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Pre-exposure to Morphine and the Attenuation of Conditioned Taste Aversion in Rats[1]

JANE STEWART[2] AND ROELOF EIKELBOOM

Department of Psychology, Concordia University, Montreal, Canada

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STEWART, J. AND R. EIKELBOOM. *Pre-exposure to morphine and the attenuation of conditioned taste aversion in rats.* PHARMAC. BIOCHEM. BEHAV. 9(5) 639–645, 1978.—Three experiments were done using male Wistar rats to determine whether the mechanisms underlying the attenuation of a conditioned taste aversion to morphine by pre-exposure to the drug were similar to those involved in the development of tolerance to the analgesic response to morphine. This was tested by determining whether the effect of pre-exposure on conditioned taste aversion was situation-specific. In Experiment 1 it was found that having different environments for the pre-exposure injections and for the conditioning injections of morphine had no effect on the attenuation of the taste aversion. This finding was replicated in Experiment 2 in which it was also found that the attenuation of the analgesic effect, tested for in the same animals, was specific to the environment in which repeated injections were given. It was concluded that the attenuation of conditioned taste aversion involved processes different from those responsible for the attenuation of the analgesic effect of morphine. Experiment 3 showed that pairing the pre-exposure injections of morphine with one distinctive taste stimulus prevented the attenuation of the conditioned taste aversion to a second taste stimulus. These results suggest that different associative processes are responsible for the two types of attenuation.

Conditioned taste aversion Analgesia Morphine Tolerance

SEVERAL pharmacological agents, including those that animals self-administer, can be used as unconditioned stimuli for the establishment of conditioned taste aversions. Of particular interest is the fact that avoidance of flavored liquids has been observed following their pairing with ethanol [3,8], amphetamine [2, 7, 20] and morphine [11, 14, 16]. Pre-exposure to these drugs prior to their pairing with the flavored liquid, however, weakens or eliminates the development of the aversion [3, 9, 12, 13, 20]. Several explanations of the pre-exposure effects have been suggested. Amit and Baum [1] proposed that pre-exposure reduces the novelty of the drug experience and thereby makes it less effective as an unconditioned stimulus. Similarly, Vogel and Nathan [26] suggest that habituation occurs to drug related stimuli through pre-exposure. Cappell *et al.* [9] have suggested that, through some unspecified tolerance mechanism, the drug loses its effectiveness as an unconditioned stimulus. Others have invoked an explanation in terms of prior conditioning to situational elements in the pre-exposure period (see [5]).

The finding that "unpaired" pre-exposure to the unconditioned stimulus slows the emergence of conditioned response is not new [19,23]. Explanations in terms of reduced salience of the unconditioned stimulus or of habiutation of responses to the unconditioned stimulus have been common. It has been pointed out, however, that the paradigms used in most pre-exposure experiments are the same as those in which "blocking" [15,21] develops in experiments on compound conditioning [6]. One can postulate that during pre-exposure, an association between the test environment and the unconditioned stimulus is learned by the animal [4,20]. According to blocking principles, this prior conditioning should interfere with the subsequent learning, in the same environment, of an association between a newly introduced element and the original unconditioned stimulus. It follows from this argument that the effects of pre-exposure should be situation-specific, in that pre-exposure in one environment should not interfere with conditioning in a different environment.

Although the theoretical basis for the prediction is quite different, a similar prediction about situation-specificity of repeated exposure to morphine arises out of Siegel's work (see [24,25]). In a series of experiments aimed at elucidating the basis of the development of tolerance to the analgesic effects of morphine, he has shown that if rats receive repeated injections of morphine in one situation and are then tested in a second situation, no tolerance is evident in the second situation. If, however, the pre-test injections and the analgesia test injections are given in the same situation, the expected tolerance to the analgesic effect is observed.

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[2]Requests for reprints should be sent to : Jane Stewart, Department of Psychology, Concordia University, 1455 de Maisonneuve Blvd., Montreal, Québec, Canada, H3G 1M8.

