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BRIEF COMMUNICATION

Morphine Enhances Hedonic Taste Palatability in Rats

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DOYLE, T. G., K. C. BERRIDGE AND B. A. GOSNELL. *Morphine enhances hedonic taste palatability in rats.* PHARMACOL BIOCHEM BEHAV 46(3) 745–749, 1993. – The question of whether opiates stimulate feeding by enhancing taste pleasure was investigated by examining the effect of morphine upon hedonic and aversive reactions to taste (tongue protrusions, gapes, etc.). Rats (n = 12) were given SC injections of morphine (4 mg/kg) or equal volumes of isotonic saline 2 h after the start of their daily light cycle. Food intake was measured in a 2-h test. On days when they were given morphine, rats ate significantly more food than when given saline. Hedonic and aversive taste reactions were elicited by an infusion of sucrose–quinine solution into the mouth and were measured subsequently in a slow-motion video analysis. The same rats that showed an increase in food intake after treatment with morphine showed a significant increase in their positive hedonic responses. Aversive reactions were unchanged by morphine. The results support the hypothesis that morphine enhances feeding by increasing the hedonic palatability of food.

Morphine Taste Palatability Hedonic Food intake Feeding behavior Opioid

FOOD and fluid intake is stimulated by opioid agonists and suppressed by opioid antagonists. Three years after Holtzman (26) found that the opiate antagonist naloxone reduced food intake in food-deprived rats, Grandison and Guidotti (22) reported that β-endorphin stimulated food intake in satiated rats. Work done in years since has extended the phenomenon of opioid-induced feeding to many different species, including rats, mice, pigeons, sheep, and humans (1,13,27). Feeding induced by systemic opioid agonist administration lasts 1 to 3 h, following an initial 1-h period when food intake is suppressed [(see for example (30,33)].

Evidence suggests that opioid agonists stimulate feeding by acting on receptors within the brain. Opiates injected in several different brain areas can produce feeding behavior (17,21,31,40). Both mu and kappa classes of opioid receptors have been implicated in feeding facilitation (41,49).

In spite of an immense amount of work done to characterize the role of opioid ligands in feeding behavior, the psychological mechanisms by which endorphins mediate their effects on feeding have yet to be established. Candidates have included hypotheses that opioid ligands act by enhancing food palatability [e.g., (10,12,13,15,18,42,51,52)], inhibiting caloric satiety [e.g., (28)], or reducing neophobia (17). The present study was designed to test the hypothesis that opioid agonists stimulate feeding by enhancing the sensory pleasure of taste, using affective reactions as an assay of sensory pleasure.

The hypothesis that opioid ligands alter food palatability has been based primarily on changes in food intake patterns produced by opioid agents. A variety of opioid receptor antagonists (including naloxone) selectively attenuate the preference for highly palatable foods in rats (11). Conversely, intracerebroventricular injections of the mu opioid agonist DAGO and the delta agonist DTLET increase the intake of a saccharin solution over that of water or of a less concentrated saccharin solution in nondeprived rats (19).

Intake studies provide evidence for a facilitation of feeding by opioid agonists, but cannot determine whether an increase in food intake occurs because the drug has changed the hedonic perception of the taste's palatability or because of some other reason. The taste reactivity test developed by Grill and Norgren (24), on the other hand, can be used to selectively measure changes in the hedonic and aversive perception of tastes (23). For example, just as human subjective ratings of taste pleasure are changed by manipulations such as caloric satiety or taste aversion learning [e.g., (7,45)], so are hedonic and aversive reactions to taste (such as tongue protrusions, paw licks, gapes, and chin rubs) altered by physiological (e.g., hunger), psychological (e.g., taste aversion conditioning), and

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pharmacological (e.g., benzodiazepine) manipulations that control feeding (2,25,50). Manipulations that suppress or increase feeding by acting via psychological mechanisms separable from taste pleasure (e.g., associative pairing with shock or amphetamine, 6-OHDA lesions, electrical LH stimulation, etc.), on the other hand, do not alter hedonic or aversive taste reactivity patterns (3,4,43,45,50).

