Pharmacology Biochemistry and Behavior, Vol. 62, No. 2, pp. 203–208, 1999

0091-3057/99 $–see front matter

PII S0091-3057(98)00148-8

Altering Dietary Levels of Protein or Vitamins and Minerals Does Not Modify Morphine-Induced Analgesia in Male Rats

ROBIN B. KANAREK, KRISTEN E. D'ANCI, JEANNE M. PRZYPEK AND WENDY FOULDS MATHES

Department of Psychology, Tufts University, Medford, MA 02155

Received 29 October 1997; Revised 16 March 1998; Accepted 24 March 1998

KANAREK, R. B., K. E. D'ANCI, J. M. PRZYPEK AND W. F. MATHES. *Altering dietary levels of protein or vitamins and minerals does not modify morphine-induced analgesia in male rats.* PHARMACOL BIOCHEM BEHAV **62**(2) 203–208, 1999.—Previous research has demonstrated that chronic intake of nutritive sweet solutions, but not nonnutritive sweet solutions, enhances morphine's analgesic potency. To separate out the effects of sweet taste from other changes in dietary intake, which result when rats consume a sucrose solution, the effects of altering dietary levels of protein, or vitamins and minerals on morphine-induced analgesia were examined. In Experiment 1, 40 male Long–Evans rats were fed standard chow or a semipurified diet containing either 10, 20, or 40% protein. Three weeks later, antinociceptive responses to morphine were examined using the tail flick procedure. Tail flick latencies were measured immediately prior to and 30, 60, and 90 min after the administration of morphine sulfate (0.0, 1.25, 2.5, and 5.0 mg/kg, SC). At all three measurement times, antinociceptive responses increased directly as a function of the dose of morphine, but did not differ as a function of diet. In Experiment 2, 24 rats were maintained on either standard laboratory chow or semipurified diets containing 20% protein and either 100% or 25% of the recommended levels of vitamins and minerals for 3 weeks. Tail flick latencies were measured immediately prior to and 30 min after injections (SC) of 2.5 mg/kg morphine sulfate. This procedure was repeated until a cumulative dose of 10.0 mg/kg was obtained. Tail flick latencies increased significantly as a function of drug dose, but did not differ across dietary conditions. These results demonstrate that the increase in morphine-induced analgesia seen in rats consuming a sucrose solution is not due to alterations in either protein or micronutrient intake. © 1999 Elsevier Science Inc.

Morphine Analgesia Protein Vitamins Minerals Tail flick Diet Antinociception

RECENT studies have demonstrated that prolonged intake of palatable fluids alters the antinociceptive actions of opioid drugs in experimental animals [e.g. (4,7,10,11,15,16,20,25,27, 31,36). However, the results of these studies are not consistent. Intake of sweet solutions has been found to both increase (10,11,16,25,27,36) and decrease (4,7,15,20,31) sensitivity to the antinociceptive properties of opioid drugs. For example, morphine-induced analgesia is enhanced in rats drinking a caloric sucrose or Polycose solution in addition to water relative to controls given only water (10,11,25,27,36). In contrast, morphine-induced analgesia is not affected or reduced in rats chronically consuming sweet tasting but minimally caloric saccharin solutions (4,7,10,11,20,31).

The differences observed in morphine-induced analgesia following chronic intake of a caloric sweet solution vs. a noncaloric sweet solution may be related to alterations in nutrient intakes. When rats are given water, laboratory chow and a palatable nutritive solution (e.g., a 32% sucrose or Polycose solution), they consume approximately 50% of their calories from the solution and 50% from chow. Because chow contains 20–25% protein, in this situation, protein intake is reduced to 10–12% of total caloric intake. Additionally, the vitamin and mineral content of the diet is decreased by half. In contrast, when a nonnutritive saccharin solution is provided, neither protein nor vitamin and mineral intakes are reduced. Thus, it is possible that the elevation in morphine-induced analgesia seen in conjunction with the chronic intake of caloric sweet solutions is a consequence of reduced intake of protein or vitamins and minerals. To determine if reductions in protein or micronutrient intake contribute to alterations in mor-

Requests for reprints should be addressed to Robin B. Kanarek, Department of Psychology, Research Building, 490 Boston Ave., Tufts University, Medford, MA 02155.

phine-induced analgesia observed in rats drinking a palatable caloric solution, the present studies examined the effects of altering dietary levels of protein and vitamins and minerals on morphine's antinociceptive properties.