Siegel's explanation for this situation-specific effect is that the attenuation of the analgesic action of morphine results from the conditioning of anticipatory, compensatory, or opponent, responses to the situation cues associated with the repeated injections. When the situational cues are not present, no such responses are elicited, and, as a result, the morphine exerts its original pharmacological effect.

The purpose of the series of experiments reported here was to determine whether the mechanisms that have been called upon to account for the development of tolerance to the analgesic properties of morphine might also account for the attenuating effects of pre-exposure on conditioned taste aversion. As a first step it was necessary to determine whether the conditioned taste aversion based on morphine was in fact situation-specific. In Experiment 1 this was tested directly by varying the pre-exposure environment. In Experiment 2, the attenuation of a conditioned taste aversion was compared to the attenuation of analgesia in the same animals. Finally, in Experiment 3, an attempt was made to block the pre-exposure attenuation effect by pairing the pre-exposure injections of morphine with a distinctive taste stimulus.

EXPERIMENT 1

METHOD

Treatment of Animals

Thirty male Wistar rats (Canadian Breeding Farm and Laboratories) weighing between 175–200 g were used in this experiment. The animals were individually housed and maintained on a 14 hr light/10 hr dark cycle. After the first few days in the laboratory the animals were placed on a water-deprivation schedule consisting of access to water for 15 min per day at 3:00 p.m.; this schedule remained in effect throughout the experiment. All liquids were presented in graduated drinking tubes with stainless steel spouts. Food was available at all times in the home-cage. The first treatment session (Day 1) began after 7 days on the restricted water schedule. In order that animals should be drug-free at the time of injection and at the time of testing, treatments were given on alternate days beginning at 9:00 a.m.

Procedure

Pre-exposure treatment. The animals were assigned to 3 groups of 10 animals each; a "home-cage-morphine" group, a "distinctive-environment-morphine" group, and a "home-cage-saline" group. The former two groups received intraperitoneal injections of 10 mg/kg morphine sulphate in a 20 mg/ml Ringer solution, while the latter received equivalent-volume injections of physiological saline.

Animals from the home-cage-morphine and the home-cage-saline groups were weighed in the animal room on each pre-exposure day at about 9:00 a.m. and were immediately returned to their cages. One hour later they were lifted from the cage and given the appropriate injection (morphine or saline). At 9:15 a.m. the distinct-environment-morphine animals were transported as a group to a different room for weighing. After weighing they were placed in a plastic basket that had been rubbed with oil of cloves to provide a strong distinctive odor. One hour later they were given the morphine injection. They remained together in the basket in the room until 1:00 p.m. and were then returned to their home cages. All animals received four such pre-exposure treatment, on Days 1, 3, 5 and 7; on alternate days they remained in their home cages.

Saccharin-morphine pairings. The saccharin-morphine pairings began on Day 9. One hour after the daily weighing, a 2.5% solution of saccharin in tap water was presented to all animals for 15 min in the home cage. Within 5 min of the removal of saccharin, animals in all 3 groups were lifted from their cages, given the standard morphine injection and then returned to their cages. The animals received three such saccharin-morphine pairings on Days 9, 11 and 13. On Day 15 the experiment was terminated following removal of the saccharin solution. The amount of saccharin consumed was recorded on test Days 9, 11, 13 and 15.

RESULTS

The mean amount of saccharin solution consumed on each of the 4 days of test is shown in Fig. 1. It can be seen that only the home-cage-saline group developed a conditioned taste aversion over the 3 test days. For the data analyses the scores were transformed using the square root transformation for small numbers $x' = x^{1/2} + (x+1)^{1/2}$ as suggested by Winer ([28], p. 399). All post hoc comparisons between means were made using the Scheffé test, and as recommended .10 was used as the acceptable significance level ([22], p. 71). The analysis of variance carried out on the scores for ths first day of saccharin drinking (Day 9) prior to the morphine pairing showed the apparent group differences not to be significant, $F(2,27)=2.71$, $p<0.09$. A two-way analysis of variance, groups×days, carried out on the drinking scores for the next 3 days (Days 11, 13, and 15) yielded significant effects for groups, $F(2,27)=12.59$, $p<0.001$, for days, $F(2,54)=16.38$, $p<0.001$, and for the groups×days interaction, $F(4,54)=12.97$, $p<0.001$. The latter reflects the decrease in saccharin consumption only by animals in the home-cage-saline group. A comparison made between the scores of the two morphine pre-exposed groups failed to show any significant difference between them ($F<1$), whereas the two morphine pre-exposed groups differed from the saline pre-exposed group ($p<0.05$).

