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Unsignaled Morphine Delivery Does Not Disrupt the Development of Associative Morphine Tolerance in the Rat

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CEPEDA-BENITO, A. AND S. T. TIFFANY. *Unsignaled morphine delivery does not disrupt the development of associative morphine tolerance in the rat.* PHARMACOL BIOCHEM BEHAV **54**(3) 575–580, 1996. – When morphine administration is paired with a distinctive context, tolerance to morphine's analgesic effects comes readily under the associative control of the drug-paired context. These associative tolerance effects are eliminated when a relatively short (i.e., 6 h) interdose interval (IDI) is used for conditioning. Contemporary models of learned tolerance explain the absence of learning at short IDIs by positing that residual morphine effects from a recent drug exposure disrupt the formation of drug-context associations. The present studies examined the impact of unsignaled morphine injections given 6 h prior to drug-context pairings on the development of associative tolerance. Analgesia was measured by the tail-flick method, and tolerance levels were assessed by dose-response curve methodology. Morphine preexposure had no detectable influence on the acquisition of associative tolerance when rats were tested immediately after conditioning, after a 30-day rest interval, or after a 30-day period of daily saline injections in their home-cage environment. These data suggest disruption of associative tolerance effects at short IDIs is not attributable to residual effects of morphine from the immediately preceding trial.

Associative Nonassociative Morphine Tolerance Tail flick Unsignaled morphine delivery

THERE is considerable evidence that learning processes can influence the development of drug tolerance (2,37). For example, it has been established that distinctive environmental cues reliably paired with morphine administration can become conditioned stimuli (CSs) that produce associative tolerance effects (7,30,32,34,35). However, in light of numerous examples of tolerance developing independently of drug-environment contingencies (1,13,20,38), it is generally accepted that learning may not account for all instances of tolerance. Consequently, most contemporary learning-based models of tolerance acknowledge tolerance may be acquired via both associative and pharmacological (or nonassociative) routes (2,25,31).

The habituation account of associative and nonassociative tolerance (2,36) posits tolerance mechanisms are elicited to the extent the drug's stimulus properties are already represented or primed in working memory. These stimulus properties can be primed nonassociatively, through a recent presentation of the drug itself (self-generated priming), or associatively, through the presentation of stimuli predictive of drug delivery (associatively generated priming). The magnitude and persistence of self-generated priming is assumed to be related positively to dose and negatively to interdose interval (IDI). Tolerance developing independently of predictive cues is attributed to the accumulation of self-generated priming across successive drug administrations. This nonassociative tolerance is expected to dissipate after drug administration is discontinued, whereas associatively based tolerance should display excellent retention.

Recent investigations have produced clear support for several major predictions of the habituation model (2). For example, we injected rats with a series of high doses of morphine either paired or unpaired with a distinctive context at a short (6 h) or a long (96 h) IDI (29). Tolerance developing at the long IDI was context dependent and displayed retention over a 30-day interval [see also (7,33)]. In contrast, although com-

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parable in magnitude to the tolerance displayed by animals receiving morphine at the long IDI, tolerance acquired at the short IDI was uninfluenced by contextual contingencies of drug delivery and dissipated completely by the 30-day retention test.

An interesting feature of these results was that conditions conducive to the development of nonassociative tolerance (i.e., short IDI) eliminated the development of associative tolerance. This finding, which has been replicated in other research from our laboratory (5,8,28), was explicitly predicted by the habituation model of tolerance (2). According to this theory, at a short IDI, self-generated priming from prior conditioning trials intruding into a current trial would reduce the effectiveness of the drug unconditioned stimulus (US) in instigating steps necessary for associative learning [see also (36)]. From this priming perspective, the disruption of learning at the short IDI arises from massed exposure to morphine over the course of tolerance development.

The homeostasis model of tolerance (25) has provided a related account of disruption of associative tolerance effects at short IDIs. The homeostasis model suggests drugs paired with contexts at short IDIs result in a backward pairing of the drug US with the CS, which is not particularly conducive to the acquisition of associative effects (21). That is, to the extent unconditioned responding to the drug from a given trial continues to be present on a subsequent trial, the animal will be exposed to a backward CS/US contingency.

