Conditioned taste preference produced by pairing a taste with a low dose of morphine or sufentanil

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Abstract. Taste conditioning produced by pairing a taste with low doses of morphine or sufentanil was studied in rats in five experiments. Conditioned taste preferences were obtained with a trace conditioning procedure in which ingestion of a flavored solution was followed by an injection of sufentanil, either 0.25 mcg/kg in experiment 1 or 0.50 mcg/kg in experiment 2. Morphine produced less consistent results than sufentanil. When a similar trace conditioning procedure was used with morphine, a dose of 0.25 mg/kg produced no observable taste conditioning in experiment 3 while 0.42 mg/kg was marginally effective in producing a conditioned taste aversion in experiment 4. In experiment 5, however, conditioning of a taste preference was produced by 0.42 mg/kg morphine with a simultaneous conditioning procedure in which the morphine injection preceded ingestion of the flavored solution. The simultaneous procedure was presumed to facilitate the conditioning of taste preference by minimizing the conditioning of taste aversion.

Key words: Conditioned taste preference – Morphine – Sufentanil

Pairings of a taste with morphine at a dose that has a demonstrable rewarding effect have been shown to cause conditioned taste aversion (CTA) rather than conditioned taste preference (CTP). For example, 10 mg/kg morphine produce CTA when paired with a taste, even though that dose of morphine produces conditioned place preference when paired with a place (Sherman et al. 1980a). Also, rats run faster in a straight alley to a goal box containing food when morphine is administered there but nonetheless develop a CTA to the food (White et al. 1977). Similar findings that drugs with rewarding effects cause CTA rather than CTP have been obtained with amphetamine and apomorphine (Wise et al. 1976; Reicher and Holman 1977; Sherman et al. 1980b). These findings strongly imply that CTP cannot be produced by pairing a taste with a rewarding drug.

Recently, however, Mucha and Herz (1985, 1986) have produced CTP in rats by repeatedly pairing the ingestion of a flavored solution with a very low dose of a mu-opioid receptor agonist: morphine, sufentanil, or fentanyl. The purpose of the present experiments was to replicate the finding of CTP induced by sufentanil (experiments 1 and 2) and by morphine (experiments 3–5). Taste conditioning with these opiates appears to be critically dependent on dose. Mucha and Herz (1985) found that out of a range of doses, only two intermediate doses of sufentanil were effective in producing CTP. Somewhat lower and higher doses had no effect, while the highest dose resulted in a reduced preference for the taste paired with sufentanil. The intermediate doses of sufentanil that produced CTP in the study by Mucha and Herz (1985), 0.25 mcg/kg and 0.50 mcg/kg, were used in experiments 1 and 2, respectively. The procedures of the two experiments were otherwise the same and were modelled after those of Mucha and Herz (1985).

Morphine seems to yield less consistent results than sufentanil. Mucha and Herz (1985) obtained CTP with morphine at a dose of 0.25 mg/kg and CTA with a somewhat higher dose, 0.42 mg/kg. Subsequently, however, 0.50 mg/kg morphine was found to be effective in producing CTP while 0.25 mg/kg was ineffective (Mucha and Herz 1986). Moreover, six taste-morphine pairings were needed to obtain reliable effects although three pairings of taste with sufentanil were sufficient (Mucha and Herz 1985). In experiments 3 and 4 of the present series, six taste-morphine pairings were given and the doses of morphine were 0.25 mg/kg and 0.42 mg/kg, respectively.

In experiment 5, the conditioning procedure was modified to increase the probability of demonstrating CTP induced by morphine. Instead of the trace conditioning procedure used above, in which ingestion of the flavored solution was completed prior to the injection of morphine, the simultaneous conditioning procedure was used. That is, a rat was first injected with morphine and then given access to the flavored solution. This procedure should facilitate morphine CTP for two reasons. First, it should decrease the likelihood of producing CTA that would mask CTP. Sherman et al. (1980a) found that a morphine dose of 10 mg/kg did not produce CTA when it was injected immediately before exposure to a flavor, although that same dose was effective when injected after ingestion of the flavored solution. Second, it permits temporal overlap between the taste stimulus and the rewarding effect of morphine. Such temporal overlap may facilitate CTP, since it is important for the conditioning of a place preference. A trace conditioning procedure in which exposure to the place stimulus is completed before the injection of morphine produces no detectable conditioned place preference, whereas the simultaneous procedure is effective (Sherman et al. 1980a).
Materials and method

Animals. In each of experiments 1–4, there were 19–21 male Sprague-Dawley rats with mean weights of 192 g, 193 g, 330 g, and 329 g, respectively. In experiment 5, the 30 male Sprague-Dawley rats had a mean weight of 207 g. In all experiments, the rats had continual access to food but access to liquids was restricted as indicated below.