DISCUSSION

In this first experiment pre-exposure to morphine in both the home-cage group and the distinct-environment group attenuated the development of a conditioned taste aversion to morphine. Regardless of the situation under which morphine was administered, pre-exposure had the attenuating effect. There are several possible explanations of this result. The most obvious is that the effects of pre-exposure, at least as they affect a conditioned taste aversion, occur independent of the environmental situation. It is possible, however, that the distinctive environment used in this study was not different enough from the home-cage environment; the drug effects may have been paired with some salient features common to both, for example, with the injection procedure itself. Another possibility is that any differential effects that might have resulted from different pre-exposure and test environments, were masked by a limit to the amount of saccharin solution the animals could consume in the 15-min test period. A second experiment was done to test these alternative explanations.

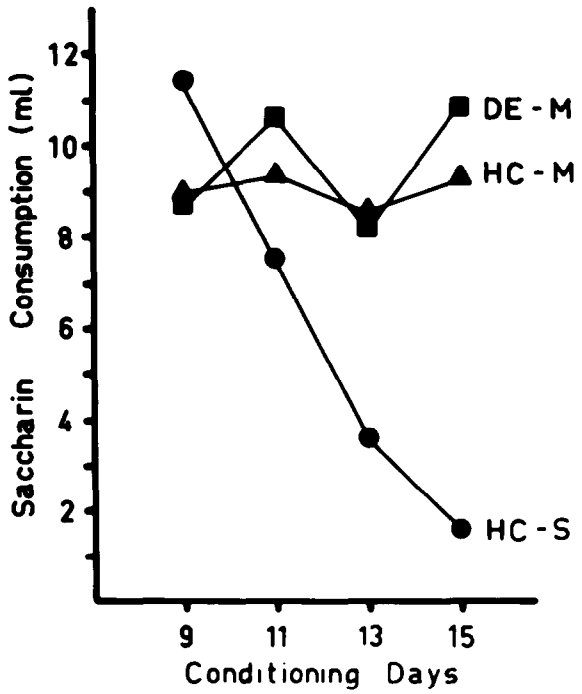

FIG. 1. Mean amount of saccharin solution consumed by the three groups studied in Experiment 1, "home-cage-saline" (HC-S), "home-cage-morphine" (HC-M), "distinct-environment-morphine" (DE-M).

EXPERIMENT 2

The tolerance that develops to the analgesic effects of morphine has been shown to be situation-specific [24,25]. Animals repeatedly exposed to morphine in one situation show no attenuation of the analgesic response to morphine when tested in a second situation. In order to determine whether the "distinctive environment" used in our experiment was distinctive enough to become differentially conditioned to some aspect of the response to morphine, we decided to test for the attenuation of the analgesic effects of morphine at the same time, in the same animals, as we tested for the attenuation of the conditioned taste aversion. All injections were given subcutaneously. No difference in the magnitude of the conditioned taste aversion was expected due to route of administration [11].

In this experiment an additional control group that received only saline injections was run through all aspects of the experiment. This group permitted us to establish whether animals were capable of drinking more of the saccharin solution in the 15 min access period than the other groups pre-exposed to morphine.

METHOD

Animals

Forty male Wistar rats weighing between 175–200 g were used in this experiment. The housing, deprivation schedule, and time schedule of treatments were the same as in Experiment 1.

