# Naltrexone, an opioid blocker, alters taste perception and nutrient intake in humans

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BERTINO, MARY, GARY K. BEAUCHAMP, AND KARL ENGELMAN. *Naltrexone, an opioid blocker, alters taste perception and nutrient intake in humans.* Am. J. Physiol. 261 (Regulatory Integrative Comp. Physiol. 30): R59–R63, 1991.—To test the hypothesis that reduced food intake produced by opioid blockade is due to a reduction in the pleasant aspects of tastes, 18 fasted male college students rated the intensity and pleasantness of soup that contained various concentrations of NaCl and of Kool-Aid that contained various concentrations of sucrose at hourly intervals after ingesting either naltrexone (50 mg) or a placebo in a double-blind study. Hunger, fullness, nausea, and current mood state were also assessed. Lunch followed and food intake was recorded. After placebo, the pleasantness of the salted soup increased as lunchtime approached. After naltrexone, however, soup pleasantness remained unchanged across time. Similar changes were obtained for perceived sweetness and pleasantness of Kool-Aid and for the perceived saltiness of soup. Naltrexone also blocked the increases in hunger ratings that occurred across time in the placebo condition. Nausea was higher after naltrexone. After naltrexone, subjects consumed ~500 kcal less at lunch than after placebo. Analysis of covariance suggested that decreased hunger (but not nausea or taste pleasantness) accounted for the naltrexone-induced reduction of food intake.

salt; sweet; food intake; mood

ENDOGENOUS OPIOIDS are morphinelike substances released at many sites in the body in response to a variety of environmental stimuli. The resultant opioid occupation of brain receptors can affect an organism's subsequent interactions with environmental stimuli.

Endogenous opioids may modulate food and fluid intake. In nonhuman animals, small doses of opioid agonists increase intake of palatable diets and palatable solutions, whereas opioid antagonists decrease intake of the same items (see Ref. 16 for review). Opioid agonists and antagonists appear to influence food intake by lengthening and shortening the feeding bout, respectively. Opioid agonists and antagonists also influence macronutrient intake. In rats, morphine increases the proportion of calories selected as fat and suppresses the proportion selected as carbohydrates (12). Naloxone decreases the proportion selected as fat (13). It has been hypothesized that effects of opioids on macronutrient intake may be achieved through alteration of pleasurable aspects of feeding, notably taste (16).

In humans, opioid agonists can also increase food intake (14) and antagonists can decrease food intake in a single meal (1, 5, 7, 17, 18). Opioid antagonists may influence macronutrient selection in humans. Naloxone depressed intake of cheese sandwiches and chocolate biscuits without affecting intake of orange segments or lemon drink (18). Naltrexone also decreased the pleasantness of the taste of glucose solutions but not salt solutions in human volunteers (6). It is possible that the naloxone-induced reduction of food intake and/or changes in nutrient selection are a direct consequence of the decreased pleasantness of selected tastes.

Opioid antagonists could produce the above differential effects on salt and sweet taste in at least two ways. One possibility is that antagonists affect only tastes that are calorically meaningful. However, this hypothesis is inconsistent with the observation that intake of and preferences for noncaloric salt solutions increased in rats after administration of a small dose of the agonist morphine (2). Another possibility is that antagonists decrease the pleasantness of only pleasant tastes. Although there is much evidence that the taste of salt water is pleasant to rats, most humans rate the taste of salt in water as either neutral or unpleasant (e.g., Ref. 3). Therefore, in humans, salt taste pleasantness may appear unaffected after naltrexone administration because the taste of salt water is intrinsically neutral or unpleasant and thus unaffected by the administration of opioid antagonists. Because humans prefer many foods to be salted, it would be more appropriate to use salted foods to test the effect of opioid antagonists on salt taste preference.

The following experiment was designed to address a number of questions: *1*) is the decreased food intake observed after naltrexone administration a result of altered taste perception? *2*) does naltrexone alter nutrient selection in humans, and if so, is that alteration related to taste perception? and *3*) does naltrexone reduce the pleasantness of the taste of salt in food?