The explanations offered by the habituation and the homeostasis models for the attenuation of conditioned tolerance effects at a short IDI assume a recent presentation of morphine will selectively inhibit the formation of morphine-cue associations. Alternatively, massed exposure to morphine might disrupt learning in general. That is, at a short IDI, residual intoxication from a recent administration of a drug may prevent any form of conditioning on a current trial (4,29).

Although differing in their details, the priming (2), backward conditioning (25), and intoxication (4) accounts of disrupted associative tolerance at short IDIs attribute this effect to the influence of closely spaced morphine administrations on conditioning. According to these hypotheses, a dose of morphine given shortly before a morphine-context pairing should disrupt the formation of an association between that context and the drug. The present research tested this prediction by investigating the effect on associative tolerance of a pretrial dose of morphine given shortly before a morphine-context pairing. In light of research showing that 6 h IDI schedules disrupt associative tolerance effects (5,8,28,33), animals in Experiment 1 received an unsignaled morphine dose 6 h prior to each of eight context-paired morphine injections separated by a 96-h IDI. The 96-h IDI procedures utilized in this research have produced robust associative tolerance effects in previous investigations (5–8,28,32,33,35). A reduction in associative tolerance as a result of pretrial exposures to morphine 6 h prior to each conditioning session would support the aforementioned hypotheses. Experiment 2 further examined the associative nature of any tolerance effects produced in the first experiment by testing for the presence of tolerance after a 30-day retention period. Experiment 3 utilized an extinction procedure (6) to investigate the extent to which any tolerance produced in these studies was controlled associatively by handling and injection cues accompanying morphine administration (6,10). In combination, these experiments provided a comprehensive analysis of the associative impact of pretrial morphine exposures on conditioned tolerance effects.

EXPERIMENT 1

Method

Subjects, drugs, and analgesia assessment. The subjects, 123 male Holtzman rats 96 to 99 days old on testing, were housed individually in cages located in a colony room. The dose of morphine sulfate (expressed as the salt) used during Tolerance Development was 20 mg/kg. Tolerance test doses ranged from 1 to 20 mg/kg. Morphine was dissolved in saline with the concentration of sodium chloride adjusted so that each dose was isotonic with physiological saline. Solutions were injected intraperitoneally in a volume of 1.25 ml/kg. Analgesia was assessed by the tail-flick method, which measured the latency for the rat to remove its tail from a radiant heat source generated by a 125 W prefocussed light bulb. The methodological procedures followed in this research closely parallel those we have used in our previous research (33,35). We refer the reader to these sources for a more detailed description of the experimental procedures.

Habituation and tolerance development. Prior to morphine exposure, the rats were habituated to saline injections and handling procedures for 14 days. During tolerance development, rats were given eight exposures to a distinctive context with each exposure separated by 96 h. Animals were carried from their home cage to the room serving as the distinctive context, injected with saline or morphine, and placed in a plastic holding box. Each animal was given mock tail-flick trials, with the light bulb activated but not directed at the rat's tail, at 30 and 60 min after its injection. The animal was returned to its home cage after the 60 min mock tail flick. Six hours prior to distinctive context exposures, each rat was injected with either saline or morphine in its home-cage environment. All animals were also given a home-cage saline injection 48 h after each distinctive context exposure. Rats were assigned randomly to four treatment conditions: morphine-primed distinctive context (MPDC), distinctive context (DC), home cage (HC), and saline control (SC). During distinctive context exposures, MPDC and DC animals received morphine, and HC and SC animals received saline. The injection delivered 6 h prior to each distinctive context exposure consisted of morphine for MPDC and HC animals and saline for DC and SC animals.

Tolerance test and data analyses. The test session occurred in the distinctive context 96 h after the last context exposure of the tolerance development phase. Each animal was carried to the distinctive context and injected with morphine. To construct dose-response curves (DRCs), each condition was divided into four subgroups ($n \geq 7$) with each subgroup receiving a different test dose of morphine. Tail-flick assessments were given at 30 and 60 min after the injection. The average of the three consecutive tail-flick trials conducted 30 min after the injections were subjected to multiple regression analysis (9). Tail-flick latencies were regressed on log-dose level, group condition, and the interaction of these two variable sets. The variables were forced into the equation in the order listed. Effects for group conditions were evaluated by the use of dummy coding for pair-wise comparisons. Differences between any pair of groups were indexed by a significant group effect. Parallelism of DRCs was evaluated by examining interactions between condition effects and log-dose level.