If opioid agonists facilitate feeding by enhancing the palatability of food, then one would expect that rats treated with morphine would display enhanced hedonic responses to a taste. In the present study, we used the taste reactivity test to ascertain whether opioid-induced feeding is mediated by an increase in the perceived hedonic palatability of food. We report that hedonic taste reactivity to a bittersweet solution was enhanced by a morphine injection that stimulated food intake in nondeprived rats.

METHOD

Subjects

Twelve male Sprague-Dawley rats (520–650 g) were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg). Each rat was implanted with two chronic oral cannulae for mouth infusion to permit later taste reactivity testing. The oral cannulae (constructed of heat-flared PE 50 tubing, Teflon anchor, and 23-ga steel external connector) entered the mouth lateral to the first maxillary molar, ascended within the zygomatic arch, and were anchored to the dorsal skull with bone screws and acrylic cement. The rats were housed individually in suspended wire cages on a 14L : 10D cycle. Free access to food and water was provided throughout the experiment.

Drugs

Rats were given 4 mg/kg of morphine sulfate dissolved in isotonic saline (NaCl) or isotonic saline alone, SC. Prior to the experiment they had received one injection each of 2 mg/kg morphine. All injections occurred 2 h after the beginning of the light cycle.

Experimental Groups

On each day of the experiment, the rats were divided into two treatment groups: morphine-treated and saline-treated. Each day half of each group of rats was tested for food intake and the other rats were tested for taste reactivity. The entire experiment was conducted over 4 days so each rat received morphine and saline injections twice: morphine with the taste reactivity test; saline with the taste reactivity test; morphine with the food intake test; saline with the food intake test. The order of tests was counterbalanced across rats.

Food Intake Procedure

After injections with morphine or saline, rats were immediately returned to their cages and presented with two preweighed pellets of Purina rat chow (mean weight 14 g). Paper towels were placed under the cages to collect any spillage of food. Pellets and paper towels were replaced with new (preweighed) pellets and towels 60, 90, and 120 min after injections. The remaining pellets and the spillage were weighed and recorded for each time interval.

Taste Reactivity Procedure

Taste reactivity tests were carried out between 3.5 and 4 h after the beginning of the light cycle (i.e., 90–120 min after drug injection), which is the time when the morphine-induced feeding effect was expected to be at its maximum (pilot observations). During the 2-h interval between the injection and the taste reactivity test, food was removed from the rats' cages. Each rat was tested once for each drug treatment for taste reactivity to a solution that contained 7% sucrose and 0.01% quinine HCl. This bittersweet solution has been found to elicit a mixture of hedonic and aversive reactions in untreated rats in our lab. Pure sucrose solutions elicit only hedonic reactions, and therefore have a "floor effect" regarding the ability to elicit detectable changes in aversive reactions that might be caused by morphine. Pure quinine solutions have the same limitation regarding hedonic reactions. The sucrose-quinine mixture was chosen to permit detection of palatability changes in either direction (i.e., hedonic or aversive).

In the taste reactivity test, a rat's oral cannula was connected to a delivery tube (PE 50 tubing with PE 10 nozzle), and the rat was allowed to habituate to the taste reactivity chamber for 2 min. The transparent floor of the chamber was suspended over a mirror, which reflected a view of the face and mouth into the close-up lens of a video camera. The trial lasted 60 s, during which the delivery tube infused 1.0 ml of the taste solution into the rat's mouth at a constant rate. Reactivity to the taste was videotaped for later slow-motion analysis. For the purpose of analysis, taste reactivity scores from rats that fed in response to morphine administration were analyzed separately from those of rats that failed to show morphine-induced feeding.

Video Analysis

From the videotaped record, frequency counts were determined for the occurrence of hedonic and aversive reactions (23,24). Videotapes were scored by an observer who did not know the exact experimental conditions of each rat. Hedonic reactions were the following: lateral tongue protrusions (nonrhythmic) lasting about 160 ms; rhythmic tongue protrusions along the midline with a cycle of roughly 160 ms; and paw licking. Aversive reactions were the following: gapes—large openings of the mouth and jaw lasting about 125 ms; chin rubbing—bringing the chin in direct contact with the floor and projecting the body forward; face washing—either a single wipe with the paws over the face or a bout of several wipes; forelimb flails—shaking of the forelimbs back and forth; paw treading—forward and backward movement of the forepaws in synchronous alternation; rapid headshaking—rapid lateral vibration of the head and neck. Continuous rhythmic tongue protrusions were scored in bouts of up to 2 s. All other actions were counted each time they occurred.