## METHODS

*Subjects.* Eighteen male [mean 20.9 ± 0.56 (SE) yr] University of Pennsylvania undergraduates were recruited. Potential subjects were questioned as to their use of prescription, over-the-counter, or illegal drugs; none reported any current use of illegal drugs. They were given a physical examination including a 24-h urine collection, which was screened to ensure that the subjects were free of exogenous opioids. Potential subjects were

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then given a preliminary taste test (see below) to ensure that they showed moderate liking of salt and to determine whether they could do the taste test properly. A salt-attitude questionnaire was administered (11) to ensure that they were not on a low-sodium diet and that they did not have extremely negative attitudes toward salt. A urine sample was analyzed for sodium and creatinine content to corroborate the taste test and questionnaire results. The experimental protocol was approved by the University of Pennsylvania's Committee on Studies Involving Human Beings and by the Clinical Research Center Advisory Committee. All subjects gave informed consent before participation. Subjects were told that naltrexone, an opioid antagonist, was being used to study the effects of endogenous opioids on performance.

*Experimental manipulation.* Subjects fasted overnight (including no breakfast) and in the early morning came to the Clinical Research Center of the Hospital of the University of Pennsylvania for two 4-h sessions scheduled 3–4 wk apart. During one session they received 50 mg naltrexone hydrochloride (Du Pont Pharmaceuticals), and during the other session they received an identical-appearing placebo. Tablets were packaged by the hospital pharmacy and dispensed by the research nurses in a double-blind manner. Half the subjects received naltrexone during the first session. Fifteen minutes after either naltrexone or placebo was administered, the subjects assessed hunger, fullness, nausea, and mood. Taste tests and the visual analog scales for hunger, fullness, nausea, and mood were administered 1, 2, and 3 h after drug ingestion. At the end of the first taste test, the subjects ordered lunch from a menu (to be delivered after testing) from the research kitchen of the Clinical Research Center. Subjects could select either regular or extra-large portions from a number of selections of soups, salads, entrees, vegetables, crackers, desserts, fruits, condiments, and beverages. Thus subjects were not served a standard meal. Lunch was served after the end of the third taste test. Intakes of food and fluid during lunch were measured and recorded by the research dietitian.

The main object was to collect taste ratings during the period when naltrexone had its greatest effect on taste. Based on previous work, it was surmised that naltrexone would have its greatest effect ~90–120 min after the drug was ingested (6). The measures taken at 1, 2, and 3 h postingestion bracket this time.

*Taste tests.* Subjects tasted, expectorated, rinsed with water, and then rated the saltiness and pleasantness of a concentration series of NaCl (0, 0.08, 0.18, and 0.35 M) in Campbell's low-sodium vegetable soup that had been strained of noodles and vegetables. Ten-milliliter samples were presented at two temperatures, alternating between hot (~53°C) and room-temperature soup (~21°C). Three replications of each 10-ml sample were presented randomly with the restriction that each concentration in the temperature series should be presented before a concentration was repeated. Subjects rated saltiness and pleasantness on 10-cm visual analog scales. To ensure that any effects on taste ratings observed were in fact due to taste, subjects also rated the odor of the soup at the beginning of each taste test session.

After the soup taste test, subjects similarly rated the sweetness and pleasantness of a concentration series of sucrose (0, 0.15, 0.32, and 0.70 M) in cherry Kool-Aid. The samples were presented cold (~14°C) and at room temperature (~21°C). The testing procedure was identical to that used for the soup. One complete taste test (including both soup and Kool-Aid samples) lasted 20–30 min.

*Hunger, fullness, nausea, and mood assessment.* Subjects rated their current levels of hunger, fullness, and nausea on 100-mm lines where one end was labeled "not hungry" (or "not full" or "not nauseated") and the other end was labeled "extremely hungry" (or "extremely full" or "extremely nauseated"). Subjects also indicated their present state in regard to 15 moods on a 100-mm visual analog bipolar scale (4).