EXPERIMENT 1

This experiment examined the effects of alterations in dietary protein levels on morphine-induced analgesia. Animals were divided into four dietary groups. Animals in the first group received ground Purina chow, the diet used in most previous studies assessing the effects of nutritional variables on the actions of opioid drugs (10,11,16,25–27). The second group was fed a semipurified diet containing a level of protein (20%) similar to that found in Purina chow. The third group was fed a semipurified diet containing 10% protein. The amount of protein consumed by these animals thus was similar to that of rats that reduce chow intake by approximately 50% when given a sucrose solution as an additional source of calories (10,11,16,25–27). The final group was fed a 40% protein diet because previous work suggested that high protein diets might enhance morphine's analgesic potency (5). Because previous research indicated that chronic but not acute exposure to sucrose solutions increased morphine-induced analgesia (10), rats were maintained on the diets for 3 weeks before nociceptive tests were conducted.

METHOD

Animals

Forty male VAF Long–Evans rats (Charles River Laboratories, Kingston, NY), weighing 200–-250 g at the beginning of the experiment, were used. Animals were housed individually in standard stainless-steel cages in a temperature-controlled room (21 ± 1°C) maintained on a reverse 12 L:12 D cycle (lights on: 2000 h).

Diets

Animals were matched on the basis of body weight, and then assigned to one of four dietary groups. Each group (n = 10) was given ad lib access to tap water and either ground Purina Laboratory Rodent Chow #5001 (3.3 kcal/g) or a semipurified diet containing 10, 20, or 40% protein (Table 1). All diets were presented in Wahmann LC-306A nonspill food cups. Food and fluid intakes and body weights were measured for 3 weeks prior to the initiation of nociceptive tests.

Drugs

Morphine sulfate (generously supplied by the National Institute on Drug Abuse) was dissolved in 0.9% sterile saline and administered subcutaneously in a volume of 1 ml/kg.

Procedure

Pain sensitivity was assessed using the tail-flick test (9). Animals were placed on the tail-flick apparatus (Endie Instrument Co., Montpelier, VT) with their tails gently smoothed into a groove containing a photocell. A light source was activated, which terminated when the animal moved its tail or after 9 s had elapsed. A cutoff time of 9 s was chosen to prevent tissue damage to the animal's tail. During all tests, rats were gently held with a clean cloth by the same experimenter. Baseline tail-flick latencies were determined by using the median of three tail-flick tests separated by approximately 15 s. Animals then were injected with morphine sulfate (0.0, 1.25, 2.5, and 5.0 mg/kg, SC) and tail flick latencies measured 30, 60, and 90 min after injections. Each animal received each dose of morphine. Drug injections were given in a random order to animals with a minimum of 5 days intervening between injections.

All procedures were approved by the Tufts University Institutional Animal Care and Use Committee.

Data Analysis

One-way analyses of variance were used to analyze daily food intake and body weight data.

Prior to statistical analysis, antinociceptive data were converted to percent maximal possible effect (%MPE) which was calculated as follows: %MPE= [(test tail flick latency − baseline latency)/(maximal latency − baseline latency)] × 100. Maximal latency was the cutoff time of 9 s. Data then were analyzed with two-way ANOVAs (diet by dose) with dose as a repeated measure.

RESULTS

Food Intake and Body Weight

Daily food intake varied significantly as a function of diet, $F(3, 39) = 18.28$, $p < 0.05$. Rats fed laboratory chow ate significantly more food per day than rats fed any of the semipurified protein diets (Table 2). Because the caloric content of the chow diet (3.3 kcal/g) and the protein diets (4.1 kcal/g) differed, food intake also was calculated on a kilocalorie basis.

