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Dietary Modulation Of Mu And Kappa Opioid Receptor-mediated Analgesia

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KANAREK, R. B., J. PRZYPEK, K. E. D'ANCI AND R. MARKS-KAUFMAN. *Dietary modulation of mu and kappa opioid receptor-mediated analgesia.* PHARMACOL BIOCHEM BEHAV **58**(1) 43–49, 1997.—Research has demonstrated that intake of palatable carbohydrates and fats enhanced morphine-induced analgesia (MIA) in Sprague–Dawley rats. To determine if the effects of palatable foods on nociceptive responses would generalize to other strains of animals and other opioid agonists, the present experiments investigated whether intake of palatable foods would: a) alter MIA in Long–Evans rats, and b) alter analgesia produced by drugs acting at kappa opioid receptors. In experiment 1, adult male Long–Evans rats were fed Purina chow alone or chow and either a 32% sucrose solution, a 0.15% saccharin solution, or hydrogenated vegetable fat. Using a tail-flick apparatus, nociceptive responses, measured as percent maximal possible effect (%MPE), were examined after morphine administration [0.0, 1.0, 3.0, and 6.0 mg/kg subcutaneously (SC)]. %MPEs varied directly as a function of dose and were significantly greater for rats fed chow and either sucrose or fat than for rats fed chow alone or chow and saccharin. Experiment 2 compared the analgesic effect of the kappa opioid receptor agonist U50,488H (0, 5.0, 10.0, and 20.0 mg/kg SC) in rats fed chow alone or chow and a 32% sucrose solution. Administration of U50,488H led to analgesia. However, %MPEs did not vary directly as a function of dose. %MPEs of rats fed chow and sucrose were significantly greater than those of rats fed chow alone after injections of 10.0 and 20.0 mg/kg U50,488H. Experiment 3 compared the analgesic effect of U50,488H (5.0, 10.0, 15.0, and 20.0 mg/kg SC) in rats fed chow alone or chow and either a 0.15% saccharin solution or hydrogenated vegetable fat. Administration of U50,488H led to analgesia. However, %MPEs did not vary directly as a function of dose or as a function of diet. %MPEs of rats fed chow and fat were significantly greater than those of rats fed chow alone after injection of 5.0 mg/kg U50,488H. © 1997 Elsevier Science Inc.

Analgesia Sucrose Saccharin Fat Morphine U50,488H Kappa opioid receptors Mu opioid receptors Long–Evans rats

OVER the past 15 years, a substantial body of evidence has accumulated indicating a relationship between the endogenous opioid system and the intake of palatable foods and fluids (33). In support of this relation, it has been reported that administration of opioid agonists intensifies preferences for palatable foods and fluids [e.g., (14–16,29)]. Drugs that act at kappa opioid receptors are particularly effective in stimulating the ingestion of palatable foods. To illustrate, injections of the selective kappa opioid receptor agonists U50,488H and tifluadom lead to rapid increases in food intake relative to intake following saline injections in rats consuming a highly palatable diet (14–16,29).

Research demonstrating that intake of sucrose solutions and dietary fat alters pain sensitivity in experimental animals also provides evidence for a relation between endogenous opioid peptides and palatable foods (7,19,24,25,35,37,41,49, 51). Male Sprague–Dawley rats consuming a standard laboratory diet and either a sucrose solution or hydrogenated vegetable fat respond more rapidly on a tail-flick apparatus than rats eating only chow. However, when injected with morphine, a mu opioid receptor agonist, rats consuming chow and either the sucrose solution or vegetable fat display longer tail-flick latencies than those given only chow (35,41,49).

Prior work has indicated that strain differences may influence animal's responses to opioids and other psychoactive drugs [e.g., (4,8,11,17,39,46,48,50,54)]. Over 25 years ago, Borgan and colleagues (8) reported that morphine-treated Wistar rats were more aggressive than similarly treated Sprague–Dawley rats. More recently, using the same strains of rats, Carroll and coworkers (11) observed that food deprivation

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enhanced drinking of the opioid drug etonitazene by Wistar rats but depressed intake of the drug solution by Sprague–Dawley rats. Strain differences also may influence the analgesic potency of opioid drugs (4,45,47,48,50). In a tail-immersion procedure, mice of the C57BL strain were more sensitive to the analgesic action of morphine than were mice of the CBA, BALB, or DBA strains (50). Moreover, Lieblich and colleagues (39) reported that rats selectively bred to consume high levels of saccharin solutions were less sensitive to the analgesic actions of morphine than were rats bred to drink low levels of saccharin. Most studies examining the effects of diet on opioid-induced analgesia have used Sprague–Dawley or other strains of albino rats. However, because strain differences may influence opioid-induced analgesia, and it has been suggested that nonalbino strains may be more appropriate for drug tests (17), the present experiments examined the effects of dietary variables on nociceptive responses in hooded Long–Evans rats.

