context and eight injections in its home cage environment. The distinctive context consisted of a dimly lit room with white noise (75 dB) played continuously over a loudspeaker. The room was scented with cinnamon air fresheners. The room housed plastic breeding boxes ($35 \times 31 \times 16$ cm) containing wood shavings and covered with wire-mesh tops. The tail-flick apparatus also was located in this room.

Exposure to the distinctive context was identical for all subjects. Each animal was taken from its home cage, brought into the distinctive context, injected with either morphine or saline, and placed in a plastic breeding box. Thirty minutes after its injection, the animal was placed on the tail-flick apparatus and the light beam was activated three times but was not focused on the tail. After these three mock trials, the animal was returned to its plastic box. At 60 min after its injection, the animal had three additional mock tail-flicks and was then returned to its home cage. Each animal also was weighed and injected with either morphine or saline in its home cage at a time halfway between exposures to the distinctive context.

Subjects were randomly assigned to one of 10 conditioning groups, with 36 rats per group. Animals in four DC groups (DC-6-LOW, DC-96-LOW, DC-6-HIGH, DC-96-HIGH) received either low or high doses of morphine in the distinctive context at an interdose interval of either 6 or 96 h. All DC groups received saline injections in their home cage environment. Animals in four HC groups (HC-6-LOW, HC-96-LOW, HC-6-HIGH, HC-96-HIGH) received either low or high doses of morphine in the home cage environment at an IDI of either 6 or 96 h. All HC groups received saline injections paired with the distinctive context during each conditioning session. Saline

control groups (SC-6 and SC-96) received saline in both DC and HC environments with an interval between DC exposures of either 6 or 96 h.

Tolerance Testing. At the completion of tolerance development, animals were assessed for tolerance in the distinctive context after an interval of time (6 or 96 h) corresponding to the IDI used for their conditioning. During test sessions, all animals were injected with morphine in the distinctive context. Four different test doses were used for each group to construct dose–response curves. Dose levels were selected based on pilot work and results from initial cohorts. The subjects were tested by an experimenter blinded to the subject's conditioning and dose history. Tail-flick latency was measured 30 and 60 min after the time of morphine injection.

Data Analyses. Data from each of the three trials for tail-flick assessment at 30 and 60 min were averaged to produce mean tail-flick latencies for each subject. Multiple regression analyses (5), with test doses converted to a logarithmic scale, were used to make pairwise comparisons of dose–response curves of specific groups and group combinations [e.g., (15,17)]. Tail-flick latencies were regressed on morphine-log dose level and group-condition variables. Parallelism of dose–response curves was evaluated by inspection of Group × Dose interactions. Data from the 60-min assessment were not analyzed because analgesic effects for animals receiving low morphine doses had dissipated at that time.

Results

Figure 1shows the average latencies from the three consecutive tail-flick trials conducted 30 min after the injection of morphine for each of the 10 treatment groups. The straight lines represent the best-fitting lines for each condition calculated with tail-flick latency regressed on log dose of morphine. The results of the treatment groups using a long (96-h) IDI with either a high (20-mg/kg) or low (5-mg/kg) dose of morphine during conditioning are shown in Fig. 1A and B, respectively. The data indicate that the animals that had received morphine explicitly paired with the distinctive context at a long IDI during conditioning (groups DC-96-HIGH and DC-96-LOW) developed associative tolerance. Among the animals receiving the high dose of morphine, the DRC for the animals given morphine paired with the distinctive context (DC-96-HIGH) was shifted significantly to the right of the animals given morphine in the home cage (HC-96-HIGH) [$sR^2 = 0.069$, $F(1, 67) = 8.42$, $p < 0.05$]. In addition, the HC-96-HIGH animals showed significant tolerance compared with the SC-96 animals [$sR^2 = 0.033$, $F(1, 66) = 4.20$, $p < 0.05$]. The DRC of animals receiving the low dose of morphine in the distinctive context at the long IDI (DC-96-LOW) also showed a significant shift to the right of the dose–response curve of animals receiving the same dose in the home cage (HC-96-LOW) [$sR^2 = 0.046$, $F(1, 67) = 6.98$, $p < 0.05$]. HC animals given a low dose of morphine at this long IDI demonstrated no significant tolerance [$F(1, 66) = 3.67$, $p > 0.05$]. Although both DC-96 groups displayed associative tolerance, the tolerance magnitude of the animals conditioned with the high dose (DC-96-HIGH) was significantly higher than that of the animals receiving the low dose (DC-96-LOW) [$sR^2 = 0.053$, $F(1, 67) = 6.74$, $p < 0.05$].