TABLE 1
COMPOSITION OF PROTEIN DIETS

10% Protein	20% Protein	40% Protein	
100 g	200 g	400 g	Casein (ICN Biomedicals, Aurora, OH)
400g	350g	250g	Cornstarch (Harlan, Teklad Diets, Madison, WI)
400 g	350 g	250 g	Dextrin (Harlan, Teklad)
50 g	50 g	50 g	Safflower Oil (Hollywood Foods)
40 g	40 g	40 g	AIN Salt Mix (ICN Biomedicals)
30 g	30 g	30 g	Vitamin Fortification Mix (ICN Biomedicals)
1 g	1 g	1 g	DL-Methionine (ICN Biomedicals)

Each diet contained 4.1 kcal/g. Energy intake of the diets was calculated using 4 kcal/g for protein and carbohydrate, and 9 kcal/g for safflower oil. The Vitamin Fortification Mix contains dextrose as a medium for the vitamins, which added approximately 116 kcal to each diet.

No differences in energy intake were observed as a function of dietary conditions (Table 2). Although rats fed chow or the 40% protein diet gained more weight across the experiment than rats fed either the 20% or 10% protein diet, this difference was not significant (Table 2).

Antinociceptive Response

Averaged across injection days, baseline tail-flick latencies did not differ as a function of diet (chow = 2.48 ± 0.47 s; 10% protein diet = 2.21 ± 0.35 s; 20% protein diet = 2.37 ± 0.52 s; 40% protein diet = 2.33 ± 0.86 s). %MPEs increased significantly as a function of drug dose 30, $F(3, 144) = 59.55$, $p < 0.001$, 60, $F(3, 144) = 25.32$, $p < 0.001$, and 90 min, $F(3, 144) = 17.25$, $p < 0.001$, following drug injections (Fig. 1). However, at no time point did antinociceptive responses differ as a function of diet.

EXPERIMENT 2

Experiment 2 examined the effects of altering the levels of micronutrients in the diet on morphine-induced analgesia. One group of animals was fed Purina chow. A second group was given the 20% diet used in the previous study with the same level of vitamins and minerals as used in Experiment 1 (100% group). The third group was given the 20% diet, with 25% of the recommended level of micronutrients for rats (6). Preliminary studies in the laboratory demonstrated no differences in morphine-induced analgesia between rats given diets containing either 100% or 50% of the recommended levels of micronutrients. Thus, in the present experiment, a lower level of micronutrients was used.

METHOD

Animals

Twenty-four male VAF Long–Evans rats (Charles River Laboratories, Kingston, NY), weighing 250–275 g at the beginning of the experiment, were used. Animals were housed individually in standard stainless steel cages in a temperature-controlled room (21 ± 11°C) maintained on a reverse 12 L:12 D cycle (lights on:2000 h).

Diets

Animals were randomly assigned to one of three groups. Each group ($n = 8$) was given ad lib access to tap water and either ground Purina Laboratory Rodent Chow #5001 or a semipurified diet containing the 20% protein diet used in Ex-

TABLE 2

MEAN (±SD) DAILY FOOD AND CALORIC INTAKE AND BODY WEIGHT GAIN FOR RATS FED EITHER LABORATORY CHOW OR A SEMIPURIFIED DIET CONTAINING EITHER 40, 20, OR 10% PROTEIN

Diet	Food Intake	Caloric Intake	Body Weight Gain Across The Experiment
Chow	27.5 ± 0.9 g*	90.8 ± 3.0 kcal	153.9 ± 36.5 g
40% Protein	22.6 ± 0.8 g	92.7 ± 3.3 kcal	162.1 ± 33.0 g
20% Protein	20.7 ± 0.7 g	84.9 ± 2.9 kcal	141.5 ± 33.8 g
10% Protein	20.9 ± 0.5 g	85.8 ± 2.0 kcal	137.5 ± 18.3 g

*Food intake of rats fed chow significantly ($p < 0.05$) greater than intakes of rats in other dietary conditions.

