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Beyond Sweet Taste: Saccharin, Sucrose, and Polycose Differ in Their Effects Upon Morphine-Induced Analgesia

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D'ANCI, K. E., R. B. KANAREK, R. MARKS-KAUFMAN. *Beyond sweet taste: Saccharin, sucrose, and Polycose differ in their effects upon morphine-induced analgesia.* PHARMACOL BIOCHEM BEHAV **56**(3) 341–345, 1997.—The effects of saccharin, sucrose, or Polycose intake on morphine-induced analgesia (MIA) were examined in 40 adult male Long-Evans rats. Rats were tested for MIA on a tail-flick apparatus following acute (5-h) and chronic (3-wk) intake of a 0.15% saccharin solution, a 32% sucrose solution, a 33.68% Polycose solution, or water. During the chronic phase, all rats were given a choice between the test solution and water. Morphine sulfate was administered according to a cumulative dosing procedure beginning with 2.5 mg/kg morphine. The same dose was administered every 30 min. Tail-flick latencies were measured immediately prior to injections and 30 min following each injection. After acute intake of flavored solutions or water, there were no differences in MIA as a function of diet. However, after drinking the flavored solutions or water for three weeks rats drinking Polycose or sucrose showed significantly enhanced MIA relative to rats drinking saccharin. Rats drinking Polycose also showed enhanced MIA relative to rats drinking water. Comparison between the acute and chronic phases of the study demonstrated that tolerance to morphine's analgesic effects did not develop in rats drinking Polycose or sucrose, but did develop in rats drinking saccharin or water. The results support the hypothesis that, in addition to palatability, the nutritive value of flavored solutions influences MIA. **Copyright © 1997 Elsevier Science Inc.**

Morphine Analgesia Pain Sucrose Polycose Saccharin Rats Opiates Palatability Sweet taste Polysaccharide Mu receptor Tail-flick Tolerance

CHANGES in the analgesic potency of morphine following consumption of palatable foods provide evidence of a link between the hedonic properties of foods and the endogenous opioid system (e.g., 16,19,23,24). The effect of sweet-tasting substances in moderating morphine-induced analgesia (MIA) is well established (e.g., 3,4,7,12,16). However, intake of sweet substances does not always produce the same alteration in MIA. Some research shows that intake of sweet solutions reduces sensitivity to morphine's analgesic properties (3,9,12), whereas other research shows sweet intake increases sensitivity to the pain relieving effects of morphine (7,10,15,16,23). One explanation for these discrepant findings relates to differences in the sweet substances presented to the animals. Rats given access to a sweet saccharin cocktail show suppressed MIA (3,9,12) while rats given sucrose solutions show enhanced MIA (16,23). Although these stimuli are sweet and are readily consumed by rats, they differ in caloric content.

In addition to sweet solutions, other palatable nutritive substances may affect the endogenous opioid system (27). Polycose, like sucrose, is a carbohydrate. Although it is not sweet tasting like sucrose, there is a strong positive response to Polycose. Rats will readily consume it and prefer it to sucrose and maltose (25). Polycose does not produce the same taste sensation as sucrose, as measured by its effects on cephalic phase insulin release (26), on the nucleus tractus solitarius (11) or on the chorda tympani nerve (26). These findings suggest that Polycose would be a useful tool in determining the relative roles of sweetness and palatability in the dietary mediation of MIA.

The purpose of the present experiment was to compare the effects of caloric and non-caloric palatable solutions on MIA. Furthermore, the caloric solutions were divided into sweet (sucrose) and non-sweet (Polycose) palatable solutions. Previous research (7) suggests that there are differences in dietary-mediated MIA resulting from duration of exposure to palatable fluids. Rats were tested for MIA following acute

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(5 h) and chronic (3 wk) access to a saccharin solution, a sucrose solution, a Polycose solution, or tap water.