Figure 1C and D shows the dose–response curves for the groups given either a high or low dose, respectively, at the short (6-h) IDI. The tolerance magnitude for the group that had received the high dose of morphine in the distinctive context (DC-6-HIGH) was not significantly different from the HC-6-HIGH group [$F(1, 66) = 2.05$, $p > 0.05$]. However, morphine-experienced animals (HC-6-HIGH and DC-6-HIGH) exhibited significant tolerance compared with SC-6 animals [$sR^2 = 0.057$, $F(1, 102) = 9.00$, $p < 0.01$]. Similar results were found with dose–response curve comparisons of short IDI treatment groups that received the low dose of morphine during the conditioning phase of the study. There was no significant difference between the groups receiving morphine either paired or unpaired with the distinctive context (HC-6-LOW and DC-6-LOW) [$F(1, 67) = 1.13$, $p > 0.05$], but the DRC for the combined experimental groups (HC-6-LOW and DC-6-LOW) showed a significant shift to the right in relation to the SC-6 group [$sR^2 = 0.051$, $F(1, 67) = 9.57$, $p < 0.01$].

Analyses of the slopes of the DRCs of tolerant groups relative to SC conditions revealed that, with two exceptions, all DRC shifts were parallel. Both the HC and DC groups in the low-dose, long-IDI conditions displayed significantly steeper slopes than the SC-96 group [$sR^2 = 0.035$, $F(1, 65) = 4.86$, $p < 0.05$, and $sR^2 = 0.049$, $F(1, 60) = 7.01$, $p < 0.05$, respectively]. In light of this effect, separate comparisons (*t*-tests) of the HC and SC conditions were conducted at each of the three test doses shared by these two groups to determine whether evidence of HC tolerance might emerge at any test dose. None of these comparisons was significant, suggesting that, regardless of the test dose, HC animals in the low-dose, long-IDI condition displayed no tolerance[2,p.31].

The manipulation of IDI appeared to have an effect on DRCs of SC animals, with short-IDI animals generally producing more analgesia than long-IDI ones [$sR^2 = 0.074$, $F(1, 67) = 9.38$, $p < 0.05$]. This difference in control groups renders direct comparisons of the impact of IDI on tolerance magnitude in morphine experienced animals somewhat difficult. Consequently, analysis of covariance, with dose as a covariate, was used to control statistically the difference in SC conditions. This analysis suggested the IDI manipulation had no significant effect on the level of DC tolerance in animals conditioned with either high or low doses (Fs < 1).

Discussion

96-h IDI. The results of this study provided clear evidence of associative tolerance in animals receiving morphine explicitly paired with the distinctive context at the long IDI. With both high and low conditioning doses, DC animals were significantly more tolerant than HC animals, even though both groups had identical exposure to the drug during conditioning. The magnitude of this associative effect was influenced by the level of conditioning dose, with DC animals conditioned with the higher dose showing greater tolerance than those conditioned with the lower dose. This pattern of results replicates previous findings from our laboratory showing that tolerance developing in animals given either a high or low dose at relatively long IDIs exhibits substantial context specificity, with the degree of this tolerance a positive function of conditioning dose (2,15–17).