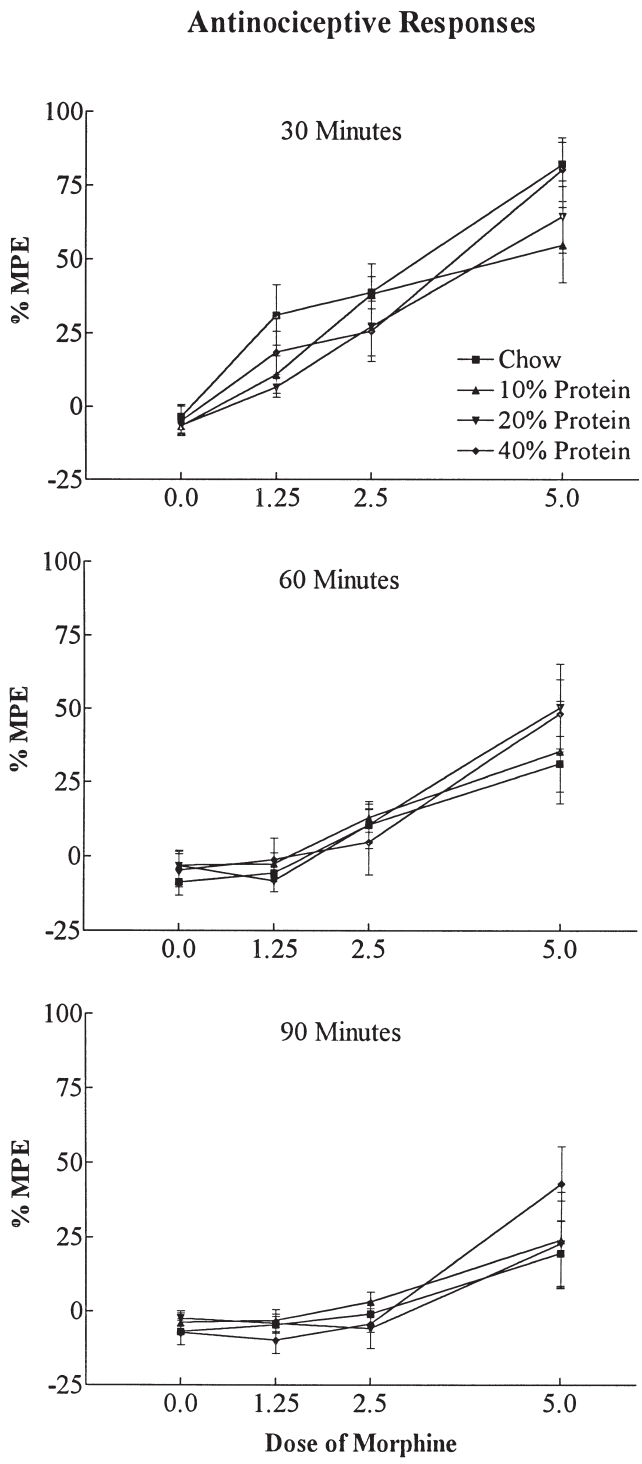

FIG. 1. Mean ± SEM percent maximal possible effects (%MPEs) 30, 60, and 90 min following morphine administration for rats fed ground Purina chow or semipurified diets containing either 10, 20, or 40% protein.

periment 1 with either 100% or 25% of the recommended allowance of vitamins and minerals for rats (6). All diets were presented in Wahmann LC-306A nonspill food cups. Food and fluid intakes and body weights were measured daily for 3 weeks prior to the nociceptive tests.

Drugs

Morphine sulfate was dissolved in 0.9% sterile saline at a concentration of 2.5 mg/kg. The drug was administered subcutaneously in a volume of 1 ml/kg.

Procedure

Pain sensitivity was tested using the tail-flick test described in Experiment 1. On the day of nociceptive testing, baseline tail flick latencies were determined using the median of three tail-flick tests, separated by approximately 15 s. Because maximal antinociceptive responses were observed 30 min following drug injections in Experiment 1, a cumulative dosing regime in which drug injections were separated by 30 min was used in this study. Immediately after determining baseline latencies, rats were injected with 2.5 mg/kg morphine and returned to their cages for 30 min. Tail-flick latencies then were measured again and rats injected with 2.5 mg/kg morphine. This procedure was repeated until a cumulative dose of 10.0 mg/kg was obtained.

Data Analysis

Food and body weight data were analyzed as described in Experiment 1. Antinociceptive responses were analyzed using a two-way ANOVA (diet by dose), with dose as a repeated measure.