METHOD

Animals

Forty male Long-Evans VAF rats (Charles River, Portage, MI), weighing between 225-250 g at the beginning of the experiment, were used. Animals were individually housed in standard hanging stainless-steel cages in a temperature-controlled room (22 ± 2°C), maintained on a 12:12 h reverse light-dark cycle (lights on at 2000 h). All manipulations were conducted under red lights during the middle of the dark phase (1330-1700 h).

Feeding and Diets

All animals were given ad lib access to ground Purina chow (#5001). Water was freely available to all rats throughout the experiment, except as noted. During the acute and chronic phases of the experiment rats were divided into four dietary groups. Ten rats were given a 32% w/v sucrose solution and ten rats were given a 33.68% w/v Polycose® solution (Ross Laboratories; Columbus, OH). Each of these solutions provides 1.28 kcals/ml. Ten rats were given a 0.15% saccharin solution and the final ten rats were given a second bottle of water. Previous research demonstrated that rats consume similar amounts of a 32% sucrose solution and a 0.15% saccharin solution across a 24-h period (19). Chow was presented in Wahman LC306A (Timonium, MD) stainless-steel food cups with lids. The cups were clipped to the cage floors to prevent spillage. Both water and the flavored solutions were presented in glass bottles fitted with drip-proof stainless-steel spouts. Chow and liquid intakes and body weights were measured every other day. The positions of the bottles were switched at the time of weighing to preclude the development of side preferences.

Drugs

Morphine sulfate, generously provided by National Institute on Drug Abuse, was dissolved in physiological saline at a concentration of 2.5 mg/ml. Injections were administered subcutaneously in a volume of 1 ml/kg.

Nociceptive Testing

Pain thresholds were assessed by the radiant heat tail-flick method (6). All animals were taken into the procedure room and placed on the tail-flick apparatus (Emdie Instrument Co., Montpelier, VT) with their tails smoothed into the tail groove. All rats were held gently in a clean cloth by the same experimenter. The light source was activated and remained focused on the tail until the rat moved its tail thus switching the light off, or until 9 s had elapsed. A 9 s cut off point was employed to prevent excessive tissue damage to the tail.

A baseline measure was determined by using the median of three tail-flick tests, separated by approximately 15 s. Immediately after determining the baseline latency, the animals were injected with 2.5 mg/kg of morphine and returned to their cages for 30 minutes. Tail-flick latencies were again measured, and the animals were again injected and returned to their cages for another 30 minutes.

Acute Presentation of Liquids

All animals were water deprived overnight for a total of 15 h to encourage drinking. Rats in each dietary group were given their new solutions to drink. The animals were permitted to drink the respective liquids for 5 h before the nociceptive testing commenced. The cumulative dose procedure was curtailed at 10.0 mg/kg as rats were showing maximal analgesia.

Chronic Presentation of Liquids

Once the nociceptive testing for the acute phase of the experiment was completed, all rats were given ad lib access to water and their respective solution for 3 wk. At the end of this three-week period, nociceptive tests were conducted a second time. The cumulative dose procedure was extended to 15.0 mg/kg.

Body Composition

One week subsequent to the second nociceptive test, animals were deeply anesthetized with pentobarbital. Naso-anal length was measured with a ruler to the nearest 0.5 cm. Epididymal fat pads were removed via a midline abdominal incision and were weighed to the nearest 0.1 g. Rats were then euthanized with an intracardiac injection of pentobarbital.

Statistical Analysis

The data were analyzed with repeated measures two factor ANOVAs (diet by dose) and repeated measures three factor ANOVAs (diet by dose by phase of experiment). Post-hoc comparisons were done using t-tests to determine differences among latencies for specific doses. Pearson's r was calculated to determine a correlation between either body weight or total kilocalories consumed and analgesic response. Area under the curve (AUC) was calculated using the nociceptive data from the chronic test period and analyzed with a one-way ANOVA (diet). The level of significance was set at $p < 0.05$. Analyses of nociceptive data were conducted on the percent maximal possible effect (%MPE) which was calculated as follows:

$$\%\text{MPE} = \left(\frac{\text{test latency} - \text{baseline latency}}{\text{maximal latency} - \text{baseline latency}}\right) \times 100$$

where maximal latency is the cut off time of 9 s (8). Body composition data were analyzed with one factor ANOVAs (diet). Analyses were conducted with Lee Index values which were calculated as follows (13):

$$\text{Lee Index Value} = 3\,\frac{\text{body weight}}{\text{Naso-anal length}}$$