*Data analysis.* The intensity and pleasantness ratings for soup and Kool-Aid were analyzed separately. Replications for each stimulus within a single hourly taste test were averaged together. Because preliminary analyses showed that order of drug administration did not influence the results, taste ratings were analyzed with temperature, time, drug, and concentration as main factors. Simple effects tests were performed on the significant interactions. When there were more than two levels of a repeated-measure factor, Greenhouse-Geisser corrections of the degrees of freedom were used. Similar analyses of variance were conducted on the mood data with drug and time as main factors. Nutrient analyses of the foods selected and the food actually eaten were made using Nutritionist's III, release 3.0, a nutrient database software package. Nutrient intakes were subjected to one-way analyses of variance (repeated measures) with drug as the main factor.

## RESULTS

*Taste tests.* There was a significant time-drug interaction on the rated saltiness of soup [$F(2, 34) = 3.55$, $P < 0.05$; Fig. 1, *top right*]. Simple effects tests revealed that at 60 min after naltrexone administration, soup was rated as tasting more salty than after placebo administration ($P < 0.05$). This difference appears to be due to the low saltiness ratings after placebo administration during the 1st h compared with the 2nd and 3rd h. After naltrexone, ratings of saltiness were relatively stable throughout the 3 h of testing. Simple effects tests supported these observations in that the change in saltiness ratings across time was significant in the placebo condition ($P < 0.05$) but not in the naltrexone condition. Additionally, as the salt concentration increased, soup was rated as tasting saltier [$F(3,51) = 231.35$, $P < 0.0001$; data not shown]. Drug treatment did not have differential effects on saltiness at different concentrations of salt in soup.

The pleasantness ratings of soup were also significantly affected by the time-drug interaction [$F(2,34) = 10.67$, $P < 0.002$; Fig. 1, *bottom right*]. Simple effects tests revealed that the time after placebo administration affected the rated pleasantness of soup [$F(1.6,27.7) = 6.49$, $P < 0.008$], with the greatest pleasantness at 180 min. After naltrexone, time did not affect pleasantness ratings. Thus, as in the intensity ratings, naltrexone had

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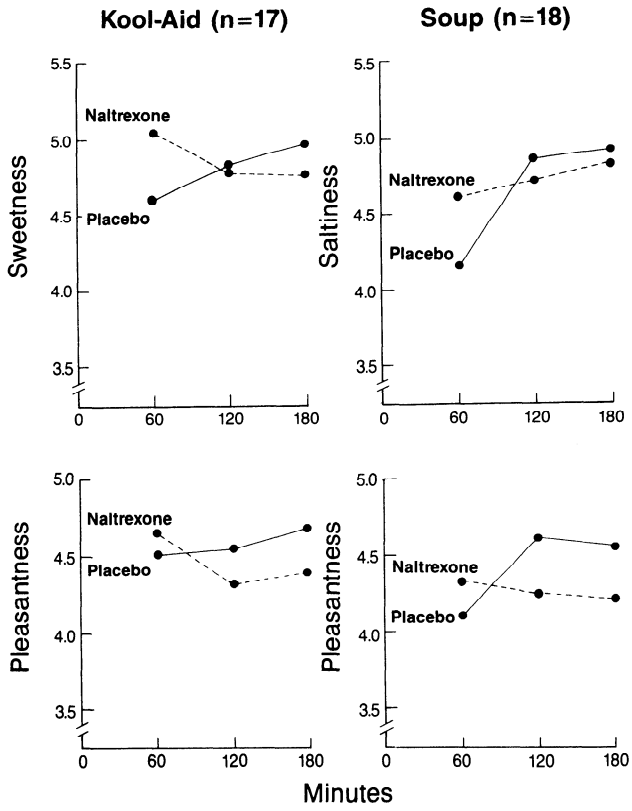


FIG. 1. Visual analog taste ratings of intensity and pleasantness of soup and Kool-Aid 60, 120, and 180 min after naltrexone or placebo administration. Because drug and placebo treatments did not differentially affect ratings at different concentrations, ratings are averaged over all concentrations. For example, the average sweetness rating for all 4 concentrations of sucrose in Kool-Aid 60 min after naltrexone treatment was ~5.0 (*top left*).

stabilized taste ratings in hungry people. Concentration influenced pleasantness ratings [$F(3,51) = 20.70$, $P < 0.00001$; data not shown]. Finally, soups were rated as tasting more pleasant when they were hot [$F(1,17) = 10.92$, $P < 0.005$; data not shown]. Drug condition did not affect the rated pleasantness of the smell of soup.