Results and Discussion

The average tail-flick latencies for the four treatment conditions are shown in Fig. 1. The straight lines represent the best-fitting line calculated with tail-flick latency regressed on

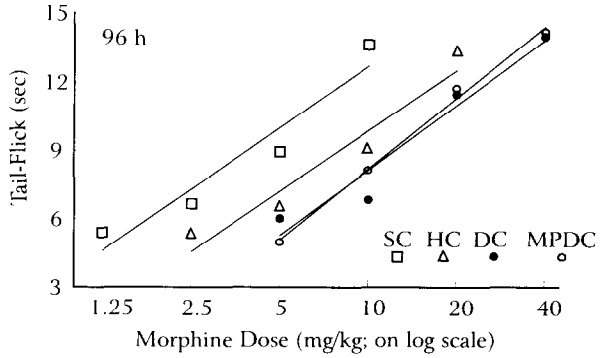

FIG. 1. Mean tail-flick latency 96 h after last conditioning session for each dose group as a function of log-morphine dose for each condition. SC = saline control; HC = morphine explicetly unpaired with distinctive context; DC = morphine explicetly paired with distinctive context; MPDC = morphine given 6 h prior to pairing morphine with distinctive context.

log-morphine dose for each condition. The DRC for animals given the priming dose of morphine prior to each morphine-context pairing (MPDC) was not significantly different from the DRC of the animals receiving morphine paired exclusively with the context (DC), $F < 1$. The DRCs of those animals given morphine in the distinctive context (DC and MPDC) were shifted significantly to the right of animals receiving morphine exclusively in their home cage environment (HC), $sR2 = 0.041$, $F(1, 61) = 7.41$, $p < 0.01$, and $sR2 = 0.035$, $F(1, 63) = 6.41$, $p < 0.025$, respectively. Finally, The HC animals were significantly more tolerant than the SC animals, $sR2 = 0.119$, $F(1, 56) = 19.68$, $p < 0.001$. All DRC shifts were parallel as indicated by the absence of a dose × condition comparison interaction, Fs < 1.19.

The difference in tolerance magnitude between DC and HC conditions shows that animals that had morphine paired with the distinctive context developed associative tolerance to morphine's analgesic effects [see also (6,7,28,33,35)]. There was no evidence in this study that exposure to morphine 6 h prior to each morphine-context pairing impeded the development of this context-specific tolerance effect. These results suggest a recent administration of morphine before a conditioning trial did not disrupt the acquisition of an association between morphine and the context. However, this conclusion assumes the tolerance observed in the MPDC animals was an associative effect controlled exclusively by the distinctive context.

There are alternative explanations of these data compatible with the possibility that priming exposures to morphine interfered with contextual conditioning in MPDC animals. One possibility is that priming doses eliminated associative effects in MPDC animals, and that tolerance in MPDC and HC animals was exclusively nonassociative in nature. Under this scenario, MPDC animals would have developed greater tolerance than HC animals because the former received twice as much morphine as the latter over the course of tolerance development. A related possibility is that tolerance in MPDC animals represented the combined influence of attenuated associative tolerance and some degree of nonassociative tolerance. Finally, tolerance in the MPDC and HC animals may have been controlled associatively by injection cues rather than the distinctive context. Previous research has shown that the injection ritual is capable of supporting associative tolerance effects (6,10). If MPDC and HC animals were utilizing injection cues to predict the delivery of morphine, the MPDC rats' greater number of pairings and greater probability of reinforcement would explain why these rats acquired more tolerance than HC rats. That is, MPDC rats received twice the number of pairings of morphine with injection cues as HC rats (16 vs. 8, respectively) and were twice as likely as HC rats to receive morphine in the presence of those cues (66.6 vs. 33.3%, respectively).