There was evidence of tolerance development in HC animals given the high dose at the long IDI. This effect, which we have routinely observed in our research using similar conditioning procedures (2,3,15–17), appears to represent an associative effect with animals using the injection ritual as a CS to predict morphine delivery (4). However, HC tolerance was not observed in animals given a low dose of morphine (16). This finding is consistent with a conditioning account of HC tolerance at the long IDI, in that a higher morphine dose would be likely to produce greater conditioning. Indeed, the finding of stronger DC tolerance as a function of dose is consistent with the hypothesis that a stronger drug US should produce greater conditioning (1).

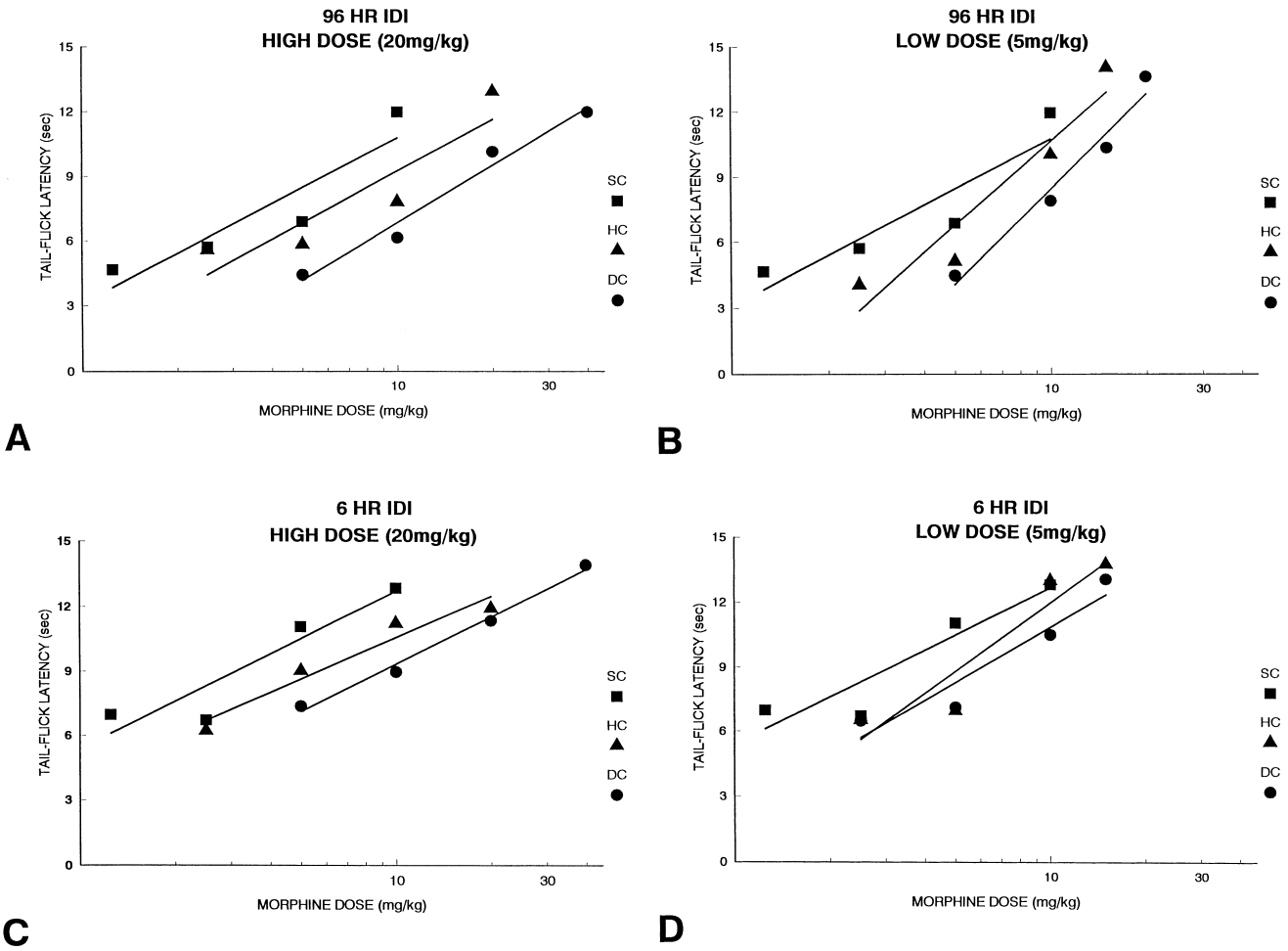

FIG. 1. Mean tail-flick latency on the test sessions for each dose group as a function of log-morphine dose for each of the treatment conditions. The straight lines for each condition represent the best-fitting line calculated with tail-flick latency regressed on log dose of morphine. DC = morphine explicitly paired with the distinctive context; HC = morphine explicitly unpaired with the distinctive context; SC = saline controls. Animals were conditioned with 20 mg/kg (A and C) or 5 mg/kg (B and D) of morphine sulfate at a 96-h (A and B) or 6-h (C and D) IDI with the test 96 or 6 h after the end of conditioning.

6-h IDI. Results from conditions using the short IDI show tolerance development that was relatively unaffected by contextual contingencies. The absence of any context effect following exposure to high doses of morphine at a short IDI suggests that this tolerance was nonassociative in nature and that associative processes had little detectable influence on tolerance development. These findings replicate the results of Tiffany et al. (15) and demonstrate that conditions