There was a significant time-drug interaction on the rated sweetness of Kool-Aid [$F(2,32) = 7.50$, $P < 0.003$; Fig. 1, *top left*]. As with soup, simple effects tests at 60 min revealed that Kool-Aid tasted less intense after placebo compared with naltrexone [$F(1,16) = 7.96$, $P < 0.02$]. In the placebo condition, the rated sweetness of Kool-Aid increased over time ($P < 0.03$), whereas after naltrexone there were no significant changes as a function of time (Fig. 1). Sweetness ratings increased with concentration [$F(3,48) = 200.89$, $P < 0.0001$; Fig. 1; data not shown]. The temperature-concentration interaction was significant [$F(3,48) = 4.43$, $P < 0.02$] with subjects rating cold 0.70 M sucrose Kool-Aid as sweeter than the same concentration at room temperature ($P < 0.02$). However, the difference in mean sweetness ratings was slight (8.7 vs. 8.5).

There was a significant time-drug-concentration interaction on the rated pleasantness of Kool-Aid [$F(6,96) = 2.84$, $P < 0.03$; Fig. 1, *bottom left*]. Simple effects revealed a time-drug interaction at 0.15 [$F(2,32) = 4.74$, $P < 0.02$] and 0.32 M sucrose [$F(2,29) = 5.68$, $P < 0.02$]. The effects were different at the different concentrations. At 0.15 M sucrose, Kool-Aid pleasantness increased slightly across time after the placebo, whereas the pleasantness of the same condition decreased slightly over time after naltrexone. At the higher sucrose concentration (0.32 M), Kool-Aid pleasantness remained stable (and high) in the placebo condition, whereas in the naltrexone condition, Kool-Aid pleasantness decreased during the 2nd h after drug administration.

*Food selection and intake.* Naltrexone had no effect on the caloric content or the macronutrient composition of the foods selected from the lunch menu. Subjects selected similar amounts of proteins, carbohydrates, and fats when on naltrexone or placebo. However, administration of naltrexone decreased actual caloric intake from 1,955 to 1,389 kcal [$F(1,16) = 8.10$, $P < 0.02$; Fig. 2]. Decreases among carbohydrates, fats, and proteins were not equal (Fig. 3). The proportion of calories contributed by fat showed a significant decrease from 45 to 41% [$F(1,16) = 5.34$, $P < 0.04$], and the proportion contributed by carbohydrates increased slightly but significantly from 40 to 45% [$F(1,16) = 5.69$, $P < 0.03$]. The proportion of calories from protein was unchanged.

*Hunger, fullness, nausea, and mood assessment.* Ratings of hunger were significantly less in the naltrexone condition [$F(1,15) = 4.99$, $P < 0.05$; Fig. 4]. Simple effects revealed a significant drug effect on the last hunger rating (~225 min after the drug was administered; $P < 0.05$). Ratings of nausea were significantly greater in the naltrexone condition [$F(1,15) = 6.05$, $P < 0.03$; Fig. 4].