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

RESULTS

Acute Intake of Liquids

Rats drank at least 15 ml of the liquid provided to them. Amount of liquid consumed during the 5 h availability period differed significantly as a function of liquid type [$F(3, 36) = 11.98$; $p < 0.0001$]. When the intake data were subjected to Bonferroni t-tests, rats given saccharin drank significantly more fluid than rats drinking water, Polycose, then finally sucrose.

There were no significant differences as a function of diet for baseline tail-flick latencies (water = 2.52 ± 1.0 s; saccha-

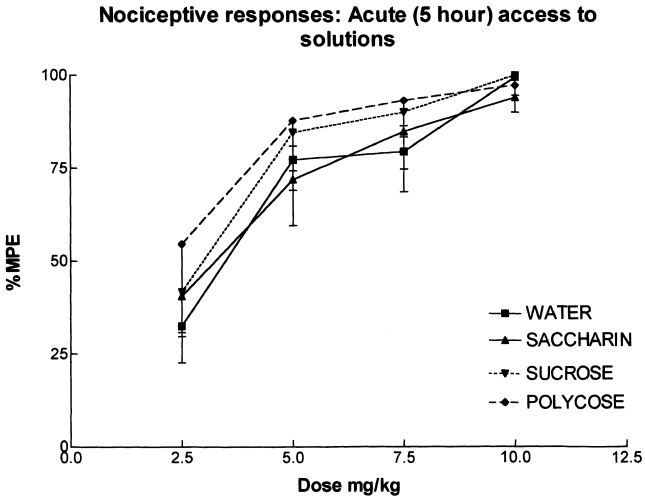

FIG. 1. Nociceptive responses (mean %MPE's ± SEM) after 5 h of exposure to a 32% Polycose solution (dashed line), a 32% sucrose solution (dotted line), a 0.15% saccharin solution (solid line with triangle), or water (solid line with square).

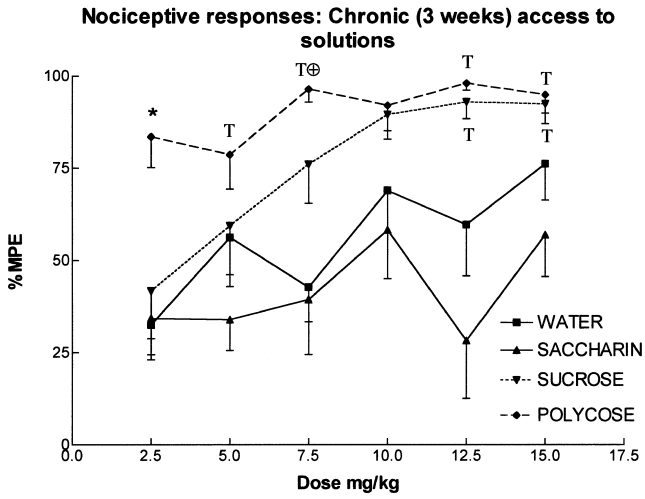

FIG. 2. Nociceptive responses (mean %MPE's ± SEM) after 3 wk of exposure to a 32% Polycose solution and water (dashed line), a 32% sucrose solution and water (dotted line), a 0.15% saccharin solution and water (solid line with triangle), or two water bottles (solid line with square). * indicates %MPEs of rats drinking Polycose significantly ($p < 0.05$) greater than those of all other groups. T indicates that %MPEs of rats drinking Polycose or sucrose significantly ($p < 0.05$) greater than those of rats drinking saccharin, ⊕ indicates that %MPEs of rats drinking Polycose significantly ($p < 0.05$) greater than those of rats drinking water.

rin = 2.70 ± 1.12 s; sucrose = 2.88 ± 1.2 s; Polycose = 2.35 ± 0.94 s).