conducive to the formation of nonassociative tolerance disrupt the acquisition of associative tolerance. As with the high-dose groups, animals conditioned with the low dose at the short IDI displayed tolerance that was not influenced systematically by drug–context pairings. These findings suggest that both high and low doses of drug delivered at a short IDI promoted the development of nonassociative tolerance and simultaneously disrupted the acquisition of associative tolerance.

The depiction of the tolerance at the low-dose, short IDI as nonassociative rests on the absence of a context-specific influence in these conditions. However, it is possible that the tolerance observed represents an associative effect, with some other drug-predictive cue, such as the injection ritual, serving as the CS. For example, it is conceivable that massed exposure to the context at the short IDI might have effectively eliminated the ability of these stimuli to support conditioning (19), whereas the associative potential of injection cues might be relatively unaffected by such massed exposures. To interpret the results of this study adequately, it is important to determine the associative or nonassociative nature of the tolerance in the short IDI conditions.

EXPERIMENT 2

This experiment examined the nature of the tolerance present in the short IDI condition by using a 30-day retention test to compare the tolerance developed in the HC-6-LOW and HC-6-HIGH groups. Past studies from this laboratory have shown associative tolerance exhibits excellent retention (4,15,17), whereas nonassociative tolerance dissipates rapidly [e.g., (15)]. In light of these previous findings, the tolerance in HC-6-HIGH animals should display little or no retention, an outcome in support of the contention that this tolerance is nonassociative. Similarly, the loss of tolerance in the HC-6-