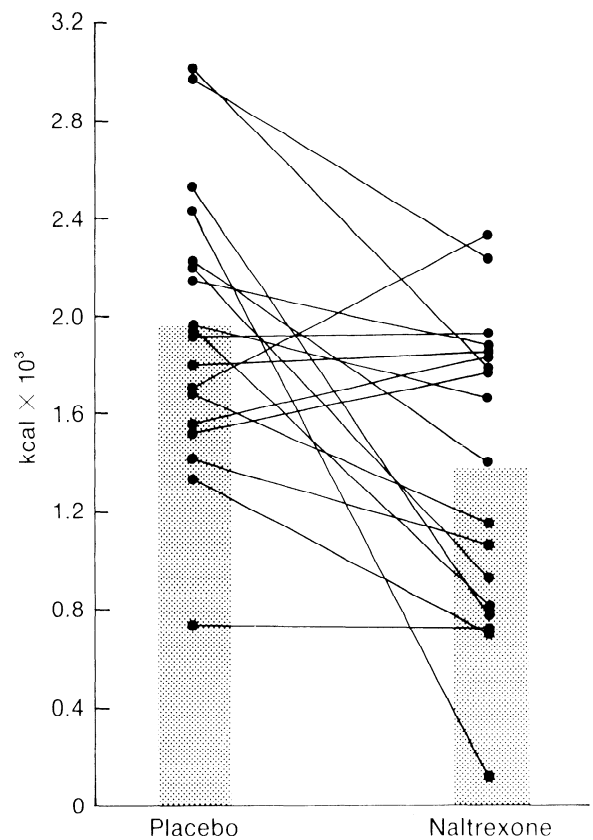


FIG. 2. Caloric intake under placebo and naltrexone conditions. Each pair of filled circles connected by a line represents amount of calories consumed under placebo (*left*) and naltrexone (*right*) by a subject. Bars, mean values for 18 subjects under 2 conditions.

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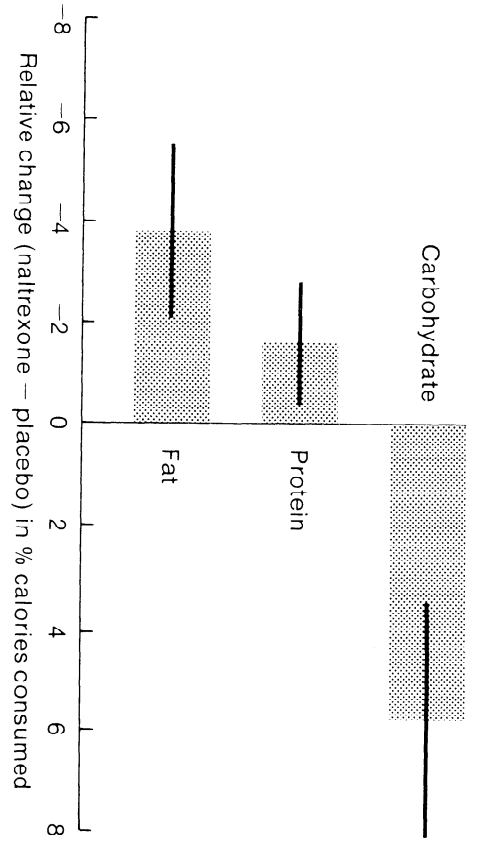


FIG. 3. Relative (naltrexone − placebo) changes in macronutrient consumption (means ± SE difference score).

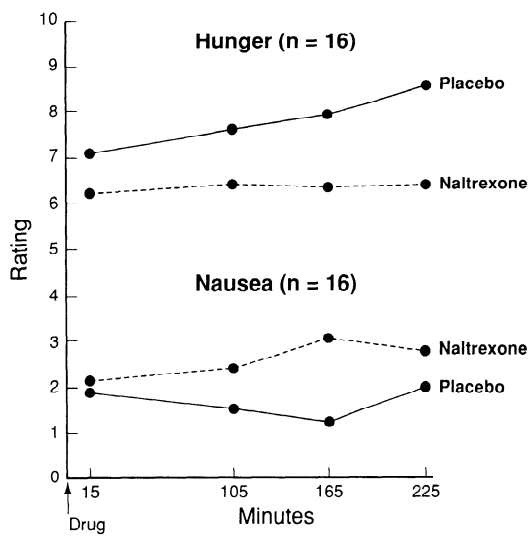


FIG. 4. Visual analog ratings of hunger (*top*) and nausea intensities (*bottom*) under naltrexone and placebo conditions.