RESULTS

Food Intake and Body Weight

Daily food intake differed significantly as a function of diet, $F(2, 23) = 33.58$, $p < 0.01$. Rats fed chow (28.8 g ± 0.75) ate significantly more food than rats fed either the 100% (23.5 g ± 0.52) or 25% (21.5 g ± 0.66) diet. Additionally, food intake of rats fed the 100% diet was significantly greater than that of rats fed the 25% diet. Caloric intake also varied as a function of diet, $F(2, 23) = 3.39$, $p < 0.05$, with rats fed the 100% diet consuming significantly more calories a day than rats fed the 25% diet (chow = 95.0 ± 2.5 kcal/day; 100% diet = 96.3 ± 2.1 kcal/day; and 25% diet = 88.2 ± 2.7 kcal/day). On the day of testing, body weights differed as a function of diet, $F(2, 23) = 5.05$, $p < 0.05$. Rats eating either chow (405.25 g ± 9.32) or the 100% diet (402.1 g ± 9.6) weighed significantly ($ps < 0.05$) more than those eating the 25% diet (369.5 g ± 7.4).

Antinociceptive Response

Baseline tail-flick latencies did not differ as a function of diet (chow = 2.7 ± 0.19 s; 100% diet = 2.9 ± 0.28 s; 25% diet = 2.9 ± 0.41 s). Antinociceptive responses increased significantly, $F(3, 71) = 16.52$, $p < 0.05$, as a function of drug dose. However, %MPEs did not differ as a function of diet, $F(2, 23) = 1.34$, $p = 0.28$ (Fig. 2).

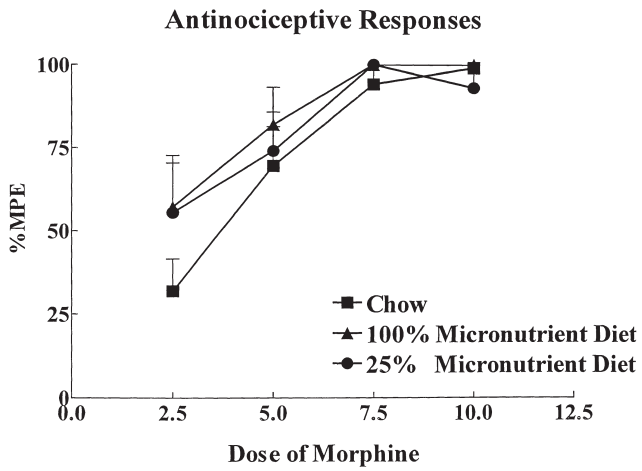

FIG. 2. Mean ± SEM percent maximal possible effects (%MPEs) following cumulative morphine administration for rats fed ground Purina chow or semipurified diets containing either 100 or 25% of the recommended allowance for vitamins and minerals for rats.

GENERAL DISCUSSION

The results of Experiment 1 indicate that the increase in morphine-induced analgesia seen in rats chronically consuming a nutritive sucrose solution (10,11,16,24,27) is not due to a reduction protein intake. No differences in antinociceptive responses to morphine were observed as a function of the protein content of the diet. These findings can be contrasted with the results of previous studies that demonstrated a direct relation between dietary protein content and the analgesic potency of morphine (5). One possible reason for this difference was level of protein tested. In the present study, the lowest level of protein used was 10%, which is above that needed by the adult rat for normal physiological functioning (19). In contrast, in previous work (5), diets with as little as 4% protein were used. These low protein diets may have compromised the health of the animals, and thereby altered the sensitivity of the animals to morphine's analgesic properties. Results of Experiment 2 provide evidence that alterations in micronutrient intake also do not contribute to the increase in morphine-induced analgesia observed in rats chronically consuming sweet-tasting nutritive solutions.

From the results of the present experiments, it cannot be concluded that a combination of reducing protein and micronutrient intake as occurs in rats drinking a sucrose solution would not affect morphine-induced analgesia. However, ongoing studies in our laboratory suggest that the decrease in intake of these essential nutrients is not responsible for the alterations in the actions of opioid drugs observed in rats consuming sucrose. In a number of studies it has been found that rats given a sucrose solution in addition to standard laboratory chow and water for extended periods (up to 20 months) continue to gain weight at levels similar to or greater than those of rats fed only chow, and suffer no observable nutritional deficiencies (21,22,24). Additionally, research investigating sucrose intake as a function of dietary protein and micronutrient levels suggests that rats regulate sucrose intake to maintain intakes of protein and micronutrients at levels sufficient for normal growth and development (24). For example, sucrose intake varied directly as a function of percent protein in rats given diets containing 10, 20, or 40% protein (24), but in all cases percent protein intake remained above the recommended minimal protein intake for adult rats (19).