Procedure

The treatment of the 5 groups of 8 animals studied in this experiment varied in terms of drug injected, injection environment, and analgesia testing. A summary of the groups and their treatments is given in Table 1. The drug consisted of either 10 mg/ml/kg morphine sulphate injected subcutaneously or an equivalent injection of physiological saline. The injection environment was either the home cage (animal room) or the distinctive environment described in Experiment 1. Analgesia testing was done 30 min after the drug injection in the animal room using the hot-plate method. The hot-plate was a thick aluminum plate which was maintained at a constant temperature, 54° ± 0.5°C by placing it on a water bath. A 20 cm diameter Plexiglas cylinder rested on the plate. A similar unheated plate, 24° ± 0.5°C served as "cold-plate" control. Paw-lick latency was measured from the time the animal was placed on the plate. The maximum time allowed on the plate was 30 sec.

Pre-exposure treatment. Groups 1 and 5 were treated identically during pre-exposure; they received saline in the home cage and were tested on the hot-plate. Group 1 served as the saline control group; the animals received only saline injections throughout the experiment. Groups 2 and 4 both received morphine in the home cage; Group 2 was tested on the hot-plate, Group 4 was placed on the cold-plate. Group 3 received morphine injections in the distinctive environment; it was not tested for analgesia during the pre-exposure period. Four pre-exposure treatments were given, on Days 1, 3, 5 and 7. In order to reduce the possibility of the development of an association between the injection procedure itself, and morphine, Group 3 was given an additional series of subcutaneous saline injections, on the day before treatment began and on the intervening days.

Saccharin-morphine pairings. Saccharin-morphine pairings began on Day 9. At 9:00 a.m. animals from all groups were weighed in the animal room; at 10:00 a.m. they were given access to the saccharin solution for 15 min in the home cage. Within 5 min of the removal of the saccharin, all animals received an injection; saline for Group 1 and morphine for the others. The animals were returned to their home cages and 30 min later were tested on the hot-plate. The same procedure were followed on Day 11; on Day 13, the experiment was terminated after the saccharin drinking.

RESULTS

Saccharin solution consumption. The mean saccharin solution consumed by the five groups on each of the test days is shown in Fig. 2. One animal had died on the first morphine day, leaving 7 animals in Group 3. As before all scores were transformed using a square root transformation. A one-way analysis of variance carried out on the scores on Day 9, prior to pairing, revealed no significant effect of pre-exposure treatment, $F(4,34)=0.34$. A group×days analysis of variance on the scores on Days 11 and 13 yielded a significant groups effect, $F(4,34)=18.92$, $p<0.001$, a significant days effect, $F(1,34)=13.40$, $p<0.001$, and a significant group×days interaction, $F(4,34)=3.91$, $p<0.02$.

Further analysis of the data to determine the source of the effects was carried out. As in Experiment 1, the home-cage-morphine animals (Group 2) and the distinct-environment morphine animals (Group 3) did not differ significantly from each other ($F<1$); neither did they differ from Group 4. These three groups, however, were significantly

TABLE 1

SUMMARY OF TREATMENTS GIVEN TO THE FIVE GROUPS OF EXPERIMENT 2

Group	Days 1, 3, 5, 7 Pre-exposure Conditions			Days 9, 11	
	Environment	Drug	Analgesia Test	Saccharin Pairings	Analgesia Test
1	Home-cage	Saline	Hot-plate	Saline	Hot-plate
2	Home-cage	Morphine	Hot-plate	Morphine	Hot-plate
3	Distinct-environment	Morphine	None	Morphine	Hot-plate
4	Home-cage	Morphine	Cold-plate	Morphine	Hot-plate
5	Home-cage	Saline	Hot-plate	Morphine	Hot-plate

