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Route of Morphine Administration Modulates Conditioned Analgesic Tolerance and Hyperalgesia

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GRISEL, J. E., E. P. WIERTELAK, L. R. WATKINS AND S. F. MAIER. *Route of morphine administration modulates conditioned analgesic tolerance and hyperalgesia.* PHARMACOL BIOCHEM BEHAV **49**(4) 1029–1035, 1994. – The present experiments investigated the effects of route of drug injection on two of the phenomena associated with repeated, cued, morphine administration. Experiment 1 examined the degree of situational specificity of analgesic tolerance following 5 days of morphine (5 mg/kg) delivered either subcutaneously (SC) or intravenously (IV). Situationally specific tolerance was only observed following IV morphine, although nonspecific tolerance was evident in both instances. Experiment 2 indicated that this difference was not due to dose, as neither 2.5 or 7.5 mg/kg SC morphine produced demonstrable situationally specific tolerance. Experiment 3 examined the putative existence of compensatory responses underlying the observed tolerance. Hyperalgesia in response to the environment in which morphine was experienced was evident in animals trained with IV morphine, but not in those receiving repeated SC injections. Potential explanations for these effects of route of administration are discussed.

Morphine Tolerance Associative tolerance Intravenous Subcutaneous Compensatory response Analgesia Hyperalgesia

TWO classes of processes have been argued to be responsible for the development of tolerance to opiates and other drugs. One class, which is nonassociative in nature, involves either dispositional or pharmacodynamic factors and emphasizes direct cellular adaptations to repeated drug exposure. Regulation at the level of the receptor, altered coupling of receptors to second-messenger systems or other noncompetitive changes in the transduction process between receptor occupation, and response consequent to stimulation are examples of how this might occur [see (5,14,26) for reviews]. The second class, often labeled conditioned tolerance is associative, and emphasizes the role of whole organism adaptations and conditioning/learning in response to repeated drug stimulation. According to these views, tolerance results from repeated cued administration of a drug, presumably as the subject forms an association between environmental stimuli and the internal reactions to the drug. A number of different arguments have been made as to how such pairings between a drug and environmental cues might lead to associative tolerance (3,12, 20,29). For example, habituation processes (3,7) and the development of conditioned compensatory reactions that oppose the responses to the drug (17,20,22,24) have been proposed to be critical mediating mechanisms.

In practice, the distinction between nonassociative and associative tolerance often rests on the degree to which the expression of tolerance to a drug is situation specific. Situationally specific tolerance is tolerance that depends on the presence of environmental cues that had been present during the repeated drug exposures. The experimental paradigm that is used most often involves administering the drug in one environment, the vehicle, or other control procedure in a different environment, and then testing the drug effects in both environments. Differences in drug effects between the two cue conditions are said to reflect conditioned or associative tolerance [e.g., 20,29)]. A difference in reactivity to the drug between the group that has repeatedly received the drug but is

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tested in the nondrug environment and a drug-naive group would likely reflect nonassociative tolerance, although other explanations are possible.

Although both forms of tolerance operationally defined as above can be demonstrated, the factors that determine the relative ease of expression of each remain poorly understood. Factors such as drug dose and interdrug interval have been explored (6,15,28). Route of drug administration is an obvious variable of potential importance but has not been systematically studied. In the morphine tolerance literature the vast majority of experiments have involved subcutaneous (SC) and intraperitoneal (IP) injection of morphine. These routes of drug administration produce relatively slow and gradual onset of drug action (11) because the drug must be absorbed before it can be transported to central nervous system sites of action. However, if situationally specific tolerance involves a conditioning process, this slow onset would be expected to interfere with its development. In the case of situationally specific tolerance, the environmental cues (CSs) would be predicted to promote the highest degree of tolerance when there is little delay between their presentation, and the onset of the drug effect (UCS). Thus, the use of a route of administration that produces a more rapid and less gradual onset of drug action such as intravenous (IV) might be expected to facilitate the development of situationally specific tolerance. The following experiments tested this hypothesis by comparing the effectiveness of IV and SC morphine in producing situationally specific tolerance. Because SC and IP morphine do lead to situationally specific tolerance, observation of any potential enhancement required a procedure that yields only modest situational specificity. Thus, the present experiments employed procedures designed to produce only minimal situational specificity after SC injection.