Over the past 10 years, substantial evidence has accumulated for an interaction between intake of palatable foods and

fluids and the endogenous opioid system. Original support for this interaction came from studies showing that in both experimental animals and humans administration of opioid agonists and antagonists altered intake of palatable (high sucrose and/or high fat) foods and fluids to a greater degree than intake of less palatable fare [e.g. (1,8,12,13,18,29,32–34,37,40)]. Subsequent studies have demonstrated that the effects of opioid agents on intake of palatable foods and fluids are mediated centrally, most likely, in areas associated with feeding behavior (2,3,17,28,30,41).

There is also behavioral and physiological evidence that intake of palatable foods and fluids alters the activity of the endogenous opioid system. As previously stated, a number of researchers have found that long-term intake of palatable nutritive fluids increases the analgesic actions of morphine and other opioid agonists (10,11,16,25,27,36). Additionally, it has been reported that intake of high-sucrose items enhances the anorectic potency of opioid antagonists (26,37,39). The results of these studies suggest that chronic consumption of nutritive sweet tasting foods and fluids either stimulates the release of endogenous opioid peptides or alters opioid receptor binding. In support of this suggestion, Dum and colleagues (14) reported that intake of palatable foods increased the amount of beta-endorphin occupying hypothalamic receptors. More recently, it was observed that proDynorphin mRNA levels were elevated in the arcuate nucleus of rats given ad lib access to a high-sucrose/high-fat diet relative to animals fed a cornstarch based diet (38). Additionally, other studies have found that chronic intake of palatable sucrose solutions and high-fat diets increases whole-brain opioid receptor binding in rats and mice (23,35).

Although the preceding studies indicate that a relation exists between intake of palatable items and the endogenous opioid system, they do not provide a clear answer to the question of why nutritive and nonnutritive sweet-tasting fluids differentially affect morphine's analgesic actions. One explanation is that nonnutritive solutions containing saccharin are not palatable to rats. This seems unlikely, however, as intake of saccharin is equal to or greater than intake of sucrose in rats given a choice of one of these palatable solutions and water (11). A second possibility is that nutritive and nonnutritive sweet solutions differentially affect the endogenous opioid system. Support for this idea comes from experiments demonstrating that central administration of mu antagonists reduced sucrose intake, but not saccharin intake, while delta antagonists decreased saccharin but not sucrose intake (2,3). Along similar lines, sucrose intake in sham-fed rats was reduced by mu and kappa opioid antagonists, but not by delta antagonists (30). Studies examining opioid receptor binding also suggest that sucrose and saccharin have disparate effects on the endogenous opioid system. For example, compared to rats drinking only water, rats given a sucrose solution and water displayed a significant increase in whole brain opioid receptor binding affinity, while rats given a saccharin solution and water exhibited a significant reduction in receptor binding affinity (23). Future studies are planned to determine if these palatable solutions have different effects on mu, kappa, and delta opioid receptors.

Although the results of these experiments are negative with respect to the effects of dietary protein and micronutrient levels, they are important because they indicate that alterations in intakes of these nutrients are not responsible for the enhancement of morphine-induced analgesia seen in rats given chronic access to a sucrose solution.

ACKNOWLEDGEMENTS

This research was supported by a grant (#DA04132) from the National Institute on Drug Abuse to Robin B. Kanarek.