EXPERIMENTS 2 AND 3

These experiments tested the hypotheses that tolerance in MPDC animals was to some extent nonassociative in nature or to some extent controlled associatively by injection cues. It has been established that associative tolerance exhibits excellent retention long after the cessation of drug delivery, whereas nonassociative tolerance is relatively short lived [e.g., (6,28, 33,35)]. For example, pronounced levels of nonassociative tolerance have been produced by giving animals morphine injections every 6 h (5,8,33). This tolerance effect, which was comparable in magnitude to the level of tolerance observed in the DC and MPDC rats of Experiment 1, dissipated completely at a 30-day retention test (8,33). There are numerous additional studies demonstrating that profound levels of nonassociative tolerance show little retention after intervals considerably shorter than 30 days [e.g., (14,24)]. In sum, the available literature provides support for the hypothesis that tolerance present at a 30-day retention test is of an associative nature. Therefore, Experiment 2 examined the retention of tolerance in animals tested 30 days after the completion of conditioning. This experiment allowed for an examination of the extent to which tolerance in MPDC animals was controlled exclusively or even partially by nonassociative processes. Experiment 3 investigated whether tolerance in MPDC animals was mediated associatively via injection stimuli. This experiment used an extinction procedure in which animals were given a series of unreinforced presentations of the injection ritual over a 30-day retention interval. Previous research from our laboratory has shown this procedure abolishes the retention of tolerance in animals using injection cues to predict morphine delivery (6). Therefore, if associative tolerance in MPDC animals was controlled by injection stimuli, this extinction procedure should selectively disrupt this tolerance.

Method

Subjects and procedures. The subjects were 161 (Experiment 2) and 142 (Experiment 3) male Holtzman rats 126 to 129 days old on testing. The design and procedures used for the Habituation and Tolerance Development phases of these experiments were identical to those used for Experiment 1. Experiment 2 included all four treatment conditions used in Experiment 1. Three of the treatment conditions (MPDC, DC, SC) were used in the third experiment. Animals were tested 30 days after the last context exposure of the Tolerance Development phase. In Experiment 2, animals were left undisturbed in their home cage environment over the retention period. In Experiment 3, all rats received a daily saline injection in their home cage over the 30-day retention period. The HC control group in Experiment 3 was not needed because the HC rats from Experiment 2 were not tolerant to morphine's analgesic effects. That is, these rats' tolerance disappeared in the absence of extinction procedures.

Results

Experiment 2. Figure 2 (Retention) shows the DRCs for the 30 min assessments for the four treatment groups after the

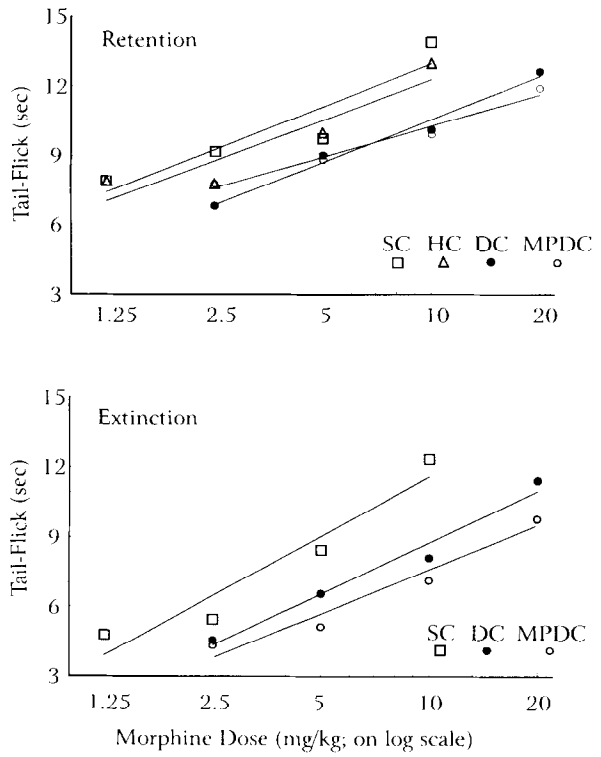

FIG. 2. (Retention/Extinction). Mean tail-flick latency 30 days after last conditioning session for each dose group as a function of log-morphine dose for each condition. During the 30-day interval, animals were either left undisturbed in their home cages (Retention), or received a daily saline injection in the home cage environment (Extinction). SC = saline control; HC = morphine explicitly unpaired with distinctive context; DC = morphine explicitly paired with distinctive context; MPDC = morphine given 6 h prior to pairing morphine with distinctive context.