EXPERIMENT 1

Morphine injections were delivered either intravenously (IV) through indwelling jugular catheters or subcutaneously (SC) to evaluate the likelihood of observing associative tolerance. Additional animals received identical handling, and either IV or SC injections, but remained morphine naive until testing. This group allowed assessment of both associative and nonassociative tolerance.

Method

Subjects. Thirty-eight male adult albino Sprague–Dawley Holtzman rats, ranging from 350 to 500 g, were maintained three to a cage in Plexiglas bins with free access to food and water. The colony room was kept on 12 L : 12 D in which the lights were switched on at 0700 and temperature was maintained at 22–23°C. The rats were acclimated to the colony room for at least 10 days prior to handling and 13 days prior to experimental manipulation. Handling consisted of habituating animals to being held, weighed, and injected with vehicle by either SC or IV routes. Three to four days before the conditioning phase of the experiment animals were transferred to individual Plexiglas bins (44 × 21 × 22 cm) where they were maintained as above throughout the experiment.

Jugular catheters. Each catheter was constructed from 10 cm of silastic tubing containing a 1 cm tube made from a 22 gauge needle and inserted 1 cm from the proximal end of the Silastic tube. The catheters were sterilized and then flushed with sterile 2% heparanized saline prior to surgery.

Surgeries were performed 3–4 days before the 5-day conditioning period. Nembutal sodium solution (50 mg/ml) was administered as a general anesthetic (at a dose of approximately 60 mg/kg). Metofane (Pitman-Moore Inc.) supplements were administered as necessary throughout surgery. Following implantation of the catheter in the external jugular vein, the distal end was exteriorized and sealed with a metal plug. The catheters were flushed with heparinized saline once daily to maintain catheter patency.

Drug administration. Morphine was delivered at a dosage of 5.0 mg/kg. Subcutaneous injections were in a volume of 1.0 ml/kg and given with 26 g 1/2″ needles on the dorsal surface of the neck. Intravenous injections were administered through a syringe married to PE-90 tubing that was fitted to a 20 g needle and calibrated to deliver morphine into the animal's catheters in a volume of 0.125 ml/kg. All IV drug injections were followed by a heparanized saline flush of 0.05 ml. Vehicle injections consisted of equivolume saline for those animals in the SC condition and 0.07 ml of the heparanized saline flush (see above) for those receiving IV injections.

Conditioning procedure. All subjects received two injections a day for 5 consecutive days, once at 0900 and once at 1400 h. All subjects were placed in Plexiglas restraining tubes (24 × 7 cm) for 60–90 min following each injection. The two injections were given in different rooms. One was brightly illuminated while the other was only dimly illuminated. There were also two types of restrainers. One was at a 20° angle to the horizontal, had a flat, corrugated cardboard bottom insert, and approximately 50 μl of vinegar applied to the anterior end of the cardboard. The other restrainer condition was horizontal, with no cardboard floor or added odor. Each animal was exposed to one tube following the first injection, and the other tube following the second with room and restraint condition consistently paired for each subject, and counterbalanced between subjects. Testing for tolerance was always conducted in the dimly lit room condition with the restrainer arrangement that the animal had experienced in that room, and so this was called the test environment (TE). The brightly lit room condition was labeled the alternative environment (AE). Rats were purposely kept in restrainers in both stimulus conditions to retard discrimination and allow for potential facilitation of conditioning. In addition, tail-flick testing is problematic in unrestrained animals. Tail flick was preferred to other potential measures such as hotplate because the measure is stable over repeated testing. Repeated testing allows for determination of the timecourse of morphine analgesia, a more sensitive measure of tolerance than single timepoint assessment.

Animals were divided into six groups. All group designations were based on the injection administered in the TE. One group (NAIVE-SC) did not receive morphine during conditioning, but was given SC saline injections in a volume of 1 ml/kg twice a day: once in TE and once in AE. Another group was given equivolume AE morphine injections once a day, and TE saline injections (SAL-SC), and a third group received morphine in the TE, and saline in the AE (MOR-SC). The remaining three groups received identical manipulations except that injections of morphine and vehicle (saline with 2% heparin) were IV (NAIVE-IV, SAL-IV, MOR-IV). After conditioning, the animals were put back into their home cages.