REFERENCES

1. Apfelbaum, M.; Mandenoff, A.: Naltrexone suppresses hyperphagia induced in the rat by a highly palatable diet. Pharmacol. Biochem. Behav. 15:89–91; 1981.
2. Beczkowska, I. W.; Bowen, W. D.; Bodnar, R. J.: Central opioid receptor subtype antagonists differentially alter sucrose and deprivation-induced water intake in rats. Brain Res. 589:291–301; 1992.
3. Beczkowska, I. W.; Koch, J. E.; Bostock, M. E.; Leibowitz, S. F.; Bodnar, R. J.: Central opioid receptor subtype antagonists differentially reduce intake of saccharin and maltose dextrin solutions in rats. Brain Res. 618:261–279; 1993.
4. Bergman, F.; Lieblich, I.; Cohen, E.; Ganchrow, J. R.: Influence of intake of sweet solutions of the analgesic effect of a low dose of morphine in randomly bred rats. Behav. Neural Biol. 44:347–353; 1985.
5. Bhargava, H. N.; Bansinath, M.; Das, S.; Matwynshyn, G. A.: Multiple opiate receptors and pharmacological response to morphine in rats maintained on diets differing in protein concentration. Gen. Pharmacol. 18:505–512; 1987.
6. Bieri, J. G.; Stoewsand, G. S.; Briggs, G. M.; Phillips, R. W.; Woodward, J. M.; Knapka, J. J.: Report of the American Institution of Nutrition Ad Hoc Committee on Standards for Nutritional Studies. J. Nutr. 107:1340–1348; 1977.
7. Calcagnetti, D. J.; Holtzman, S. G.: Intake of sweet water attenuates restraint-stress-induced potentiation of morphine analgesia in rats. Brain Res. Bull. 29:859–864; 1992.
8. Cooper, S. J.: Effects of opiate agonists and antagonists on fluid intake and saccharin choice in the rat. Neuropharmacology 22: 323–328; 1983.
9. D'Amour, F. E.; Smith, D. L.: A method for determining loss of pain sensation. J. Pharmacol. Exp. Ther. 72:74–79; 1941.
10. D'Anci, K. E.; Kanarek, R. B.; Marks-Kaufman, R.: Duration of sucrose availability differentially alters morphine-induced analgesia in rats. Pharmacol. Biochem. Behav. 54:693–-697; 1996.
11. D'Anci, K. E.; Kanarek, R. B.; Marks-Kaufman, R.: Beyond sweet taste: Saccharin, sucrose, and Polycose differ in their effects upon morphine-induced analgesia. Pharmacol. Biochem. Behav. 56:341–345; 1997.
12. Drewnowski, A.; Krahn, D. D.; Demitrack, M. A.; Naim, K.; Gosnell, B. A.: Taste responses and preferences for sweet foods: Evidence for opioid involvement. Physiol. Behav. 51:371–379; 1992.
13. Drewnowski, A.; Krahn, D. D.; Demitrack, M. A.; Naim, K.; Gosnell, B. A.: Naloxone, an opiate blocker, reduces the consumption of sweet high-fat foods in obese and lean female binge eaters. Am. J. Clin. Nutr. 61:1206–1211; 1995.
14. Dum, J.; Gransch, C.; Herz, A.: Activation of hypothalamic beta-endorphin pools by reward induced by highly palatable foods. Pharmacol. Biochem. Behav. 18:443–447; 1983.
15. Fidler, P.; Kalman, B. A.; Ziemer, H. E.; Green, K. F.: Early onset of reduced morphine analgesia by ingestion of sweet solutions. Physiol. Behav. 53:167–171; 1993.
16. Frye, C. A.; Cuevas, C. A.; Kanarek, R. B.: Diet and estrous cycle influence pain sensitivity in female rats. Pharmacol. Biochem. Behav. 45:255–260; 1993.
17. Gosnell, B. A.; Majchrzak, M. J.: Centrally administered opioid peptide stimulate saccharin intake in nondeprived rats. Pharmacol. Biochem. Behav. 33:805–810; 1989.
18. Gosnell, B. A.; Krahn, D. D.; Majchrzak, M. J.: The effects of morphine on diet selection are dependent upon baseline diet preferences. Pharmacol. Biochem. Behav. 37:207–212; 1990.
19. Hegsted, D. M.; Neff, R.: Efficiency of protein utilization in