Simple effects tests showed this effect after the first (105 min) and second (165 min) taste tests (Fig. 4). There was a tendency for the ratings of fullness to be greater in the naltrexone condition, although this was not statistically significant [$F(1,15) = 2.92$, $P < 0.11$]. Naltrexone-induced changes in mood were small. The only significant drug effect was in the feeling of competence; after naltrexone, subjects rated themselves as feeling less competent [$F(1,14) = 7.82$, $P < 0.02$].

*Analyses of covariance.* A number of analyses of covariance were performed on the pleasantness ratings of Kool-Aid and soup by use of the following covariates: sweetness or saltiness ratings, nausea ratings, and hunger ratings. It was found that none of these covariates could explain the significant differences in pleasantness ratings between the placebo and the naltrexone conditions.

The average pleasantness ratings of soup and the average pleasantness ratings of Kool-Aid during the taste test immediately before lunch (180 min after drug administration) were used as covariates in the analyses on the proportion of carbohydrate kilocalories and fat kilocalories consumed at lunch. The drug effect on the proportion of carbohydrate kilocalories consumed was no longer significant when Kool-Aid pleasantness ratings were covaried out of the analyses. Thus this drug effect may be due to alterations in the pleasantness of sweets.

Finally, 12 separate analyses were computed by use of fullness, hunger, and nausea as covariates to test whether the effects on total calories and proportion of carbohydrate, fat, and protein were mediated by fullness, hunger, and nausea. With hunger as the covariate, all significant effects of drugs on caloric, fat and carbohydrate intake were eliminated; thus differences in hunger (or some variable associated with it) would appear to explain differences in caloric intake and nutrient selection. The nausea covariate also eliminated significant effects on the selection of macronutrients but had no effect on total calories; fullness as a covariate had no effect.

## DISCUSSION

Opioid receptor blockade altered taste perception in fasted humans in a complex fashion. As lunch approached, the subjects under placebo assigned higher intensity ratings and pleasantness ratings to soup and Kool-Aid. Naltrexone treatment blocked this change, a result reminiscent of that from another study where naloxone blocked the decrease in electric taste threshold that occurred during presentation of food to fasted subjects (9). In other studies, naltrexone decreased the pleasantness of the taste of glucose solutions (6). The present study extended these previous findings by suggesting that naltrexone's effects on taste pleasantness were not related to naltrexone-induced effects on rated taste intensity. The significance of the dissociation of perceived intensity and pleasantness is unknown.

Naltrexone appears to prevent taste stimuli from becoming increasingly pleasant as food deprivation advances. Perhaps the increase in taste pleasantness that occurs during deprivation is produced by endogenous opioid release. In the food-deprived subjects, the taste of food may have stimulated opioid release, which enhanced the hedonic properties of tastes. Administration of naltrexone might block such an effect. A less likely explanation is that pleasantness was due to a placebo effect and not hunger and that naltrexone blocked the placebo effect (10).

In agreement with other studies, naltrexone produced a dramatic reduction in food intake (1, 17, 18). Unlike in previous studies, however, the reduced food intake was related to reduced hunger (6, 17, 18). The reason for the difference in the hunger effects in the present study and

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other previous studies is unknown. It may be related to the fact that in the present study the subjects showed high initial hunger ratings.

The decrease in the proportion of calories contributed by fat and the increase in the proportion contributed by carbohydrate were modest but quite consistent across subjects. Marks-Kaufman and Kanarek (13) reported decreased intake of fat calories and increased intake of carbohydrate calories in rats treated with naloxone. The current results also parallel studies where recently fed humans (8) reported low hunger levels and increased preferences for carbohydrate, similar to our subjects after ingesting naltrexone.

Although no relationships between taste ratings and total caloric intake were observed, the results do reveal an association between taste and nutrient selection. When Kool-Aid pleasantness ratings served as a covariate, the significant effect of drugs on proportion of carbohydrates consumed disappeared. Such results suggest that sweet tastes may mediate the effect of naltrexone on carbohydrate selection. This hypothesis requires further testing.