Administration of the highly selective kappa opioid receptor agonist U50,488H produces antinociception in response to a variety of noxious stimuli (6,9,27,36,42–45,47,52). It is believed that kappa opioid receptors in both the spinal cord and brain are important determinants of the antinociceptive actions of U50,488H (43). Evidence for the role of specific kappa receptors in antinociception comes from experiments demonstrating that U50,488H-induced analgesia: a) is not cross-tolerant with morphine; b) is not blocked by injections of naltrexone; but c) is blocked by administration of the selective kappa antagonist nor-binaltorphimine (nor-BNI) and intrathecal injections of an antisense oligodeoxynucleotide against the $kappa_1$ opioid receptor (13,43,44). Because kappa opioid receptors also may be particularly involved with the mechanisms that control consumption of palatable foods (14–16,29), it was deemed important to determine whether dietary variables would modify analgesic responses produced by kappa receptor agonists as well as those produced by mu receptor agonists. Preliminary evidence for dietary modulation of the analgesic potency of kappa agonists was provided by a study demonstrating that following injections of the kappa agonist ethylketocyclazocine (EKC), tail-flick latencies were significantly longer in rats fed a sucrose solution and chow than in rats eating only chow (33). However, because EKC also acts at the mu receptor, caution must be exercised in interpreting these results. To more fully assess the effects of diet on the actions of kappa agonists, the second and third experiments compared nociceptive responses to U50,488H in rats given a 32% sucrose solution and chow or chow alone (experiment 2) and in rats given either a 0.15% saccharin solution or vegetable fat and chow or chow alone (experiment 3).

GENERAL METHODS

Animals

Adult male Long–Evans rats (Charles River Laboratories, Portage, MI, USA) weighing 275–325 g at the beginning of the experiment were used. Animals were individually housed in hanging stainless-steel cages (24 × 18 × 19 cm) in a temperature-controlled room (21 ± 1°C) maintained on a reverse 12 L: 12 D cycle (lights on at 2000 h).

Drugs

Morphine sulfate, generously supplied by the National Institute on Drug Abuse, was dissolved in 0.9% saline to concentrations of 1.0, 3.0, and 6.0 mg/ml. U50,488H (Sigma Chemical Corporation, St. Louis, MO, USA) was dissolved in 0.9% saline to concentrations of 5.0, 10.0, and 20.0 mg/ml. Drugs were administered in a volume of 1 ml/kg body weight.

Nociceptive Responses

Nociceptive testing was begun 3 h after the onset of the dark cycle. Pain thresholds were assessed by the radiant-heat tail-flick method (18). Animals were placed on the platform of the tail-flick apparatus with their tails smoothed into the tail grove. All animals were gently held by the same experimenter during all tests. A light source was focused on the tail with the intensity of the light adjusted to obtain baseline tail-flick latencies of 2–4 s. To prevent tissue damage, if the rat did not respond within 9 s, the light source was automatically turned off. Prior to drug injections, three baseline determinations of tail-flick latency separated from each other by approximately 30 s were made. The median of the three determinations was used for statistical analyses.

Statistical Analyses

Data for energy intake and body weight gain across the experiment were analyzed using one-way analyses of variance (ANOVAs).

Nociceptive responses were determined by calculating the percent maximal possible effect (%MPE) using the formula recommended by Dewey and Harris (21).

$$\%\text{MPE} = \frac{\text{test latency} - \text{median baseline latency}}{9\text{ seconds} - \text{baseline latency}} \times 100.$$

Data on %MPE were analyzed using mixed model ANOVAs with diet as a between-subjects measure and dose and time after injections as within-subjects variables. Post hoc comparisons between groups were made using the Bonferroni *t*-test.

EXPERIMENT 1

Experiment 1 examined the effect of dietary conditions on nociceptive responses after morphine injections in Long–Evans rats.