young rats at various levels of intake. J. Nutr. 100:1173–1180; 1970.
20. Holder, M. D.; Bolger, G. T.: Chronic sweet intake lowers pain thresholds without changing brain mu- or delta-opiate receptors. Behav. Neural. Biol. 50:335–343; 1988.
21. Kanarek, R. B.; Hirsch, E.: Dietary-induced overeating in experimental animals. Fed. Proc. 36:154–158; 1977.
22. Kanarek, R. B.; Marks-Kaufman, R.: Developmental aspects of sucrose-induced obesity in rats. Physiol. Behav. 23: 881–885; 1979.
23. Kanarek, R. B.; Marks-Kaufman, R.: Animal models of appetitive behavior: Interaction of nutritional factors and drug seeking behavior. In: Winck, W., ed. Control of appetite. New York: John Wiley & Sons, pp. 1–25; 1988.
24. Kanarek, R. B.; Aprille, J. R.; Hirsch, E.; Gualtiere, L.; Brown, C.: A. Sucrose-induced obesity: Effect of diet on obesity and brown adipose tissue. Am. J. Physiol. 253: R158–R166; 1987.
25. Kanarek, R. B.; White, E. S.; Biegen, M.T.; Marks-Kaufman, R.: Dietary influences on morphine-induced analgesia in rats. Pharmacol. Biochem. Behav. 38:681–684; 1991.
26. Kanarek, R. B.; Mathes, W. F.; Heisler, L. K.; Lima, R. P.; Monfared, L. S.: Prior exposure to palatable solutions enhances the effects of naltrexone on food intake in rats. Pharmacol. Biochem. Behav. 57:377–381; 1997.
27. Kanarek, R. B.; Przypek, J.; D'Anci, K.; Marks-Kaufman, R.: Dietary modulation of mu- and kappa-opioid receptor mediated analgesia. Pharmacol. Biochem. Behav. 58:43–49; 1997.
28. Kelly, A. E.; Bless, E. P.; Swanson, C. J.: Investigation of the effects of opiate antagonists infused into the nucleus accumbens on feeding and sucrose drinking in rats. J. Pharmacol. Exp. Ther. 278:1499–1507; 1996.
29. Kirkham, T. C.; Cooper, S. J.: Naloxone attenuation of sham feeding is modified by manipulation of sucrose concentration. Physiol. Behav. 44:491–494; 1988.
30. Leventhal, L.; Kirkham, T. C.; Cole, J. C.; Bodnar, R. J.: Selective actions of central mu and kappa opioid antagonists upon sucrose intake in sham-fed rats. Brain Res. 685:205–210; 1995.
31. Lieblich, I.; Cohen, E.; Ganchrow, J. R.; Blass, E. M.; Bergmann, F.: Chronically elevated intake of saccharin solution induced morphine tolerance in genetically selected rats. Science 221:871–873; 1983.
32. Lynch, W. C.; Libby, L.: Naloxone suppresses intake of highly preferred saccharin solutions in food deprived and sated rats. Life Sci. 33:1909–1914; 1983.
33. Marks-Kaufman, R.; Kanarek, R. B.: Morphine selectively influences macronutrient intake in the rat. Pharmacol. Biochem. Behav. 12:427–430; 1980.
34. Marks-Kaufman, R.; Kanarek, R. B.: Modifications of nutrient selection induced by naloxone in rats. Psychopharmacology (Berlin) 74:321–324; 1981.
35. Marks-Kaufman, R.; Hamm, M. W.; Barbato, G. F.: The effects of dietary sucrose on opiate receptor binding in genetically obese (ob/ob) and lean mice. J. Am. Coll. Nutr. 8:9–14; 1990.
36. Roane, D. S.; Martin, R. J.: Continuous sucrose feeding decreases pain threshold and increases morphine potency. Pharmacol. Biochem. Behav. 35:225–229; 1990.
37. Rudski, J. M.; Billington, C. J.; Levine, A. S.: A sucrose-based maintenance diet increases sensitivity to appetite suppressant effects of naloxone. Pharmacol. Biochem. Behav. 58:679–682; 1997.
38. Welch, C. C.; Kim, E.-M.; Grace, M. K.; Billington, C. J.; Levine, A. S.: Palatability-induced hyperphagia increases hypothalamic dynorphin peptide and mRNA levels. Brain Res. 721:126–-131; 1996.
39. Yeomans, M. R.; Clifton, P. G.: Exposure to sweetened solutions enhances the anorectic effect of naloxone but not d-fenfluramine. Physiol. Behav. 62:255–262; 1997.
40. Yeomans, M. R.; Wright, P.; Macleod, H. A.; Critchely, J. A.: Effects of nalmefene on feeding in humans. Psychopharmacology (Berlin) 100:426–432; 1990.
41. Zhang, M.; Kelley, A. E.: Opiate agonists microinjected into the nucleus accumbens enhance sucrose drinking in rats. Psychopharmacology (Berlin) 132:350–360; 1997.