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Morphine and Acceptability of Putative Reinforcers

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CALCAGNETTI, D. J. AND L. D. REID. *Morphine and acceptability of putative reinforcers.* PHARMACOL BIOCHEM BEHAV 18(4) 567–569, 1983.—Rats were given the opportunity to take one of five concentrations of saccharin solutions. Intake across concentrations generated a preference-aversion curve. Morphine, 2 mg/kg, increased intake of saccharin solutions when rats were 12-hr water deprived or were not deprived. These effects with morphine are opposite to those of naloxone and strengthen the idea that there is opioid involvement in incentive motivation.

Morphine Drinking Feeding Palatability Endorphin

DATA support the assertion that naloxone's (NX) effect on intake of fluids is pharmacologically specific, i.e., an antagonist-effect at specific receptors [1, 6, 12]. Work has also begun on detailing the behavioral specificity of the NX-effect [4, 6, 10, 11, 13].

A potentially important feature of the way NX specifically modifies intake is its ability to influence the incentive value associated with ingestibles [10,14]. In a recent experiment, rats were given a choice between taking tap-water or one of five concentrations of saccharin solutions [9]. The weakest concentration was taken just slightly more than water. The next three concentrations were taken considerably more than water while the highest concentration was not preferred over water probably due to its reputed bitterness. A preference-aversion curve was generated as a consequence of presenting these various concentrations of saccharin solution. With injections of NX, rats took less fluids and, particularly, less saccharin solutions especially at the least preferred concentrations. NX led to a narrowing of the preference-aversion curve.

This work is an extension of the previous work [9, 10, 14] testing for NX's effects on acceptability of various saccharin solutions. Although we [14] had some data indicating that morphine might produce nearly opposite effects to that of NX, we did not have a test of morphine's effects with a range of solutions. Consequently, we decided to test morphine with a fuller range of the preference-aversion curve.

There is a question of what dose of morphine should be tested. Doses producing catatonia and suppression of all behavior are of little theoretical interest with respect to appetite. The dose and time after dosing selected for testing is the regimen of morphine that will clearly facilitate pressing for lateral hypothalamic brain stimulation [8]. Such a dose was selected because there may be a relationship between morphine's putative ability to modulate incentive value and morphine's known ability to facilitate pressing for direct stimulation of the brain [10].

METHOD

Subjects

Preferences for saccharin solutions were obtained from 100, Sprague-Dawley, male rats. Of the 100 subjects, 50 were initially naive to all experimental procedures while 50 had been in a testing regimen similar to that used here. The experienced rats had been given NX (maximum across tests = 6.1 mg/kg) over 2 months prior to these procedures.

Although the two groups (experienced and naive) differed considerably in age, weight (experienced rats' mean weight = 429 g, sd = 35.8; naive rats' mean = 282 g, sd = 10.1) and experimental history, similar results were obtained with both groups. Since the results from the two equally sized groups were similar, and since most comparisons of interest are across a subjects' reactivity, final analyses did not take into account the two subgroups.

Rats were caged individually in a colony room maintained at 24°C with lights on from 2300 to 1100 hr. Food was always available and water as specified. Fluids were presented in bottles equipped with ballpoint sipping tubes. To measure intakes, bottles were weighed, to the nearest 0.1 g, before and after presentation.

Procedure

The general procedure is the same used to test NX's effects [14]. Prior to introducing a concentration of saccharin, rats were placed on a water-deprivation schedule. Across 5 days, rats had only two opportunities to drink, one beginning at 1130 hr lasting 1 hr and one beginning at 2130 hr lasting 2 hr. Since eventual testing occurred during the period beginning at 1130 hr, rats were water-deprived for 12 hr at the start of testing.

Five solutions were used, each differing in concentration of artificial sweetener; 0.006, 0.05, 0.15, 0.5 and 1.0%. The sweetener was commercially available (Necta-SweetR) and its primary content was sodium saccharin. Fresh solutions

were mixed daily by dissolving the tablets in tap water.