Analgesia testing. Testing occurred in the TE on the seventh day. No manipulation was done on day 6 to insure the absence of any residual morphine effects during testing. Rats that were normally exposed to the TE in the morning (half of the animals in all six groups) were taken at their usual time, and put into their usual tubes (20° or horizontal), but on this day all were given morphine and assessed for pain sensitivity

using a modification (2) of the tail-flick test to radiant heat (8). The heat was applied to the subject's tail, which extended from the rear of the Plexiglas restrainer. Voltage to the bulb was adjusted to provide baseline latencies to radiant heat of 2–4 s in naive animals. If no flick occurred by cutoff (10 or 12 s, depending on experiment), the trial was automatically terminated to avoid tissue damage. All baseline measures were taken immediately after placement in the tubes and were the mean of three consecutive trials at 15 s intervals in which a 1 cm diameter heat beam was sequentially focused at approximately 11, 8, and 5 cm from the proximal end of the tail. Subsequent determinations consisted of a single trial at 15, 30, 45, 60, 75, and 90 min following morphine injection. The same procedure was done for the other half of the rats in the afternoon, when they, in turn, would be normally exposed to the TE. Thus, all rats were injected with morphine and tested for pain sensitivity on day 7, but one-third of the rats were tested in a context that had been associated with morphine administration, one-third were tested in a context that was specifically not paired with morphine, but rather with saline, and the last third were drug naive.

Data analyses. Factorial analyses of variance were used to assess baseline pain sensitivity. Repeated measure analysis of variance was employed to examine postdrug tail-flick latencies, and the Newman-Keuls method was utilized to further examine specific group differences. Alpha was set at 0.05.

Results and Discussion

Subcutaneous injections of morphine failed to result in situation-specific tolerance using these parameters of dose and administration. Data for tail-flick testing in SC animals are summarized in Fig. 1. There were no differences in baseline measures between groups, $F(2, 17) = 1.776$, $p > 0.10$. Repeated measure analysis of the postmorphine tail-flick latencies demonstrated a significant main effect of group, $F(2, 15) = 6.54$, $p < 0.01$. The effect of time of testing was also significant, $F(5, 75) = 4.736$, $p < 0.001$. There was not a significant interaction between group and tail-flick measure, $F(10, 75) = 1.229$, $p > 0.05$.

Newman-Keuls multiple comparisons indicated that both drug groups were different from the naive group ($p < 0.05$), but not different from each other, indicating nonassociative but not associative tolerance to morphine following SC injections.

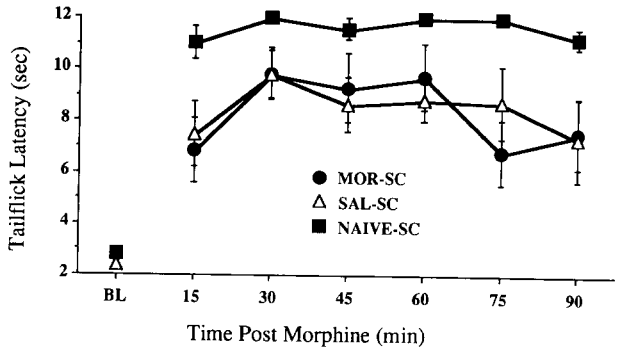

FIG. 1. Time course of tail-flick latencies following administration of 5 mg/kg SC morphine on day 7 after 5 days of morphine exposure. Animals were either drug naive (NAIVE-SC) or conditioned to receive morphine (MOR-SC), or saline (SAL-SC) in the TE (test environment).

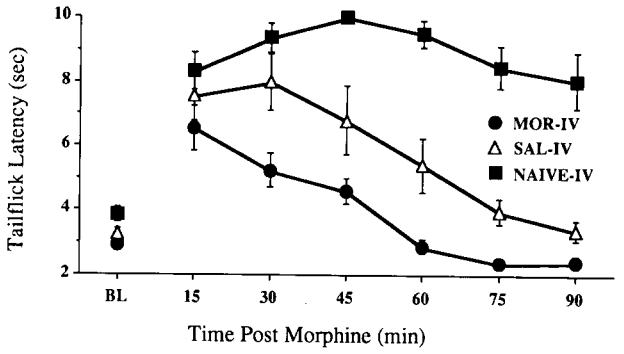

FIG. 2. Time course of tail-flick latencies following administration of 5 mg/kg IV morphine on day 7 after 5 days of morphine exposure. Animals were either drug naive (NAIVE-IV) or conditioned to receive morphine (MOR-IV) or saline (SAL-IV) in the TE.