30-day rest period. There were no DRC differences between the MPDC and the DC groups, or between the SC and HC groups, all Fs < 1. Each of the DRCs for DC and MPDC rats revealed a shift to the right of the DRC of the HC animals, $sR2 = 0.049$, $F(1, 78) = 5.20$, $p < 0.05$ and $sR2 = 0.038$, $F(1, 81) = 4.00$, $p < 0.05$.

Experiment 3. Figure 2 (extinction) shows the DRCs for the 30-min assessments for the three treatment groups after the 30-day period of daily saline injections in the home-cage environment. There were no DRC differences between the MPDC and the DC groups, $F(1, 92) = 2.51$, $p > 0.05$. Each of the DRCs for DC and MPDC rats revealed a shift to the right of the DRC of the SC animals, $sR2 = 0.093$, $F(1, 91) = 17.55$, $p < 0.001$ and $sR2 = 0.153$, $F(1, 92) = 25.71$, $p < 0.001$. All DRC shifts were parallel as indicated by nonsignificant dose × group interactions in both Experiment 2 and Experiment 3, Fs < 3.58.

GENERAL DISCUSSION

The results provided no evidence that, within the drug administration parameters used in this research, an unsignaled morphine dose given shortly before a signaled morphine dose disrupted the development of associative morphine tolerance. Rats receiving a high morphine dose 6 h prior to each of eight morphine doses paired with a distinctive context developed context-specific morphine tolerance. The retention of MPDC tolerance and absence of any difference between the MPDC and the DC conditions in Experiments 2 and 3 corroborated the associative nature of this tolerance [see also (6)]. Any nonassociative processes contributing to tolerance in MPDC rats should have dissipated at the 30-day retention test and produced a differential tolerance effect between MPDC and DC rats. Moreover, after an extensive regime of unreinforced saline injections, morphine-primed rats continued to be as tolerant as DC rats. The finding that these extinction procedures had no impact on MPDC tolerance suggests that this tolerance was not supported associatively by the injection cues that accompanied drug administrations. It should be noted these findings were obtained with the use of dose-response curve methodology, which allows for the detection of fairly small differences in tolerance levels [e.g., (4–6,33–35)]. In light of the power of this methodology to discern even modest effects, it seems highly likely that, had it existed, we would have found some difference between the MPDC and DC conditions in at least one of the three experiments.

The present results challenge two major theories of conditioned drug tolerance. The habituation model specifically predicts that "if signaled morphine doses are preceded by unsignaled morphine doses, the amount of associatively primed tolerance acquired will be an inverse function of the unsignaled morphine dose. The influence of an unsignaled morphine dose, of course, decreases as the IDI increases" [(2), p. 102]. In turn, the homeostasis model explains that at high doses and short IDIs "the persistence of UCR activation from a preceding drug delivery will overlap with the presentation of the conditioned stimulus (CS), making for backward conditioning" [(21), p. 400].

In an effort to reconcile the present results with these predictions, it could be said the 6 h IDI was not short enough, or the 20 mg/kg priming dose was not high enough, to disrupt associative tolerance development. However, previous research has consistently found that 6 h IDI schedules interrupt the development of associative morphine tolerance in rats receiving morphine explicitly paired with a distinctive context [e.g., (5,28,33)]. Moreover, this effect has been obtained even when a 5 mg/kg morphine dose was used for tolerance development (28).