RESULTS

Intake

Morphine enhanced food intake by more than 400% in the 90–120-min interval after injection [ANOVA, $F(1, 10) = 10.456$, $p < 0.01$], as shown in Fig. 1. Rats given morphine ate 1.79 ± 0.43 g of rat chow in this time period, as opposed to 0.36 ± 0.22 g on days when they received saline. Morphine had no significant effect on food intake prior to 90 min after injection. All but one rat ingested food at some time during the 2 h following morphine injection.

Taste Reactivity

When taste reactivity data from all of the rats were included for ANOVA, rats given morphine showed more he-

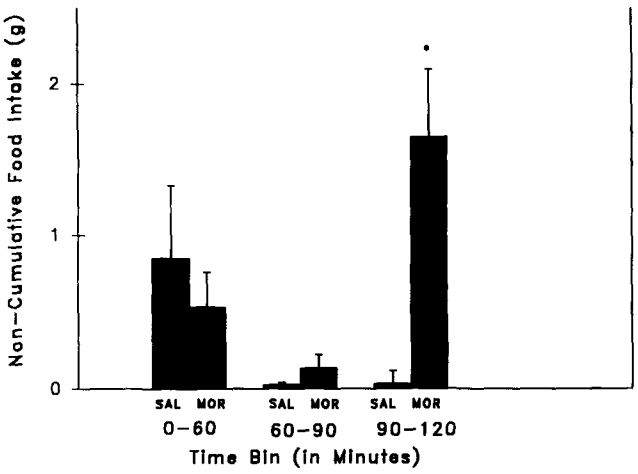

FIG. 1. Food intake (g) of rats (n = 12). Noncumulative measurements were taken 60, 90, and 120 min after SC administration of morphine (4 mg/ml). *Denotes significance at $p < 0.01$.

donic responses (5.08 ± 0.45) to the sucrose-quinine solution than rats given saline (1.5 ± 0.24), but the result was not significant, $F(1, 11) = 1.769$, $p = 0.2088$. However, if only the rats that ingested food during the 2 h after they were given morphine were included in the analysis, excluding the rat that did not eat after morphine (i.e., the "morphine feeders"; n = 11), hedonic reactions were significantly increased by the opiate injection, $F(1, 10) = 5.842$, $p = 0.0349$ (Fig. 2). Morphine had no effect on aversive reactions in either analysis.

DISCUSSION

The taste reactivity data from this study suggest that the opiate agonist, morphine, enhances taste pleasure at a time when it also enhances feeding. For the one rat in this study in which the number of hedonic reactions was not enhanced (the "nonfeeder" that was eliminated from the group for statistical reanalysis), it is possible that morphine's sedative effects may have masked the drug's hedonic effects on taste. This is suggested by the observation that this rat displayed a complete absence of any mouth movements on the day it was given morphine, but, instead, did nothing but allow the solution to drip passively out of its mouth. For the 11 rats that showed morphine-induced feeding, morphine did enhance hedonic reactions to a bittersweet taste.

Several questions remain concerning the relation of opioid-induced feeding and hedonic enhancement. First, is the time course of the two phenomena identical? The hedonic enhancement of taste palatability is detectable when the hyperphagic effect of morphine is at its peak, but feeding shows a biphasic response to morphine: an early suppression followed by later enhancement. It is not yet known whether opioid-induced hedonic enhancement also follows a biphasic course. It is possible that taste pleasure, like feeding, is suppressed or at least not enhanced soon after morphine administration. Alternatively, it may be that hedonic enhancement occurs immediately after morphine administration but fails to stimulate early eating because of other competitive effects of morphine that tend to suppress feeding (e.g., sedation). Another question concerns the relation between the opioid enhancement of taste pleasure we have found and other pharmacological manipulations that enhance hedonic taste reactions, such as high doses of benzodiazepines [e.g., (50)]. Are both types of hedonic enhancement acting on different stages within the same taste evaluation system? Is there interaction between the effects of these different agents?