Repeated IV injections of morphine did result in situation-specific tolerance. Data from tail-flick testing are summarized in Fig. 2. Two of the animals were excluded from the experiment due to the development of clogs in their catheters, which resulted in seven animals tested in the context that was associated with morphine, (MOR-IV), seven drug-experienced animals tested in an environment which, for them, was associated with saline (SAL-IV), and six drug-naive (NAIVE-IV), but otherwise identically handled, rats. Examination of postmorphine tail-flick latencies showed a significant effect of both group, $F(2, 17) = 31.094$, $p < 0.001$, and measure, $F(5, 85) = 26.042$, $p < 0.001$. The interaction was also significant, $F(10, 85) = 4.882$, $p < 0.001$.

Newman-Keuls analysis of predrug tail-flick latencies determined that the NAIVE-IV baseline tail-flick measures were different from both the SAL-IV group and the MOR-IV group ($p < 0.05$), which did not differ from each other ($p > 0.05$). Further comparisons confirmed that all groups differed from each other following morphine injection, indicating both associative (NAIVE-IV vs. SAL-IV, $p < 0.01$) and nonassociative tolerance (MOR-IV vs. SAL-IV, $p < 0.01$).

Analgesia observed in animals repeatedly exposed to SC morphine in the context in which they were later tested under morphine (MOR-SC) was not different from that of rats equally exposed to the test context in association with saline injections (SAL-SC). Each of these groups were different from NAIVE-SC rats. Because MOR-SC rats were not different from SAL-SC animals, it can be concluded that situationally specific tolerance did not occur, perhaps due to submaximal conditioning parameters. However, the fact that both of these groups were less analgesic than similarly handled, but drug-naive rats does indicate the presence of nonsituationally specific tolerance as a result of the repeated drug administration.

When animals were given IV injections, there was still a distinct nonassociative tolerance evidenced by the differences between NAIVE-IV and SAL-IV groups. In this study, however, situation specific associative tolerance did occur because MOR-IV rats were less analgesic on the test day than were SAL-IV animals.

EXPERIMENT 2 AND 2A

In Experiment 1, the same amount of morphine was administered SC and IV. The rationale was that morphine effects

would be expected to have very different rates of onset with the two different routes of administration. However, the same amount of morphine delivered in these two ways might have many other differences and so constitute nonequivalent dosages. Thus, it might be that some other dose of SC morphine would have yielded evidence for cue-specific tolerance. Experiment 2 examined both a lower and a higher SC dose of morphine using identical procedures as above. Moreover, Experiment 1 did not contain a demonstration that SC morphine produces slower and more gradual analgesic effects than does IV morphine with the present doses. This was because the first tail-flick measurement was taken 15 min after morphine administration. Experiment 2A provided a more detailed timecourse of 5 mg/kg SC and IV morphine action.

Method

Subjects and procedure. Thirty-two male Sprague–Dawley rats, weighing between 330–400 g and housed and handled as in Experiment 1, were divided into four groups. Two of these received morphine in the TE (either 7.5 or 2.5 mg/kg delivered SC in a volume of 1 ml/kg) and equivolume saline in the AE, once a day for 5 consecutive days. The other two groups were injected with either dose of morphine in the AE, and received saline in the TE. Again, groups were counterbalanced for injections by both time of day and specific environment (horizontal and 20° tubes). No manipulation was done on day 6. On day 7, animals were all injected with their usual dose of morphine in the TE at the time they normally experienced the TE. Analgesia testing was carried out as in Experiment 1.

Experiment 2A employed 12 rats of the same characteristics as above, of which half were implanted with IV jugular catheters as in Experiment 1. All animals were injected with 5 mg/kg morphine either IV or SC. Tail-flick latencies were determined 2, 4, 6, 8, 10, 15, 30, 45, 60, and 90 min after injection.