Alternatively, the habituation model could be expanded by a consideration of the impact of massed CS exposure on associative effects [see (36)]. According to the priming theory of conditioning (36), two stimuli should become associated to the extent they are simultaneously rehearsed in memory. As the habituation model predict, a stimulus already primed in memory by a prior presentation will interfere with rehearsal of another presentation of the same stimulus. This model emphasized the self-generated priming of the US as the blocking mechanism by which recent drug administrations interfered with the simultaneous rehearsal of morphine (the US) and the distinctive context (the CS). However, simultaneous rehearsal of the CS-US association could also be disrupted by a self-priming of the CS. This argument can explain both the disruption of associative tolerance in the 6-h IDI design (28,33) and the absence of disruption of associative tolerance in the 6-h morphine-primed design. The 6 h IDI design utilizes closely spaced morphine exposures and closely spaced context exposures. Conversely, the morphine-primed design represents closely spaced morphine exposures and widely dispersed distinctive context exposures. Unfortunately, it is not clear why self-priming from the CS, but not the US, should disrupt conditioning. Moreover, it seems reasonable to expect the self-

priming of a drug to persist longer than the self-priming of exteroceptive stimuli. These authors suggested that self-generated priming of drug effects may last longer than a self-generated priming of exteroceptive stimuli because drug effects may last many hours, whereas retentive capacity of exteroceptive stimuli in short-term memory is usually measured in seconds (2).

Beyond the habituation and the homeostatic model's predictions regarding associative and nonassociative tolerance development, the fact that the administration of noncontingent USs did not significantly diminished the association between morphine and the distinctive context deserves further inquiry. On the surface, our data seem to be problematic for CS-US contingency models of classical conditioning. According to contingency models, the introduction of unsignaled USs should have reduced the magnitude of the conditioned response because it reduced the CS-US contingency [e.g., (12,16,23,26)]. Most influential theoretical models of the impact of intertrial USs on conditioning assume that associations formed between these USs and the experimental context either reduce the associations formed between the CS and the US (27) or attenuate the expression of the CS-US learning [e.g., (3,22)]. However, within our procedures there is no clearly identifiable experimental context that could compete with the distinctive context or CS. Therefore, these models would not necessarily predict a reduction in conditioning responding within our paradigm. Likewise, although no US preexposure interference effects in associative tolerance have been reported, the present data do not necessarily challenge previous findings from drug-conditioning paradigms where preexposure to the US shortly before the CS-US conditioning session has blocked learning [e.g., (11)]. It is possible that higher priming doses or shorter preexposure intervals would produce a US preexposure effect within an associative tolerance paradigm.

The disruption of associative tolerance in the 6-h IDI design, relative to the 96-h IDI design (28,33) is compatible with the common finding in classical conditioning paradigms that massed conditioning trials, in relation to spaced trials, tend to produce weaker or slower acquisition of conditioned responding [e.g., (16–18)]. It has been argued (27) that, with spaced conditioning trials subjects have greater nonreinforced exposure to the experimental context during the intertrial interval, which should result in the extinction of any associations formed between the US and the experimental context. When trials are massed, there is less opportunity for extinction of experimental context-US associations, thus decrementing the associative strength acquired by the CS. However, as noted earlier, we do not present the distinctive context or CS within a superordinate experimental context. Therefore, the discrepancy of the results found between the 6-h IDI design and the 96-h IDI design require another interpretation.

An alternative explanation for the disruption of associative tolerance effects at a short IDI emerges from Jenkins' relative waiting time (RWT) hypothesis (18). This hypothesis predicts the strength of the CS-US association is an inverse function of the ratio of the average time the subject waits for the US while being exposed to the CS to the average time the subject waits between US presentations in the experimental setting. That is, for a given waiting time in the CS per US, the strength of the association between the CS and the US will decrease as the average time between US presentations decreases. Within the 6-h IDI, the 96-h IDI, and the morphine-primed designs, the average waiting time in the CS per US is the same (i.e., animals receive an injection right after they enter the distinctive context, where they stay for 1 h). Conversely, the overall waiting time per US presentation varies markedly across these designs. The average waiting periods per US in the 96-h IDI and the morphine-primed designs are 96 h and 48 h, respectively. The average waiting period in the experiment for the 6-h IDI design is much shorter—6 h. According to the RWT hypothesis, we should expect greater associative strength in the groups with low RWT in the CS per US (1 out of 96 and 1 out of 48 h, respectively) than in the group with a greater RWT in the CS per US (1 out of 6 h). This interpretation is further supported by the finding (35) that a 12-h IDI design (1 out of 12 h) reduced the associative tolerance effects found with a 24-h IDI and a 96-h IDI designs. The RWT hypothesis could be further tested by observing the effects of maintaining the IDI constant while systematically varying the length of the distinctive context exposure. This could be achieved by gradually delaying the interval between the time of entrance to the distinctive context and the time of drug delivery while keeping constant the exposure time to the CS after the drug is administered.