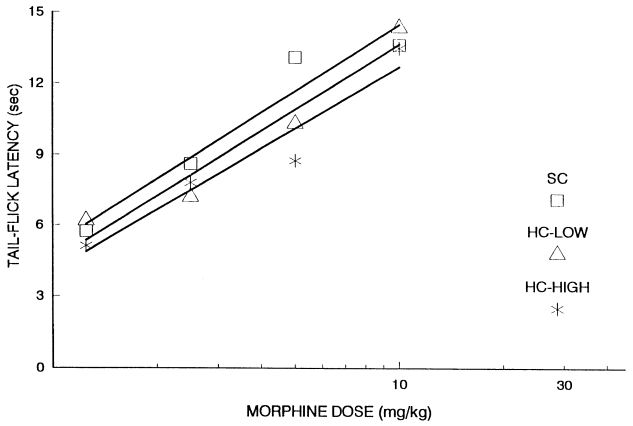

FIG. 2. Mean tail-flick latency on the test sessions for each dose group as a function of log-morphine dose for each of the treatment conditions. The straight lines for each condition represent the best-fitting line calculated with tail-flick latency regressed on log dose of morphine. SC = saline controls; HC-HIGH = morphine explicitly unpaired with the distinctive context conditioned with 20 mg/kg of morphine sulfate; HC-LOW = morphine explicitly unpaired with the distinctive context with 5 mg/kg of morphine sulfate. Animals were conditioned at a 6-h IDI with the test 30 days after the end of conditioning.

LOW animals would also suggest that tolerance that developed in identically conditioned animals in the previous study was nonassociative. In contrast, evidence of tolerance retention in these animals would suggest that this tolerance was supported through associative processes.

Methods

The subjects were 90 experimentally naive male rats of the same strain and age of those in Experiment 1. The design and procedures used for the habituation and tolerance development phase of this study were identical to those used for Experiment 1. Subjects were assigned randomly to one of three conditioning groups, with 30 rats per group. Animals in two HC groups (HC-6-LOW, HC-6-HIGH) received either low or high doses of morphine in the home cage environment at a 6-h IDI. Both HC groups received saline injections paired with the distinctive context during each conditioning session. Saline control groups (SC-6) received saline in both distinctive context and home cage environments with an interval between DC exposures of 6 h. Animals were tested for tolerance retention 30 days after their last exposure to the distinctive context. The animals remained undisturbed in their home cages during the retention interval. The procedures for tolerance testing were identical to those used in Experiment 1.

Results and Discussion

The average tail-flick latencies for the 30-min assessment for the three treatment groups tested after the 30-day retention interval are shown in Fig. 2. It is clear from these data that tolerance was not retained in either experimental group. The dose–response curves for the animals given the high dose of morphine and the animals given the low dose of morphine in the home cage during tolerance development (HC-6-HIGH and HC-6-LOW) were not significantly different [$sR^2 = 0.008$, $F(1, 53) = 1.13$, $p > 0.05$]. In addition, the combined dose–response curve for these two groups was not different from the saline control group [$sR^2 = 0.018$, $F(1, 80) = 3.85$, $p > 0.05$]. The analyses showed no significant Dose × Group interactions, suggesting parallelism of DRCs.

The absence of retained tolerance in the HC-6-HIGH animals replicates previous findings from this laboratory (15) showing that tolerance developing after massed exposure to high doses of morphine is likely a nonassociative effect. The absence of retained tolerance in the HC-6-LOW animals suggests the tolerance observed from this condition in Experiment 1 was also nonassociative in nature. Because this retention test indicates that the tolerance found in the HC-6-LOW group was context-independent, this finding provides evidence against the hypothesis animals stopped using the context as a drug-predictive cue but were somehow able to continue to use the injection ritual as a CS.

GENERAL DISCUSSION

This research clearly replicates previous results from long IDIs finding strong associative-tolerance effects among animals given either high or low conditioning doses. Furthermore, this research shows that massed exposure to both high and low doses of morphine at the short IDI led to the development of context-independent tolerance and eliminated context-dependent effects. The nonassociative nature of this tolerance was evident in the absence of contextual influences in tolerance magnitude in Experiment 1 and the absence of retention of this tolerance in Experiment 2. These results support the prediction made by Baker and Tiffany's (1) habituation model that conditions conducive to the development of nonassociative tolerance disrupt the acquisition of associative tolerance. In addition, the results support the model's explanation that the source of the disruption of associative effects at the short IDI is massed exposure to morphine. The findings are consistent with the contention that closely spaced exposure to the drug can lead to the build-up of priming of the drug stimulus properties (US). Such priming accumulation would be expected to generate nonassociative tolerance effects and simultaneously reduce the ability of the morphine US to support the development of an association between the morphine and the distinctive context. From this perspective, the same process that produces nonassociative tolerance simultaneously disrupts learning.