There was a significant dose effect [$F(3, 108) = 44.40; p < 0.0005$] showing that %MPEs for all groups increased as a function of drug dose. There was no significant effect for diet (Fig. 1).

Chronic Intake of Liquids

At the time of the second nociceptive test, rats drinking sucrose or Polycose were consuming more than 50% of their total kcals from the respective solution. Rats given saccharin or water drank 60 ml of the respective solution. One rat in the sucrose group spilled its sucrose bottle the day of testing and was not used. The data for the sucrose group come from the remaining nine animals.

There were no significant differences as a function of diet for baseline tail-flicks (water = 2.53 ± 0.75 s; saccharin = 3.04 ± 0.84 s; sucrose = 2.50 ± 0.63 s; Polycose = 2.27 ± 0.54 s).

The effects for dose [$F(5, 175) = 8.15; p < 0.0005$] and for diet [$F(3, 35) = 10.45; p < 0.0005$] were highly significant. For the water, sucrose, and Polycose groups, %MPE increased as a function of dose. Animals drinking Polycose had consistently higher %MPEs than all other groups followed by rats drinking sucrose, rats drinking water and finally rats drinking saccharin. Planned post-hoc Bonferroni t-tests reveal that rats drinking Polycose had significantly higher %MPEs than rats drinking saccharin at all doses (Fig. 2).

Area under the curve (AUC) analysis yielded a significant diet effect [$F(3, 35) = 10.79; p < 0.0001$]. Post-hoc Bonferroni t-tests revealed that rats drinking Polycose had a significantly greater ($p < 0.05$) AUC than rats drinking water or saccharin. Rats drinking sucrose had a significantly greater ($p < 0.05$) AUC than rats drinking saccharin.

Analysis Across Test Times

The mean from the group drinking sucrose was used to replace the value of the rat which was removed from the experiment, to facilitate analysis. Comparison of %MPEs for all diets from the acute to the chronic phase of the experiment yielded significant results for diet [$F(3, 36) = 4.72; p < 0.01$], dose [$F(3, 108) = 38.87; p < 0.0001$], phase [$F(1, 36) = 22.18; p < 0.0001$], diet by phase [$F(3, 36) = 5.54; p < 0.005$], and dose by phase [$F(3, 108) = 7.40; p < 0.0005$]. Overall, %MPE's were significantly lower during the second nociceptive test than in the first test for rats drinking water [$F(1, 9) = 8.33; p < 0.05$] or saccharin [$F(1, 9) = 27.03; p < 0.001$]. There was a slight, non-significant decrease in %MPE for rats drinking sucrose. Conversely, for rats drinking Polycose, %MPEs increased slightly, but non-significantly, in the second nociceptive test relative to the first test.

Body Composition Analysis

Body composition data are presented as body weights, Lee Indexes, and epididymal fat pad weights (Table 1). Body weights differed as a function of diet [$F(3, 36) = 4.48; p < 0.01$]. Post-hoc Bonferroni t-tests revealed that rats drinking Polycose weighed significantly more ($p < 0.001$) than rats drinking saccharin.

Lee Index values also differed as a function of diet [$F(3, 36) = 4.04; p < 0.05$]. Post-hoc Bonferroni t-tests revealed that rats drinking Polycose had significantly higher Lee Index scores ($p < 0.005$) than rats drinking saccharin.

Weight of epididymal fat pads varied as a function of diet [$F(3, 36) = 19.175; p < 0.0005$]. Post-hoc Bonferroni t-tests revealed that rats drinking Polycose had significantly heavier fat pads than rats drinking water ($p < 0.0001$) and rats drinking saccharin ($p < 0.0005$), but did not differ from rats drinking sucrose. Rats drinking sucrose had significantly heavier fat pads than rats drinking water ($p < 0.0005$) and rats drinking saccharin ($p = 0.0005$). There was a trend for rats drinking

TABLE 1

ENDING BODY WEIGHTS (g), LEE INDEXES, AND EPIDIDYMAL FAT PAD WEIGHTS (g) (MEAN ± SD) FOR RATS DRINKING WATER, SACCHARIN, SUCROSE, OR POLYCOSE.