Apparatus. In experiments 1–4, the rats were individually housed in suspended metal cages. Training and testing procedures took place in a drinking chamber which was a clear plastic cage (45 × 25 × 20.5 cm) with a wire lid. Each chamber contained food and bedding and was located in the same room as the home cages. In experiment 5, the rats were maintained in these clear plastic cages, and no additional drinking chamber was used.

Drugs and flavored solutions. Both sufentanil citrate and morphine sulfate were prepared with saline so that the appropriate dose, measured in terms of the free base, could be injected in a volume of 1 ml/kg. In experiments 1 and 2, the doses of sufentanil were 0.25 mcg/kg and 0.50 mcg/kg, respectively; in experiment 3, the dose of morphine was 0.25 mg/kg and in experiments 4 and 5, it was 0.42 mg/kg. As indicated by the use of doses measured in micrograms rather than milligrams, sufentanil is more potent than morphine.

Two flavored solutions were used. One solution (7.48 g sodium chloride and 2.34 g monosodium glutamate per liter of tap water) had a weak salty taste. The other solution (0.05 g saccharin and 0.29 g citric acid per liter of tap water) had a weak sour taste.

Procedure: Experiments 1–4. The procedures of experiments 1–4 were similar. First, the rats were familiarized with the drinking chambers in which training and testing occurred. After 16.5 h water deprivation, each rat was placed in its own drinking chamber. After the rat had been in the drinking chamber for 15 min, a bottle was placed in the center of the lid with the spout protruding in the chamber and the rat was allowed 30 min access to water. The rat was then returned to its home cage and 6.5 h later it was given water for an additional 48 h. Then all rats were placed on a 23.5 h water deprivation schedule for 3 days so that each rat received six exposures to one flavored solution paired with morphine and the salt solution paired with saline. Training sessions occurred in the morning. In the afternoon approximately 6.5 h later the rats were given 30 min access to water each day in the home cage.

On the day after the final conditioning session, all rats were given a preference test for 24 h with the salt and sour solutions. Each rat was placed in its drinking chamber and then given access to one of the flavored solutions with the bottle positioned to the left of center. When the rat had taken a few licks of the solution, the bottle was removed and a second bottle containing the other solution was presented slightly to the right of center. When the rat had taken a few licks of this solution, the first bottle was replaced in the left position so that the rat had access to both solutions for the following 24 h. In experiments 1 and 2, the bottle of salt solution was placed to the left of the bottle of sour solution. In experiments 3 and 4, the positions of the bottles were counterbalanced across training conditions.

Procedure: Experiment 5. The rats were gradually acclimated to a drinking schedule on which fluids were available for 30 min at 1 P.M. and for 60 min at 3 P.M. This schedule was maintained throughout the experiment except on weekends. On Fridays, starting at 3 P.M., the rats were given water overnight; the water was removed on Saturday morning. On Sunday water was available on the usual schedule.

The rats were divided into two groups (n's = 15) equated with respect to body weight and the amount of water drunk on the day prior to conditioning. As in preceding experiments, Group Salt received the salt solution paired with morphine and the sour solution with saline, while the reverse held for Group Sour. At the start of each conditioning session, each rat was injected subcutaneously with morphine (0.42 mg/kg) or saline, as appropriate, and then given access for 30 min to a flavored solution from a bottle placed in the center of the lid of the clear plastic home cage. In the afternoon, all rats received the salt solution at 1 P.M., and on even days, the sour solution. There were 12 training days so that each rat received six exposures to one flavored solution paired with morphine and six exposures to the other flavored solution paired with saline.

Three days after the last conditioning trial, all rats were given a preference test with the salt and sour solutions for 24 h. For all rats, the bottle of salt solution was placed slightly left of the center of the cage lid while the bottle of sour solution was placed slightly right of center.

Data analyses. For each rat, a score of preference for the sour solution was computed as the amount of sour solution divided by the total amount of solution, salt and sour, drunk during the test. A score of preference for the salt solution can be obtained by subtraction. In each experiment, preference for the sour solution in Group Sour was compared to that of Group Salt. CTP was inferred when Group Sour exhibited a greater preference for the sour solution than Group Salt, whereas CTA was inferred when Group Sour exhibited a lower preference than Group Salt. Statistical evaluations were made using the t-test; the P values are for a two-tailed test.