In summary, these three experiments, in combination with previous research investigating the role of the IDI in the development of associative and nonassociative forms of morphine tolerance, challenge a prediction made by two major theories of drug tolerance. The results suggest that a self-generated priming of morphine (2), or perseveration of a homeostatic response (25) from a recent drug administration is not sufficient to disrupt the development of associative morphine tolerance. More generally, there is no support in these data for the argument that massed exposure to morphine in short IDI designs are responsible for disruptions in the acquisition of associative tolerance effects.

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REFERENCES

1. Ahlijanian, M. K.; Takemori, A. E. Changes in adenisine receptor sensitivity in morphine-tolerant and -dependent mice. J. Pharmacol. Exp. Ther. 236:615–620; 1986.
2. Baker, T. B.; Tiffany, S. T. Morphine tolerance as habituation. Psychol. Rev. 92:78–108; 1985.
3. Balsam, P. D. Relative time in trace conditioning. In: Gibbon, J.; Allan, L., eds. Timing and time perception. New York: New York Academy of Science; 1984:211–227.
4. Batson, J. D.; Best, M. R. Lithium mediated disruptions of latent inhibition: Overshadowing of the unconditioned stimulus in flavor conditioning. Learn. Motiv. 13:167–184; 1982.
5. Carter, B.; Tiffany, S. T. Examinations of the mu and kappa receptor specificity of associative and nonassociative morphine tolerance. Paper presented at the annual meeting of the Midwestern Psychological Association; May 1995.
6. Cepeda-Benito, A.; Tiffany, S. T. Role of drug-administration cues in the associative control of morphine tolerance. Psychopharmacology (Berlin) 122:312–316; 1995.
7. Cepeda-Benito, A.; Tiffany, S. T. Effect of number of conditioning sessions on the development of associative tolerance to morphine. Psychopharmacology (Berlin) 109:172–176; 1992.
8. Cox, L. S.; Tiffany, S. T. Associative and nonassociative toler-