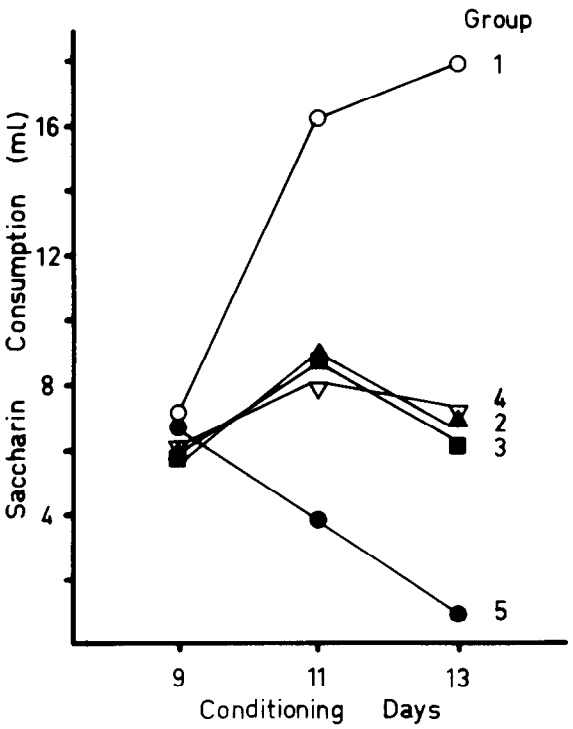

FIG. 2. Mean amount of saccharin solution consumed by the five groups of Experiment 2 in the tests for conditioned taste aversion; Group 1: "home-cage-saline-saline," Groups 2 and 4: "home-cage-morphine-morphine," Group 3: "distinct environment-morphine-morphine," Group 5: "home-cage-saline-morphine."

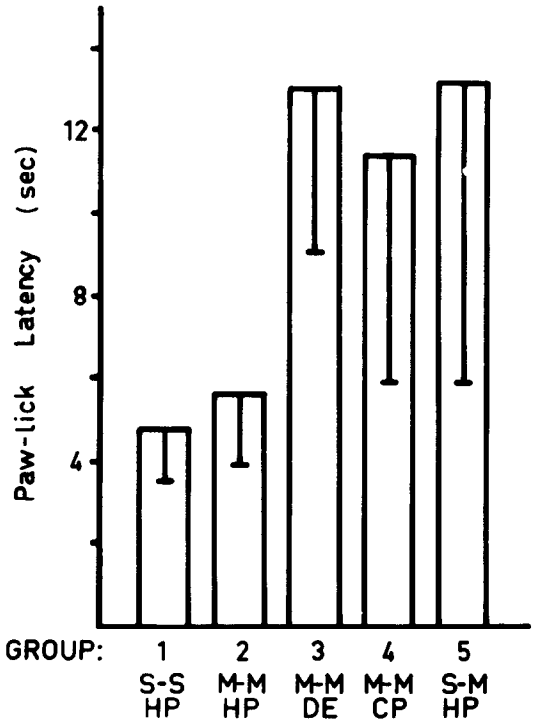

FIG. 3. Mean paw-lick latencies for the 5 groups of Experiment 2 in the tests for analgesia. Standard deviations are indicated by vertical lines. M—morphine, S—saline, HP—hot plate, CP—cold plate, DE—distinct environment.

different from the home-cage-saline group (Group 5) ($p<0.05$). As can be seen from Fig. 2, only Group 5 animals reduced consumption over days as a result of the saccharin-morphine pairings. On the other hand, animals from Group 1, that had received only saline injections throughout the experiment, consumed significantly more saccharin than did animals from Groups 2 and 3 ($p<0.05$).

Paw-lick latency. The mean paw-lick latency for Day 9, the first day when all animals were tested on the hot-plate, is shown in Fig. 3. A one-way analysis of variance yielded a significant groups effect, $F(4,34)=6.33$, $p<0.001$. Post hoc comparisons indicated that the difference between the home-cage-morphine group (Group 2) and the distinct-environment-morphine group (Group 3) was significant ($p<0.10$), whereas the difference between the home-cage-saline group (Group 5) and Group 3 was not ($F<1$). Group 3 animals had paw-lick latencies not different from those of animals receiving morphine for the first time (Group 5) in spite of the fact that they had received four injections of morphine in a different environment. Although it is not critical for the interpretation of the results of this experiment, it will be noted that animals in the "cold-plate" group (Group 4) did not show the degree of tolerance to morphine, expected on the basis of Siegel's work [25], when tested on the hot plate for the first time. Inspection of the individual scores revealed that while some animals showed clear evidence for tolerance, others appeared to be unaffected.