Results and Discussion

No evidence of associative tolerance was found following 5 days of conditioning with either 7.5 or 2.5 mg/kg morphine. Data are presented in Fig. 3. Factorial analysis of variance revealed no baseline differences between the groups, $F(3, 28) = 0.376, p > 0.10$. Repeated measure analysis of the remaining tail-flick measures indicated group differences, $F(3, 28) = 10.38, p < 0.001$, and differences in tail-flick measure, $F(5, 140) = 34.082, p > 0.001$, but the interaction was not significant, $F(15, 140) = 1.364, p > 0.05$. Newman-Keuls comparisons indicated reliable differences in tail-flick latency between the two groups receiving morphine in their usual morphine environment (MOR-SC 2.5 vs. MOR-SC 7.5; $p < 0.01$), between the two groups that normally received saline in the test context (SAL-SC 2.5 vs. SAL-SC 7.5; $p < 0.01$), but not between either MOR-SC 2.5 vs. SAL-SC 2.5 or MOR-SC 7.5 vs. SAL-SC 7.5 ($p > 0.05$).

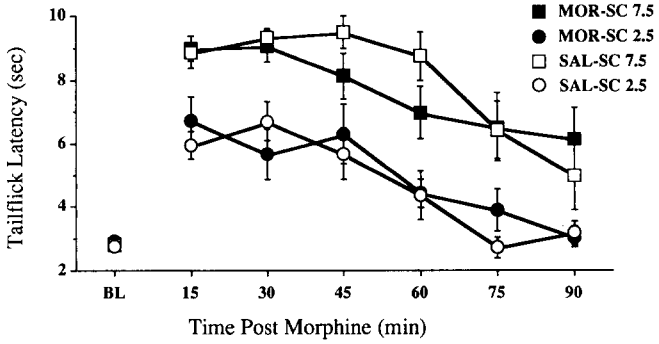

FIG. 3. Time course of tail-flick latencies in TE following administration of 2.5 or 7.5 mg/kg SC morphine on day 7, after 5 days of morphine injections given either in the TE (MOR-SC 2.5 or MOR-SC 7.5) or in the AE (SAL-SC 2.5 or SAL-SC 7.5).

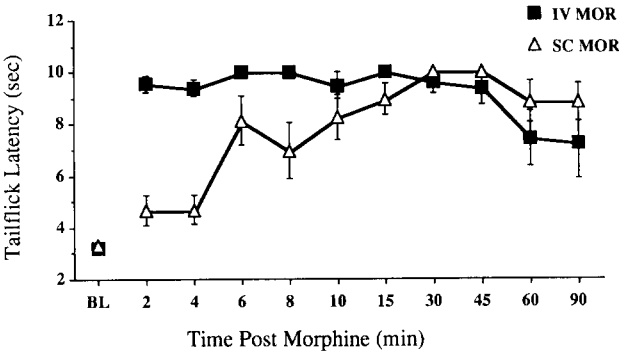

FIG. 4. Time course of morphine's acute action on tail-flick latencies following 5 mg/kg of either sc or IV morphine.

The time course of morphine action following SC and IV morphine is shown in Fig. 4. Although there was no main effect of group, $F(1, 9) = 4.479, p > 0.05$, there was an effect of time of testing, $F(9, 81) = 8.11, p < 0.001$, and an interaction between group and time of testing, $F(9, 81) = 9.788, p < 0.001$. Examination of simple effects showed that groups were significantly different ($p < 0.05$) at 2, 4, 6, and 8 min after injection.

Neither 2.5 mg/kg nor 7.5 mg/kg morphine yielded evidence of situationally specific tolerance when administered SC, supporting the results of Experiment 1. In addition, the analgesic effects of SC morphine increased much more gradually than did that of IV morphine under the conditions used in the present experiments. IV morphine produced maximal analgesia at the first measurement point, 2 min after injection. However, following SC morphine, the amount of analgesia produced increased gradually for 15–30 min, reaching the same maximal level as IV morphine at that time. A potential difficulty is that the tail-flick latencies after IV morphine were at or near the cutoff score. Thus, a ceiling effect could have obscured a continued gradual rise after IV administration. However, it is clear that onset is much faster with the IV route. There was no change from baseline until 6 min after SC morphine, while IV animals were already at ceiling at the first test point, 2 min after drug administration. These data thus support the contention that decreasing the delay between the presentation of the environmental stimuli signalling morphine and the onset of morphine's effects enhances learning, resulting in more tolerance. The gradualness of onset is open to interpretation.