In summary, the opioid antagonist naltrexone affects many aspects of feeding: taste perception of food, hunger, nutrient selection, and caloric intake. The present study with humans suggests that naltrexone's effects on macronutrient selection are mediated by the sense of taste.

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REFERENCES

1. ATKINSON, R. L. Naloxone decreases food intake in obese humans. *J. Clin. Endocrinol. Metab.* 5: 196–198, 1982.
2. BERTINO, M., M. L. ABELSON, S. H. MARGLIN, R. NEUMAN, C. A. BRUKHARDT, AND L. D. REID. A small dose of morphine increases intake of and preference for salt solutions in rats. *Pharmacol. Biochem. Behav.* 29: 617–623, 1988.
3. BERTINO, M., G. K. BEAUCHAMP, AND K. ENGELMAN. Long-term reduction of dietary sodium alters the taste of salt. *Am. J. Clin. Nutr.* 36: 1134–1144, 1982.
4. BOND, A., AND M. LADER. The use of analogue scales in rating subjective feelings. *Br. J. Med. Psychol.* 47: 211–218, 1974.
5. COHEN, M. R., R. M. COHEN, D. PICKAR, AND D. L. MURPHY. Naloxone reduces food intake in humans. *Psychosom. Med.* 47: 132–138, 1985.
6. FANTINO, M., J. HOSOTTE, AND M. APFELBAUM. An opioid antagonist, naltrexone, reduces preference for sucrose in humans. *Am. J. Physiol.* 251 (*Regulatory Integrative Comp. Physiol.* 20): R91–R96, 1986.
7. FILE, S. E., AND T. SILVERSTONE. Naloxone changes self-ratings but not preference in normal subjects. *Psychopharmacology* 74: 353–354, 1981.
8. HILL, A. J., AND J. E. BLUNDELL. Macronutrients and satiety: the effects of a high protein or high carbohydrate meal on subjective motivation to eat and food preferences. *Nutr. Behav.* 3: 133–144, 1986.
9. KOMOROWSKI, J. M., AND J. KOMOROWSKA. Naloxone modulates gustatory perception, but not insulin and c-peptide release in sham-fed humans. *Int. J. Obesity* 10: 83–89, 1986.
10. LEVINE, J. D., N. C. GORDON, AND H. L. FIELDS. The mechanism of placebo analgesia. *Lancet* 2: 654–657, 1978.
11. MALLER, O., A. CARDELLO, J. SWEENEY, AND D. SHAPIRO. Psychophysical and cognitive correlates of discretionary usage of table salt and sugar by humans. In: *Determination of Behavior by Chemical Stimuli,* edited by J. E. Steiner and J. R. Ganchrow. London: JRL, 1982, p. 205–216.
12. MARKS-KAUFMAN, R. Increased fat consumption by morphine administration in rats. *Pharmacol. Biochem. Behav.* 16: 949–955, 1982.
13. MARKS-KAUFMAN, R., AND R. B. KANAREK. Modifications in nutrient selection induced by naloxone in rats. *Psychopharmacology* 74: 321–324, 1981.
14. MORLEY, J. E., S. PARKER, AND A. S. LEVINE. Effect of butorphanol tartrate on food and water consumption in humans. *Am. J. Clin. Nutr.* 42: 1175–1178, 1985.
15. O'BRIEN, C. P., A. J. STUNKARD, AND J. W. TERNES. Absence of naloxone sensitivity in obese humans. *Psychosom. Med.* 44: 215–217, 1982.
16. REID, L. D. Endogenous opioid peptides and regulation of drinking and feeding. *Am. J. Clin. Nutr.* 42: 1099–1132, 1985.
17. THOMPSON, D. A., S. L. WELLE, U. LILAVIVAT, L. PENICAUD, AND R. G. CAMPBELL. Opiate receptor blockade in man reduces 2-deoxy-D-glucose-induced food intake but not hunger, thirst and hypothermia. *Life Sci.* 31: 847–852, 1982.
18. TRENCHARD, E., AND T. SILVERSTONE. Naloxone reduces the food intake of normal human volunteers. *Appetite* 4: 43–50, 1983.

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