Although the findings of this study demonstrated that associative tolerance did not develop under conditions conducive to the acquisition of nonassociative tolerance, the mechanism responsible for this effect has not been precisely identified. An alternative explanation for the disruption of learning may be that massed exposure to the distinctive context (CS) rather than massed morphine exposure may disrupt the development of associative tolerance (15,17). When presentations of the CS are closely spaced, a reduction of the salience of the distinctive context may be accompanied by a reduction in the conditioning supported by these stimuli (19). The current study was able to begin to evaluate the extent to which massed context exposures contribute to disruption of learning at short IDIs. The results of this study are not consistent with the findings expected had massed context exposure completely disrupted learning at the short IDI. If massed exposure to the distinctive context contributed to the disruption of learning, data from the low-dose condition would have shown neither learned effects nor the development of nonassociative tolerance. Because nonassociative tolerance appeared to develop at the short IDI with the low dose, the data do not provide support for the idea that massed-context exposure exclusively disrupted learning. Notwithstanding, the data cannot rule out the possibility that massed context exposure contributed to a disruption in associative tolerance

effects. Within Experiment 1, there was evidence of nonassociative tolerance, a massed morphine effect, even with the use of a relatively low dose of morphine. Consequently, the impact of massed context exposure in the absence of massed drug effects could not be examined in the low-dose, short-IDI condition. This outcome suggests that it may be difficult, within this tolerance paradigm, to disentangle the effect of massed US and massed CS exposures on learned tolerance. Nevertheless, the data show clearly that both associative and nonassociative processes contribute to tolerance development, and that these processes appear to operate in a mutually inhibitory fashion. However, the question of the mechanisms responsible for the disruption of learning at short IDIs remains open.

Research from this laboratory contributes to the discussion of alternative roles of massed morphine in the development and disruption of learned tolerance. Cepeda-Benito and Tiffany (4) found that a dose of morphine administered 6 h before a morphine–context pairing had absolutely no impact on the acquisition of conditioned tolerance to the distinctive context. Such results suggest that residual morphine effects from a recent exposure to the drug will not necessarily disrupt learning, and therefore, single-dose priming alone is not responsible for the disruption of associative tolerance effects (4). It may be possible that, although morphine exposure 6 h before a morphine–context pairing shows no effect on learning, morphine administration 6 h after a morphine–context pairing may impair subsequent rehearsal of this priming. This possibility could be evaluated by examining the associative impact of a morphine dose administered 6 h after each of a series of morphine–context pairings. A second possibility may be that although drug effects from a single dose may be insufficient to disrupt learning, the accumulation of some drug effect across drug administrations may affect learning. This possibility could be evaluated by assessing the extent to which a series of closely spaced morphine administrations followed by a morphine–context pairing disrupted the development of context-specific tolerance.

In conclusion, the current results clearly replicate previous findings from this laboratory and support several predictions derived from Baker and Tiffany's (1) habituation model of drug tolerance. First, these results replicate past findings demonstrating that morphine administered at long IDIs promotes the development of associative tolerance, whereas morphine administered at short IDIs produces what appears to be nonassociative tolerance (15). This outcome illustrates the fact that any comprehensive account of morphine tolerance must acknowledge the contribution of both pharmacologic and learning processes to tolerance development. Second, these findings demonstrate that tolerance magnitude is a positive function of conditioning dose and is consistent across IDIs (15,16). Third, the results demonstrate that conditions conducive to the formation of nonassociative tolerance disrupt the acquisition of associative tolerance. Such results support the habituation model's prediction of the interaction between associative and nonassociative tolerance. Finally, the findings are consistent with the model's explanation that the source of the disruption of associative effects at the short IDI is massed exposure to morphine, although, as noted above, the exact mechanisms responsible for this effect have not yet been discovered.

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