ance to morphine in the rat: Effects of dose and interdose interval. Pharmachol. Biochem. Behav. (in press).
9. Cohen, J.; Cohen, P. Applied multiple regression/correlational analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum; 1975.
10. Dafters, R. I.; Bach, L. Absence of environment-specificity in morphine tolerance acquired in nondistinctive environments: Habituation or stimulus overshadowing? Psychopharmacology (Berlin) 87:101-106; 1985.
11. Dojman, M.; Best, M. R. Interference with ingestional aversion learning produced by preexposure to the unconditioned stimulus: Associative and nonassociative aspects. Learn. Motiv. 11:522-537; 1980.
12. Durlach, P. J. Effect of signaling intertrial unconditioned stimuli in autoshaping. J. Exp. Psychol. Anim. Behav. Process. 9:374-389; 1983.
13. Ding, X. Z.; Fan, S. G.; Zhou, J. P.; Han, J. S. Reversal of tolerance to morphine but no potentiation of morphine-induced analgesia by antiserum against cholecystokinin octapeptide. Neuropharmacology 25:1155-1160; 1986.
14. Fenandes, M.; Kluwe, S.; Coper, H. The development of tolerance to morphine in the rat. Psychopharmacology (Berlin) 54: 197-201; 1982.
15. Gibbon, J.; Baldock, M.; Locurto, C.; Gold, L.; Terrace, H. S. Trial and intertrial durations in in autoshaping. J. Exp. Psychol. Anim. Behav. Process. 3:264-284; 1977.
16. Gibbon, J.; Balsam, P. The spread of association in time. In: Locurto, C. M.; Terrace, H. S.; Gibbon, J., eds. Autoshaping and conditioning theory. New York: Academic Press; 1981:219-253.
17. Gormezano, I.; Moore, J. W. Classical conditioning. In: Marx, M. H., ed. Learning processes. Toronto, Canada: Macmillan; 1969:121-203.
18. Jenkins, H. M.; Barnes, R. A.; Barrera, F. J. Why autoshaping depends on trial spacing. In: Locurto, C. M.; Terrace, H. S.; Gibbon, J., eds. Autoshaping and conditioning theory. New York: Academic Press; 1981:255-284.
19. Jenkins, H. M.; Shattuck, D. Contingency in fear conditioning: A reexamination. Bull. Psychon. Soc. 17:159-162; 1981.
20. Loomis, C. W.; Milne, B.; Cervenko, F. W. Determination of cross tolerance in rat spinal cord using intrathecal infusion via sequential mini-osmotic pumps. Pharmacol. Biochem. Behav. 26: 131-139;1987.
21. Mackintosh, N. J. Conditioning and associative learning. New York: Oxford University Press; 1983.
22. Miller, R. R.; Schachtman, T. R. Conditioning context as an associative baseline: Implications for response generation and the nature of conditioned inhibition. In: Miller, R. R.; Spear, N. P., eds. Information processing in animals: Conditioned Inhibition. Hillsdale, NJ: Erlbaum; 1985:51-88.
23. Mitchell, D. S. Trial distribution effects on postasymptotic performance and retention of the rabbit's (*Oryctolagus cuniculus*) classically conditioned nictitating membrane response. J. Comp. Physiol. Psychol. 83:346-350; 1973.
24. Patrick, G. A.; Dewey, W. L.; Hughes, F. P.; Daves, E. D.; Harris, L. S. Disposition of morphine in chronically infused rats: Relationship to antinociception and tolerance. J. Pharmacol. Exp. Ther. 205:556-562; 1978.
25. Poulos, C. X.; Cappell, H. Homeostatic theory of drug tolerance: A general model of general adaptation. Psychol. Rev. 98:390-408; 1991.
26. Rescorla, R. A. Probability of shock in the presence and absence of CS in fear conditioning. J. Exp. Psychol. 66:1-5; 1968.
27. Rescorla, R. A.; Wagner, A. R. A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In: Black, A. H.; Prokassy, W. F., eds. Classical conditioning II: Current research and theory. New York: Appleton-Century-Crofts; 1972.
28. Sanderson, L. A.; Tiffany, S. T. Associative and nonassociative tolerance: The effects of dose iterdose interval. (submitted).
29. Schindler, C. W.; Gormezano, I.; Harvey, J. A. Effect of morphine on acquisition of the classically conditioned nictitating membrane response of the rabbit. J. Pharmacol. Exp. Ther. 227: 639-643; 1983.
30. Siegel, S. Morphine tolerance acquisition as an associative process. J. Exp. Psychol. Anim. Behav. Process. 3:1-13; 1977.
31. Tabakoff, B.; Melchior, C. L.; Hoffman, P. L. Commentary on ethanol tolerance. Alcohol Clin. Exp. Res. 6:252-259; 1982.
32. Tiffany, S. T.; Baker, T. B. Morphine tolerance in rats: Congruence with Pavlovian paradigm. J. Comp. Physiol. Psychol. 95: 747-762; 1981.
33. Tiffany, S. T.; Droves, D. J.; Cepeda-Benito, A. Contribution of associative and nonassociative processes to the development of morphine tolerance. Psychopharmacology (Berlin) 109:185-190; 1992.
34. Tiffany, S. T.; Maude-Griffin, P. M. Tolerance to morphine in the rat: Associative and nonassociative effects. Behav. Neurosci. 102:534-543; 1988.
35. Tiffany, S. T.; Maude-Griffin, P. M.; Drobes, D. The effect of dose interval on the development of associative tolerance to morphine in the rat: A dose response analysis. Behav. Neurosci. 102:534-543; 1991.
36. Wagner, A. R. Expectancies and the priming of STM. In: Hulse, S. H.; Fowler, H.; Honig, K. W., eds. Cognitive processes in animal behavior. Hillsdale, NJ: Erlbaum; 1978.
37. Young, A. M.; Goudie, A. J. Adaptive processes regulating tolerance effects of drugs. In: Bloom, F. E.; Kupfer, D. J., eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press 1995:657-811.
38. Young, G. A.; Khazan, N. Comparison of abstinence syndromes following chronic administration of mu and kappa opiod agonists in the rat. Pharmachol. Biochem. Behav. 23:457-460; 1985.