DISCUSSION

The second experiment confirms and extends the results of the first, showing again that the attenuation of the conditioned taste aversion to morphine was not differentially affected by the environment in which pre-exposure occurred. The lack of a difference between the group pre-exposed in the distinctive environment cannot be attributed to a limit on the amount of saccharin solution consumable in the 15-min period; the fact that the saline control groups drank more saccharin than either of the groups receiving pre-exposure to morphine would appear to rule out a ceiling effect. This latter finding, however, indicates that some aversion to morphine persisted despite the pre-exposure treatment.

The results of the tests for analgesia, on the other hand, show quite clearly, in confirmation of Siegel's finding, that no attenuation of the analgesic effect of morphine occurred in animals pre-exposed to morphine in one environment and then given tests for analgesia in another environment. Taken together, these findings, obtained from the same animals under the same set of pre-exposure conditions, strongly suggest that the mechanism that mediates the attenuation of the conditioned taste aversion to morphine by pre-exposure is different from that which mediates the development of tolerance to the analgesic effect of morphine. If both are labelled "tolerance" phenomena, then different tolerance mechanisms will be required to explain them.

EXPERIMENT 3

Other explanations of the attenuation of conditioned taste aversion through pre-exposure to the drug have in common the idea that some aversive property of the drug is diminished through pre-exposure. While some have suggested that through pre-exposure the drug experience becomes familiar (and presumably less aversive) [1], others suggest that the response to drug-related stimuli habituates [27] or that the aversive potency of the drug is lost, perhaps through a physiological tolerance mechanism [9]. These suggestions are difficult to distinguish between experimentally. In order to differentiate between them, the attenuation produced by pre-exposure would have to be modified or blocked. Recently Mikulka, Leard and Klein [18] have shown, using lithium chloride, that the pre-exposure effect can be interfered with by preceding such pre-exposure injection by a distinctive taste; that is, by actually giving conditioning trials to a taste during the pre-exposure period. If the pre-exposure effect found with morphine were due only to loss of novelty of the drug experience or to some form of physiological tolerance to the effects of morphine, then one might expect that a second conditioned taste aversion based on a new taste stimulus would not develop with morphine. In order to examine this possibility a third experiment was carried out in which the effects of "taste-paired" and "unpaired" pre-exposure conditions were compared.

METHOD

Animals

Thirty-two male Wistar rats weighing between 175–200 g were assigned to 1 of 4 groups of 8 for this experiment. Throughout the experiment all animals were given access to water for 15 min at 9:00 a.m. each day. Treatment sessions began at 7:00 p.m. All other conditions were identical to those of the first two experiments.

Procedure

As in the previous experiments, there were two phases to treatment, pre-exposure and saccharin-morphine pairings. The treatment of the four groups throughout the experiment can be summarized as follows. One was given taste-paired morphine pre-exposures followed by saccharin-morphine pairings (NaCl-mor/sac-mor); a second was given unpaired morphine pre-exposures followed by saccharin-morphine pairings (mor/sac-mor); a first control group was given taste-paired saline pre-exposures followed by saccharin-morphine pairings (NaCl-sal/sac-mor), and a second control group was given taste-morphine pre-exposures followed by saccharin-saline pairings (NaCl-mor/sac-sal).

Pre-exposure treatment. During the pre-exposure phase of the experiment, just prior to the pre-exposure injections at 7:00 p.m., animals from 3 of the 4 groups were allowed to drink a 0.9% solution of NaCl in tap water for 15 min (NaCl). The fourth group received no liquid at this time. Following the removal of the NaCl solution, all animals immediately received an IP injection of either 10 mg/kg morphine sulphate (mor) or an equivalent injection of physiological saline (sal). These pre-exposure treatments were carried out on Days 1, 3, 5 and 7.

Saccharin-morphine pairings. After the 7:00 p.m. weighing on Day 9, all animals were presented with a 2.5% saccharin solution (sac) for 15 min. Immediately following removal of the saccharin, animals were given either the morphine (mor) or the saline (sal) injection. This procedure was repeated on Day 11. On Day 13, following the removal of the saccharin, the experiment was terminated.