Body Composition	BW (g)	Lee Index	Epididymal fat (g)
Water	445.3 ± 40.97	5.99 ± .46	2.77 ± .42
Saccharin	412.9 ± 35.29	5.71 ± .44	2.43 ± .54
Sucrose	458.4 ± 52.06	6.07 ± .65	4.80 ± 1.53*†
Polycose	489.6 ± 58.13*	6.56 ± .64*	5.67 ± 1.52*†

*indicates rats drinking Polycose or sucrose significantly ($p < 0.05$) greater than rats drinking saccharin. †indicates rats drinking Polycose or sucrose significantly ($p < 0.05$) greater than rats drinking water.

Polycose to have heavier fat pads than rats drinking sucrose ($p = 0.095$).

Correlations conducted between %MPEs and body weights, total calories consumed, and percent of calories from each nutrient yielded no significant results.

DISCUSSION

The results of this experiment support the hypothesis that different palatable substances do not have equivalent effects on opioid-mediated behaviors (14). More specifically, chronic intake of palatable nutritive solutions enhanced morphine-induced analgesia, while intake of a nonnutritive saccharin solution failed to have such an effect. During the chronic phase of the experiment, the analgesic potency of morphine was greatest in rats drinking Polycose, followed by rats drinking sucrose, water and finally, saccharin. Rats drinking the Polycose solution showed close to the maximal response to morphine's analgesic effects at all drug doses while rats drinking the sucrose solution displayed dose-dependent increases in morphine-induced analgesia. In contrast, even at the highest dose of morphine, rats drinking either water or the saccharin solution failed to show maximal antinociceptive responses. These findings suggest that nutritive value of a palatable substance may be important in determining the effects of the substance on the activity of the endogenous opioid system.

Another implication of the present findings is that intake of palatable substances differentially affects the development of tolerance to morphine's analgesic properties. Tolerance to the analgesic effects of morphine develops rapidly (5,28,29). Moreover, tolerance to the analgesic effects of a single dose of morphine can be seen for a year after the injection (5). In the present experiment, comparisons between the acute and chronic phases of the study indicated that tolerance to the analgesic effects of morphine did not develop in rats drinking either Polycose or sucrose. In fact, rats drinking Polycose showed greater antinociceptive responses to morphine during the chronic phase of the experiment than during the acute phase. In comparison, antinociceptive responses for rats drinking water or the saccharin solution were significantly lower during the chronic than acute phase of the study indicating the development of tolerance to the drug. Although not significant, there was a trend for rats drinking saccharin to show increased tolerance to morphine relative to the rats drinking water. These results are consistent with the findings of Lieblich and colleagues (17) who found that rats bred for elevated saccharin intake (LC2-Hi) showed increased tolerance to the analgesic effects of morphine following saccharin intake. Differences in the development of tolerance among dietary groups may be explained by diet-induced alterations in opiate receptor binding affinity. Rats drinking palatable, nutritive solutions may have failed to show tolerance to morphine because these solutions increased binding affinity in the endogenous opioid system (18). In comparison, saccharin intake has been associated with decreases in opiate binding affinity which may promote the development of tolerance (14).