EXPERIMENT 3

Siegel (23) has argued that associative tolerance occurs because the environmental cues present during morphine exposure come to elicit a response in the opposite direction from that produced by morphine. This conditioned compensatory response would then summate with the normal drug effect if

the organism is tested in the drug environment, thereby yielding a reduced overt response or tolerance. There is considerable controversy concerning whether such compensatory responses can be readily observed (3,12), even under conditions in which situationally specific tolerance can be demonstrated (10). Experiment 3 examined whether IV morphine would yield such a compensatory response (hyperalgesia) if animals were given saline rather than morphine on the test day. Subcutaneous administration was also studied to determine whether any compensatory responding would be specific to the IV route.

Method

Subjects and procedure. Twenty-seven adult male albino Sprague-Dawley Holtzman rats, ranging from 330 to 570 g, were housed and handled as those of Experiments 1 and 2. The conditioning schedule, environment, and procedures (including jugular catheter surgery) were identical to that of Experiment 1. Fourteen of the animals were implanted with jugular catheters 3-4 days before conditioning. In this study there were no naive animals so there were four groups (MOR-SC, SAL-SC, MOR-IV, and SAL-IV). All subjects received saline on the test day. Tail-flick analgesia testing remained the same as Experiment 1, with the exception that the level of radiant heat was adjusted to increase baseline latencies (5-7 s) to maximize the likelihood of observing any hyperalgesia that might occur.

Results and Discussion

Tail-flick latencies taken in TE after saline injection are shown in Fig. 5. Tail-flick latencies taken immediately after placement in the tubes (BL) differed among the groups: $F(3, 23) = 26.39$, $p < 0.001$. Newman-Keuls analysis indicated that all groups were significantly different at the 0.05 level except for the two saline groups, which did not differ from each other.

In contrast, tail-flick latencies for the MOR-IV group decreased and remained below those for the other three groups across the 90 min of testing. Repeated measure analysis determined that there were differences between the groups, $F(3, 23) = 5.468$, $p < 0.01$, and differences between tail-flick measures, $F(5, 115) = 5.428$, $p < 0.001$, but no significant interaction, $F(15, 115) = 0.934$, $p > 0.05$. Newman-Keuls analysis determined that MOR-IV animals were hyperalgesic relative to all other groups (MOR-SC, SAL-SC, and SAL-IV) at the 0.05 level, but that none of these differed significantly from each other.

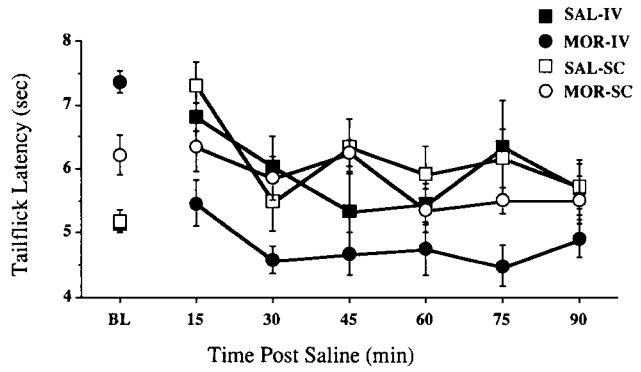

FIG. 5. Time course of tail-flick latencies in animals given either IV or SC injections of saline in the TE on day 7, after 5 days of morphine injections either in the TE (MOR-IV or MOR-SC) or in the AE (SAL-IV or SAL-SC).

The reason(s) for the baseline differences is not clear. In this experiment we decreased the bulb intensity on the tail-flick apparatus to produce baseline flicks of approximately 6 s to increase the likelihood of observing any hyperalgesia in these animals. Baseline tail-flicks were approximately 3 s in the other experiments and may have not allowed for observation of group differences as readily.