RESULTS

The mean amount of saccharin solution consumed by the 4 groups of animals in Experiment 3 is shown in Fig. 4. As can be seen from the figure, the two groups that had received NaCl-morphine pairings during pre-exposure (NaCl-mor/sac-mor and NaCl-mor/sac-sal), drank less saccharin upon first exposure to it (Day 9) than did the other two groups that had received either NaCl or morphine, but not both. The analysis of variance done, as before, on the transformed scores yielded a significant group effect for the saccharin drinking on Day 9, $F(3,30)=4.79$, $p<0.008$. The difference between the two taste-paired (NaCl-morphine) pre-exposed groups and the two other groups on Day 9 was significant at the 0.05 level.

The scores for Days 11 and 13 represent saccharin consumption following saccharin-morphine pairings. The groups $\times$days analysis of variance carried out on the transformed drinking scores for these two days yielded only a significant group effect, $F(3,30)=13.46$, $p<0.0001$. It can be seen from Fig. 4 that the unpaired pre-exposed group (mor/sac-mor) showed little evidence of an aversion to saccharin, whereas saccharin consumption in the taste-paired pre-exposed group (NaCl-mor/sac-mor) was suppressed. This difference was significant ($p<0.10$). No differences were found between the NaCl-mor/sac-mor group and the NaCl-sal/sac-mor group ($F<1$) or between the NaCl-mor/sac-sal group and the mor/sac-mor group ($F<1$).

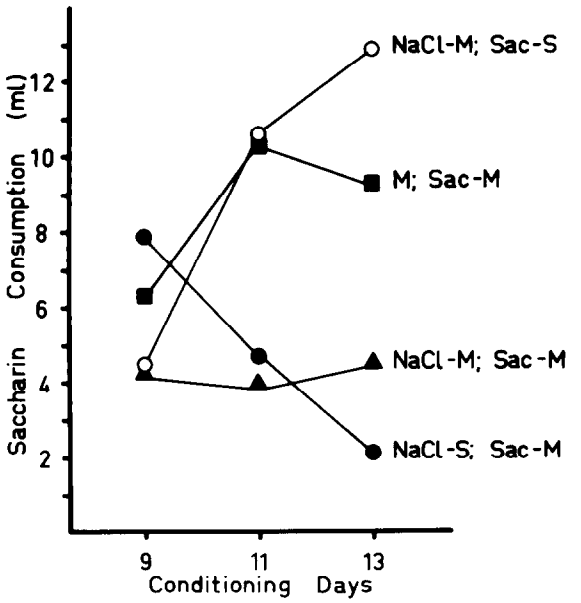

FIG. 4. Mean amount of saccharin consumed by the four groups studied in Experiment 3.

DISCUSSION

The results of this final experiment indicate that if pre-exposure to morphine is paired with a distinctive taste stimulus, subsequent conditioned taste aversion is not attenuated. Stated another way, the effect of pre-exposure to morphine on conditioned taste aversion can be blocked by prior pairing of morphine with a distinctive taste stimulus. The lesser consumption of the saccharin solution on Day 9 by the two groups that had received NaCl-morphine pairings during pre-exposure can be attributed to generalization between the two taste stimuli [10]. The fact, however, that the pairings of morphine with saccharin suppressed the subsequent saccharin drinking by the NaCl-mor/sac-mor animals, while animals in the NaCl-mor/sac-sal group showed an extraordinary resumption of drinking on Day 11, indicates that morphine had maintained its effectiveness as an aversive stimulus for the former group. This finding allows us to conclude that explanations of the pre-exposure effect in terms of reduced effectiveness of the aversive potency of the drug are not adequate in themselves. Furthermore, the fact that both the NaCl-mor/sac-mor group and the mor/sac-mor group received equal pre-exposure to morphine, and that only the mor/sac-mor showed the expected attenuation of the conditioned taste aversion would appear to require explanation in terms other than physiological tolerance.

GENERAL DISCUSSION

In this series of experiments we set out to discover whether the mechanisms that have been called upon to account for the development of tolerance to the analgesic properties of morphine [24] might also account for the attenuating effect of pre-exposure to morphine on conditioned taste aversion. This was tested first by trying to determine whether, as has been shown to be the case for analgesia tolerance, the attenuation through pre-exposure of the conditioned taste aversion was situation-specific.