After habituation to the deprivation-schedule, rats were presented during the test-session with two bottles, one containing tap-water and the other containing one of five concentrations of saccharin solution. A rat received tap-water and a particular saccharin solution throughout testing. Consequently, there were 20 rats/group with each group having an opportunity to take tap-water or one of five saccharin solutions.

Prior to the time when the two bottles were left on the cage for 1 hr, rats were allowed to sample the contents of each bottle. To "force" sampling, each bottle was put up for 5 sec. Then, the session was begun by presenting both bottles simultaneously. The bottle containing saccharin solution was put up on a different side of the cage every day. With daily presentations of the two bottles, a regimen of injections was introduced.

Two kinds of subcutaneous injections were given 30 min prior to bottle presentation: (a) 0.9% saline, 1 ml/kg, the carrier of the drug, and (b) morphine sulfate, 2 mg/kg (all injection volumes: 1 ml/kg). The regimen for one-half of the subjects was an injection of saline every day for 6 days except on the 3rd day of injections. On the 3rd day, these rats received an injection of morphine. The regimen for the other half was saline every day except for the 5th day. On the 5th day, these rats received morphine. Consequently, all rats received morphine in a cross-over experimental design.

Analyses indicated that mean intakes after saline injections showed no reliable shifts across days with the possible exception of some systematic shift toward the effect seen with morphine on the day following morphine. Since it made little difference whether rats received morphine on the 3rd or 5th day and since the first post-morphine saline injection may reflect carry-over effects, we (a) used the data from the day before morphine injection as the best estimate of what a rat would have done on the day of morphine injection had it received saline, i.e., the placebo score, and (b) summarized data without taking into account whether rats received morphine on the 3rd or 5th day. The results of these data-reductions, which follow from not seeing differences across various groupings of subjects or procedures, yielded scores for each rat representing intake under placebo and morphine.

There can be a number of indices of intake from a daily session: (a) g of water taken, (b) g of saccharin solution taken, (c) total fluid taken, and (d) a preference ratio, i.e., saccharin solution taken/total fluid taken. Since a preference ratio embodies much of the other indices and since preference-ratios were used previously to summarize the effects of NX, we report here the effects of morphine on preference-aversion ratios. The resultant scores (ratios) conform, therefore, to a 5 by 2 analyses of variance (ANOVA) for repeated measures having a factor for the five concentrations of saccharin and a factor for placebo-morphine.

Twenty-one days after the tests described above, 50 of the subjects began another testing regimen. These 50 subjects were those naive to experimental manipulations at the beginning of testing morphine. This subsequent testing was the same as that described with the following exceptions. Rats of this test were not deprived, i.e., water was continuously available except for the short time the water bottles were removed to initiate testing. The testing session was 2 hr, rather than 1 hr as in the first test. Testing ended after one-half of the rats got morphine while the other half received saline, i.e., testing was terminated on the 4th day of the regimen.

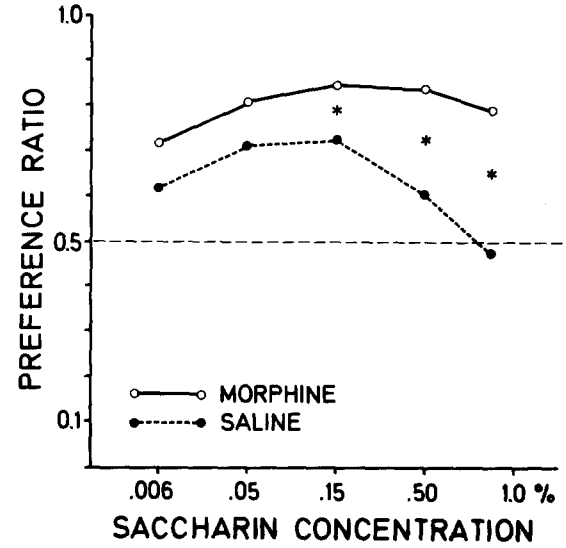

FIG. 1. Mean preference-aversion ratios for comparing morphine's effects to those of placebos. Asterisks signify $p<0.01$ from t-tests for related measures for differences at particular concentration. The $t(19)$ for differences at the 0.006% concentration = 2.74, $p<0.05$, and the $t(19)$ for the 0.05% concentration = 1.9, $p<0.10$.