Although morphine enhanced hedonic reactions to a bittersweet taste in this study, the shift in palatability was unidimensional. Aversive reactions to the bitter component of the taste were not suppressed by morphine (4 mg/kg) 90 min after the injection. This contrasts with a recent report by Parker, Maier, Rennie, and Crebolder (44) that morphine (2 mg/kg) does suppress aversive reactions to a pure quinine solution 30 min after the injection. They concluded from their results that morphine enhances the acceptability of food by acting on the aversive limb, rather than the hedonic limb of palatability (2). The reason for this difference in results between their study and ours is not clear. The suppression of aversion reported by Parker et al. occurred early after the injection. This might mean that the effect of morphine on taste palatability changes with time following an injection. Alternatively, the suppression of aversive reactions might have been produced by transient sedative effects of the drug that dissipated by the time we tested taste reactivity. Also, the level of aversive reactions elicited by our bittersweet taste was lower than that elicited by the purely bitter taste used by Parker et al. There may be response scaling parameters that constrained the effect of morphine on aversion in our study. Finally, the study by Parker et al. compared the reaction of morphine-treated rats to a separate group of saline-treated rats, while our study used a within-subject design to compare the effects of morphine and saline. Further comparison of the effects of morphine on aversive taste reactivity to different tastes and at different times is needed to know which of these possible factors is important.

These experiments demonstrate that at times when morphine facilitates feeding, it also enhances hedonic response of a rat to a sweet taste. The present findings support reward-enhancement hypotheses that have been suggested previously

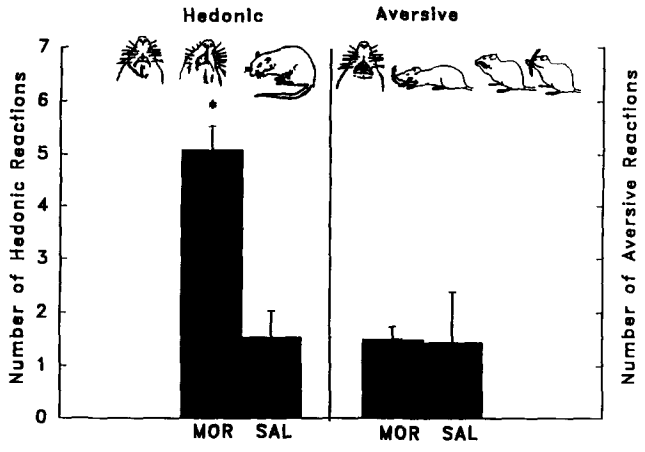

FIG. 2. Affective reactions to taste. Hedonic reactions (top left) are normally elicited by sucrose and other palatable tastes. Hedonic reactions include rhythmic midline tongue protrusion, nonrhythmic lateral tongue protrusion, and paw lick. Aversive reactions (top right) are normally elicited by quinine and other nonpalatable tastes. Aversive reactions include gape, head shake, face wash, and forelimb flail. Bars depict the number of hedonic and aversive reactions displayed by rats (n = 11) to a sucrose-quinine mixture. Taste reactivity was tested 90 min after SC administration of morphine (4 mg/kg) or saline. *$p < 0.05$.

by other investigators. These hypotheses have been based largely on observations that the effects of opioid agents on feeding depend in part on the palatability of the food that is available: opioid agents most strongly alter the intake of highly palatable foods and solutions. For example, opioid antagonists reduce the consumption of preferred sweet or salty solutions more dramatically than they reduce the consumption of water (9,32,35,39). Opioid antagonists also block the gradual acquisition of a preference for a palatable solution that is offered repeatedly (37,38). Evidence from other sources also indicates a correlation between taste palatability and the activation of opioid reward systems. For example, mice belonging to a strain that has a deficiency of opioid receptors show a weaker preference for saccharin than do other mice (53). Finally, ingestion of highly palatable food has been indicated to activate brain opioid systems (6,14,36,46–48). All of these lines of evidence suggest that the neural processing of taste palatability may involve the activation of opioid systems. The present demonstration that morphine enhances natural hedonic reactions to taste that are specifically sensitive to taste palatability supports this conclusion.

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