Although the present data imply that nutritive value, independent of sweet taste, is responsible for alterations in MIA, the suppressed MIA evidenced by rats drinking saccharin can not be explained solely as a difference in caloric intake. Saccharin is not simply sucrose with the calories removed. It is inappropriate and inadequate to compare saccharin and sucrose as such, without recognizing the post-ingestive fates of each. Saccharin is not metabolized or otherwise used by the body, in rats or humans, but is excreted unchanged (20). Sucrose, on the other hand, is broken down into fructose and glucose, and further utilized by the body as energy. Polycose is a complex carbohydrate, but it is broken down and absorbed similar to free glucose (25). Intake of both sucrose and Polycose result in post-ingestive increases in blood glucose whereas intake of saccharin simply passes through the digestive system. Clearly, the results of the present experiment argue that sweet taste per se is not the sole factor in enhancing MIA, but palatability, metabolism of the ingestant and nutritive value may also play crucial roles. An alternate possibility is that the rats which weighed more, and had more body fat, were more responsive to morphine's analgesic properties. There is evidence that obese rats fed a high fat diet display a lower sensitivity to pain than chow-fed controls (21). However, fat is a highly palatable, calorically-dense nutrient. Intake of dietary fat enhances MIA (10,15) which further supports the proposal that nutritive value as well as palatability are necessary for altering nociceptive responses, beyond the mere sweetness of the ingestant.

The effects of chronic sucrose intake on analgesic response are not gender specific. In a similar experiment undertaken by Frye and colleagues (10), intact female rats drinking sucrose for three weeks showed consistently elevated MIA over the entire test period whereas rats drinking saccharin or corn oil did not respond differently from female rats drinking water. Moreover, they found that chronic sucrose intake overcame hormonal effects on algesia. The present data, gathered from male rats, help to generalize the earlier findings regarding the effects of chronic sucrose or saccharin intake on nociceptive responses.

Several areas of research support the proposal that palatable nutritive and non-nutritive substances interact differently with the endogenous opioid system. For example, when compared to rats drinking water, rats chronically consuming a sucrose solution display a significant increase in opiate recep-

tor binding affinity in the brain, while rats drinking a saccharin solution exhibit a significant decrease in receptor binding affinity (14,18). Additionally, recent work has indicated that intakes of palatable carbohydrate solutions are mediated by different opioid receptor subtypes. Beczkowska and colleagues (1,2) reported that central administration of selective mu and kappa opiate receptor antagonists decreased sucrose but not saccharin intake. In contrast, central infusions of selective delta receptor antagonists reduced saccharin but not sucrose intake. Furthermore, intake of a complex carbohydrate solution similar to Polycose was decreased only after the administration of mu receptor antagonists (2). Their results suggest that intake of different types of palatable solutions could result in stimulation of different opiate receptor subtypes. This suggestion is interesting with respect to the present study, since Polycose and sucrose enhanced analgesia produced by morphine which has its greatest effects at the mu receptor (22). On the other hand, saccharin does not appear to affect the mu receptor, and did not potentiate MIA.

The present experiment elucidates, in part, the differences seen in earlier experiments on MIA and dietary intake. The results support hedonics as well as calories as important factors in mediating morphine's analgesic properties. Furthermore, it seems important to attend to the type of sweet stimuli to avoid the introduction of confounding variables. As seen in many experiments, sucrose and saccharin have opposing effects on MIA. Furthermore, some studies show that saccharin intake is mediated by a different receptor system than is Polycose or sucrose (1,2). It is therefore inappropriate to use sweet nutritive solutions and sweet saccharin solution interchangeably. Future research using sham-feeding and gastric loading techniques will further clarify the roles of nutritive value and palatability in mediating morphine-induced analgesia.