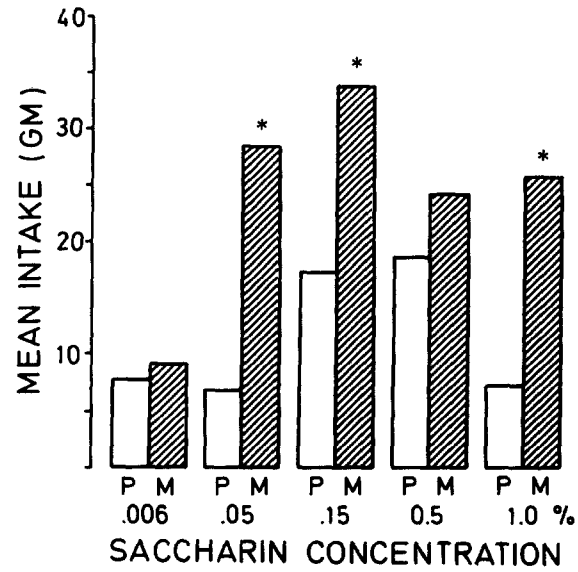

FIG. 2. The figure presents the mean grams of saccharin solution taken by nondeprived rats following placebo (P) or morphine (M). An asterisk indicates a $p<0.05$, from a t-test for independent means. The results for the concentrations of 0.006% and 0.5% were t less than 1.0, $p>0.25$.

Since without deprivation of water, rats seldom took water during the test but readily consumed some saccharin solutions, the best index of performance on this test is g of saccharin solution consumed. Since on the test day, one-half of the rats received morphine and half saline, the test conforms to a 5 by 2 experimental design having scores (g of saccharin taken) for each of the five concentrations for rats receiving saline or morphine.

In summary, rats were tested for the effects of morphine on a preference-aversion curve generated by having groups of 12-hr-water-deprived rats choose between taking tap-water or a concentration of saccharin-solution. The effects of a same dose of morphine were also tested in rats not deprived of water.

RESULTS AND DISCUSSION

Figure 1 depicts the means of preference-aversion ratios under the influence of placebo and morphine of deprived rats. An ANOVA of the data used to generate Fig. 1 yielded an $F(4,95)=2.9$, $p<0.03$ for the factor of concentrations of saccharin confirming that the various concentrations resulted in reliably different ratios.

The factor of morphine-placebo yielded an $F(1,95)=76.0$, $p<0.0001$ and the interaction factor (morphine-placebo by concentration) yielded an $F(4,95)=5.9$, $p=0.0003$. Morphine clearly enhanced the preference for most of the concentrations including the highest concentration of saccharin solution which was taken slightly less than water under placebo.

Figure 2 presents results from the test when rats were not deprived prior to testing. As can be seen, morphine greatly enhanced intake at 0.5 and 0.15% concentrations as well as at 1.0%. The ANOVA of the data of Fig. 2 yielded an $F(4,40)=4.5$, $p<0.01$ for the factor associated with the concentrations of saccharin solutions. The values for the factor of morphine-placebo were $F(1,40)=20.1$, $p<0.0001$ and for the interaction were $F(4,40)=2.0$, $p<0.12$.

These results indicate that a dose (2 mg/kg) of morphine increases intake of saccharin solutions, even solutions that were taken only modestly under a placebo. This dose broadened or expanded the preference-aversion curve. This broadening, under morphine, occurs in mildly water deprived rats as well as nondeprived rats.

In general, morphine's effect was opposite to that of NX. Because NX narrows the preference-aversion curve and morphine expands it, it is presumed that one or more of the endogenous opioid peptides would be involved, in ordinary circumstances, with similar actions. Presumably, some bodily conditions related to deprivation and a lack of motivation incompatible to ingestion trigger the release of one or more of the endorphins. Deprivation has been shown to modify levels of β-endorphin and dynorphin [2,7]. The endorphins might then act to enhance the incentive value of ingestibles. Such a postulated sequence of events is compatible with the theoretical statements of Toates [15] concerning feeding and those of others [3,5], following anatomical studies, concerning the probable functions of the endorphins.

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