In Experiment 1 it was found that, regardless of the situation in which morphine was administered, pre-exposure had an attenuating effect on conditioned taste aversion. This finding was confirmed in Experiment 2 while at the same time, the attenuation of the analgesic effect, tested for in the same animals, was shown to be specific to the environment in which repeated injections were given. Finally, in Experiment 3, it was shown that by pairing the pre-exposure injections of morphine with a distinctive taste stimulus, the attenuation due to pre-exposure could be prevented.

While we have some evidence to support Siegel's [24,25] view that the development of tolerance to the analgesic effects of morphine can be, at least in part, explained in terms of conditioned responses to the situational cues associated with morphine injections, we have no evidence that a similar mechanism can explain the effect of pre-exposure to morphine on conditioned taste aversion. Experiments 1 and 2 showed that the pre-exposure effect transferred completely between two distinctively different environments.

The fact that attenuation of the conditionsd taste aversion was not specific to the situation in which pre-exposure occurred would also appear to rule out an explanation of the effect in terms of blocking by the background cues. In order for this latter explanation to be tenable, it would be necessary to find at least some difference between the development of the conditioned taste aversion in animals pre-exposed to the drug and then given conditioning trials in the same environment, and in animals pre-exposed in a distinctly different environment. That these two environments were sufficiently distinctive to differentially elicit some aspect of the conditioned response to morphine was demonstrated by the analgesia tests in Experiment 2. It seemed clear that the factors determining the attenuation of the analgesic response were situation-specific.

These findings lead us to think that in these experiments we may be dealing with two different aspects of the overall response to morphine, perhaps mediated by different neural systems. One response to morphine is made evident by its changing analgesic action, and may be, as Siegel suggests, a compensatory response initiated by the drug's analgesic action. This response, it would appear, is easily and quickly conditioned to situational environmental stimuli. The other response, or other aspect of morphine's action, is made evident by its apparent aversive properties which are easily and rapidly associated with taste stimuli.

To return to the basic problem: What mechanisms can account for the effect of pre-exposure to morphine on conditioned taste aversion? The differential ease of conditioning postulated above would not, in itself, account for the rapid attenuation of the conditioning of the taste aversion upon repeated presentation in the absence of taste cues. The explanation must be linked to the fact that when the pre-exposure injections were paired with a distinctive taste cue (Experiment 3), subsequent conditioning to a second taste cue proceeded rapidly. We can only suggest, as have Mikulka *et al.* [18] that when an animal repeatedly experiences a drug effect in a non-contingent relation to taste cues, that somehow, the animal learns that tastes are not predictive of drug effects [17]. However, even if one could accept that such learning is possible, the situation with drugs such as morphine is further complicated by having to speculate that the animal is learning, in addition, that situational cues surrounding the injection experience are predictive of some other aspect of the response to morphine.

There are at least two other studies from which it can be

concluded that rats can learn to associate different aspects of a single drug experience to different stimulus features in its environment. Using morphine as the unconditioned stimulus, or reinforcing agent, White, Sklar and Amit [27] reported that hungry rats trained to run a straight alley for food, subsequently increased their running speed, but decreased their intake of a novel food in the goal box, when morphine injections were associated with being in the goal box. Animals performed as if a positive reinforcing effect of the drug were being associated with the place of the injections, while an aversive effect of the drug were being associated with the novel food given in the same situation. Similarly, Wise, Yokel and deWit [29] found that rats trained to self-administer amphetamine, subsequently self-administered apomorphine, and, at the same time reduced their intake of a saccharin solution that was presented for the first time with the apomorphine.

It is interesting to note that a consistent finding in all of these experiments is, that it appears to be some aversive aspect of the drugs that is easily conditioned to the taste stimuli, whereas it is the positive rewarding effect and some feature of the analgesic action that are easily conditioned to places or situational cues. These observations may provide a clue for trying to determine the different neural systems underlying the actions of such drugs. Clearly a solution to questions concerning the nature of various forms of tolerance, and their relation, if any, to the mechanisms underlying drug self-administration, is going to have to take into account these complex findings.

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