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REFERENCES

1. 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.
2. 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. 618:261–270; 1993.
3. Bergmann, F.; Lieblich, I.; Cohen, E.; Ganchrow, J. R. Influence of intake of sweet solutions on the analgesic effect of a low dose of morphine in randomly bred rats. Behav. Neur. Biol. 44:347–353; 1985.
4. Blass, E.; Fitzgerald, E.; Kehoe, P. Interactions between sucrose, pain and isolation distress. Pharmacol. Biochem. Behav. 26:483–489; 1987.
5. Cochin, J.; Kornetsky, C. Development and loss of tolerance to morphine in the rat after single and multiple injections. J. Pharmacol. Exp. Ther. 145:1–10; 1964.
6. D'Amour, F. E.; Smith, D. L. A method for determining loss of pain sensation. J. Pharmacol. Exper. Ther. 72:74–79; 1941.
7. 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.
8. Dewey, W. L.; Harris. L. S. The tail-flick test. In: Ehrenpreis, S.; Neidle, A., eds. Methods in narcotics research, New York: Marcel Dekker, 1975:101–109.
9. 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.
10. Frye, C. A.; Cuevas, C. A.; Kanarek, R. B. Diet and estrous cycle influence pain sensitivity in rats. Physiol. Behav. 45:255–260; 1993.
11. Giza, B. K.; Scott, T. R.; Sclafani, A.; Antonucci, R. F. Polysaccharides as taste stimuli: Their effect in the nucleus tractus solitarius of the rat. Brain Res. 555:1–9; 1991.
12. Holder, M. D. Responsivity to pain in rats changed by the ingestion of flavored water. Behav. Neur. Biol. 49:45–53; 1988.
13. Kanarek, R. B.; Marks–Kaufman, R. Developmental aspects of sucrose-induced obesity in rats. Physiol. Behav. 23:881–855; 1979.
14. Kanarek, R. B.; Marks–Kaufman, R. Opioid peptides: Food intake, nutrient selection, and food preference.Neurosci. Biobehav. Rev.; (in press).
15. Kanarek, R. B.; Przypek, J.; D'Anci, K. E.; Marks–Kaufman, R. Dietary modulation of mu- and kappa-opioid receptor mediated analgesia. Pharmacol. Biochem. Behav. Submitted for publication.
16. 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.
17. Lieblich, I.; Cohen, E.; Ganchrow, J. R.; Blass, E. M.; Bergmann, F. Morphine tolerance in genetically selected rats induced by chronically elevated saccharine intake. Science 221:871–873; 1983.
18. Marks–Kaufman, R., Hamm, M. W., and Barbato, G. F. The effects of dietary sucrose on opiate receptor binding in genetically obese (ob/ob) and lean mice. J. Am. Coll. Nut. 8:9–14; 1989.
19. Marks–Kaufman, R.; Kanarek, R. B.; Delanty, S. N. Sweet-tasting solutions modify the analgesic properties of morphine in rats FASEB 2:A1567, 1988.
20. Miller, S. A.; Frattali, V. P. Saccharin: In Kretchmer, N.; Hollenbeck, C. B. Sugars and sweeteners. Boca Raton: CRC Press, 1991:245–255.
21. Ramzan, I.; Wong, B. K.; Corcoran, G. B. Pain sensitivity in dietary-induced obese rats. Physiol. Behav. 54:433–435; 1993.
22. Rang, H. P.; Dale, M. M.; Ritter, J. M.; Gardner. Pharmacology. New York: Churchill Livingstone, 1995.
23. Roane, D. S.; Martin, R. J. Continuous sucrose feeding decreases pain threshold and increases morphine potency. Pharmacol. Biochem. Behav. 35:225–229; 1990.
24. Schoenbaum, G. M.; Martin, R. J.; Roane, D. S. Discontinuation of sustained sucrose-feeding aggravates morphine withdrawal. Brain Res. Bull. 24:565–568; 1990.
25. Sclafani, A. Carbohydrate taste, appetite, and obesity: An overview. Neurosci. Biobehav. Rev. 11:131–153; 1987.
26. Sclafani, A. Starch and sugar tastes in rodents: An update. Brain Res. Bull. 27:383–386; 1991.
27. Shide, D. J.; Blass, E. M. Opioid-like effects of intraoral infusions of corn oil and Polycose on stress reactions in 10-day-old rats. Behav. Neurosci. 103:1168–1175; 1989.
28. Siegel, S. Evidence from rats morphine tolerance is a learned response. J. Comp. Physiol. Psychol. 89:498–506; 1975.
29. Weeks, J. R. Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. Science 138:143–144; 1962.