GENERAL DISCUSSION

The purpose of the present studies was to explore the effect of the route of morphine injection on the potency of situationally specific tolerance observed. Rats repeatedly received morphine in one context defined by the room, restrainer angle, restrainer flooring, odor, and time of day, and saline in a context involving a different room, restrainer, restrainer flooring, odor, and time of day. The rats were then all tested for the analgesic potency of morphine in the same environment, which was the morphine-paired environment for some of the rats and the saline-paired environment for others. Both SC and IV morphine administration led to the development of tolerance, as indicated by reduced analgesic potency in animals that had repeatedly experienced morphine as compared to controls that had never before experienced morphine. However, the stimulus conditions present during testing affected morphine responsivity only in animals that had received morphine IV. Here, rats for whom the test environment had previously been paired with morphine were less analgesic than were rats for whom the test environment had accompanied saline. In contrast, morphine reactivity following SC administration was unaffected by stimulus conditions. Furthermore, the inability of SC morphine under the present conditions to produce observable associative tolerance was not a function of morphine dose. Neither 2.5, 5.0, nor 7.5 mg/kg morphine produced associative tolerance when morphine was given SC.

The kinetics of morphine analgesic action after SC and IV injection differ in a number of ways that might account for the facilitation of environmental control of tolerance by the IV route. Morphine action after SC delivery was slow in onset and probably gradual in development relative to that observed after IV administration. IV administration resulted in maximum observable analgesia by 2 min after drug injection, while animals administered morphine SC did not reach a comparable level of analgesia for at least 15 min. Both of these temporal factors would be expected to interfere with the development of environmental context-morphine conditioning. The slow onset after SC administration of necessity results in a long temporal interval between initial exposure to the cues associated with morphine and the morphine drug state. That is, the conditioned stimulus (CS) unconditioned stimulus (UCS) interval is much longer with SC than IV morphine, assuming that the UCS is considered to be the drug effect(s) rather than the injection itself. The expectation from this factor would be weaker conditioning after SC than after IV morphine. In addition, the gradual nature of the increase in morphine action after SC delivery would permit early or weak portions of the drug state to become a cue for the later more potent state or action, thereby competing with the external cues for the acquisition of associative strength. IV injection is likely to minimize the competition from internal cues and maximize the likelihood of utilizing salient external stimuli

associated with drug effects. Thus, the contribution of IV administration toward the production of stimulus context modulation of tolerance is readily explicable if classical conditioning is, indeed, the mechanism responsible for situationally specific tolerance.

It should be carefully noted that situational modulation of morphine tolerance has been reported after SC delivery (1,6,7,20-22,25,27,30). Thus, the argument is not that IV administration is necessary to observe this phenomenon. The use of different cue conditions, number of pairings, intermorphine interval, etc., might well have produced situational control. Our intent was to choose parameters that would mitigate against strong situational control so that it could be determined whether route of administration modulates the relative amount of situational and nonsituational tolerance. The conclusion drawn is simply that use of the IV route enhances the proportion of tolerance that is situationally specific. In the present experiments, the cues, number of pairings, intermorphine interval, etc., were held constant, and route of injection was shown to be a potent variable. These conditions were evidently subthreshold for associative learning to be observed in animals administered morphine SC. Thus investigators interested in studying situationally specific tolerance might consider possible benefits resulting from IV morphine delivery. It is also the case that opiate use by humans most often involves IV administration.

The occurrence of a hyperalgesic reaction in the morphine environment that was observed when morphine was not given also deserves comment. There has been considerable debate as to whether contextual control of tolerance is or is not produced because the drug context comes to elicit a compensatory reaction that then summates with the usual effects of the drug (3,10,28). Part of the controversy has revolved around whether compensatory responses in reaction to drug-related cues indeed even occur (4,12,13,16,18). Furthermore, alternative explanations have been offered for reported demonstrations of hyperalgesia and hyperthermia after repeated morphine (3,9,19). Prior experiments that have reported hyperalgesia or hyperthermia in reaction to morphine-related cues have involved repeated hot plate exposure or rectal probe use, and the stressfulness of these procedures has been argued to have been critical and to have produced results that only appear to be compensatory reactions. This sort of argument cannot be made here. Rats that had experienced IV morphine in the TE context did become hyperalgesic relative to controls when placed in the TE environment without morphine. This facilitation of tail flick to radiant heat is all the more impressive when it is recognized that these rats responded to the TE context with an initial increase in tail-flick latency. It would be difficult to explain this apparent compensatory response as being the result of some general feature of the procedure such as restraint, tail-flick testing, etc., because it only occurred following IV administration. The fact that contextual control and compensatory responding covaried by occurring under the same set of conditions (IV administration) and failed to occur under the same conditions (SC administration) lends some support to theories that point to compensatory responses as the basis of contextual control of tolerance.

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