Methods

Animals and dietary conditions. Forty-three male Long–Evans rats were used. All rats were given ad lib access to water and to ground Purina rodent chow (#5001) presented in a Wahmann LC306A stainless-steel nonspill food cup. In addition to chow and water, 10 rats were given hydrogenated vegetable fat (Crisco; Proctor & Gamble, Cincinnati, OH, USA), 11 rats were given a 32% sucrose solution, and 11 rats received a 0.15% sodium saccharin solution. The fat was presented in 75-ml glass cups, and the sucrose and saccharin solutions were presented in glass water bottles with rubber stoppers and nonleaking stainless steel drinking spouts. The concentration of the saccharin solution was chosen on the basis of previous work (35,41) demonstrating that, under dietary conditions similar to those used in this experiment, rats consumed equivalent amounts of a 0.15% saccharin solution and a 32% sucrose solution.

Procedure. Animals were given 4 weeks to adapt to handling and dietary conditions. Body weights and nutrient intakes were measured every other day. Testing for nociceptive responses was then initiated. Baseline tail-flick latencies were determined as described in the General Methods. Rats then were injected subcutaneously (SC) with morphine sulfate (0, 1.0, 3.0, and 6.0 mg/kg), and tail-flick latencies were measured 30,

TABLE 1

MEAN (± SEM) DAILY CALORIC INTAKE AND BODY WEIGHT OF RATS FED CHOW ALONE OR CHOW AND EITHER SUCROSE, SACCHARIN, OR FAT

Diet Group	Chow Calories (kcal)	Additional Calories (kcal)	Total Calories (kcal)	Body Weight Gain (g)
Chow alone	88.4[a]		88.4[a]	117.9[a]
Chow and saccharin	97.2[a]		97.2[ab]	138.7[ab]
Chow and sucrose	55.6[b]	46.9[a]	102.5[bc]	162.6[b]
Chow and Crisco	46.3[b]	64.5[b]	110.8[c]	175.4[b]

Numbers in each column not sharing a common superscript are significantly ($p < 0.05$) different from each other.

60, and 90 min following injections. Each animal received each dose of morphine in a counterbalanced order. Drug injections were separated by a minimum of 5 days.

Results

Energy intake and body weight. Total daily caloric intake varied significantly [$F(3, 39) = 14.03$, $p < 0.01$] as a function of diet (Table 1). Animals fed chow and either Crisco or the 32% sucrose solution consumed significantly ($ps < 0.05$) more calories per day than did rats fed only chow. Additionally, daily caloric intake of rats fed chow and fat was significantly ($p < 0.05$) greater than that of rats given chow and the saccharin solution. Analysis of intake of individual nutrients revealed that rats fed sucrose and chow consumed a significantly ($p < 0.01$) higher percentage of their calories from chow than rats fed Crisco and chow (Table 1).

Although in previous studies rats consumed similar amounts of the 0.15% saccharin solution and the 32% sucrose solution, in the present study there was a trend ($p < 0.06$) for daily intake of the saccharin solution (50.2 ml/day) to be greater than intake of the sucrose solution (39.1 ml/day).

Body weight gain across the experiment differed significantly [$F(3, 39) = 6.57$, $p < 0.01$] as a function of diet and paralleled energy intake (see Table 1).

Nociceptive responses. Baseline tail-flick latencies did not differ as a function of dietary conditions (chow only, 2.7 s; chow plus 32% sucrose, 2.7 s; chow plus 0.15% saccharin, 2.4 s; chow plus Crisco, 2.2 s).

Nociceptive responses measured as %MPE varied significantly [$F(3, 117) = 84.00$, $p < 0.01$] as a function of the dose of morphine (Fig. 1). For all dietary conditions, %MPE was directly related to the dose of morphine. %MPEs were significantly ($ps < 0.05$) greater following injections of 3.0 and 6.0 mg/kg than after injections of 0.0 or 1.0 mg/kg morphine. Moreover, %MPEs were significantly ($ps < 0.05$) greater after injections of 6.0 mg/kg than after injections of 3.0 mg/kg morphine.

Nociceptive responses also varied significantly [$F(2, 78) = 35.08$, $p < 0.01$] as a function of time following injections. The effect of morphine on %MPE was most pronounced 30 min following injections and then decreased as a function of time.

As shown in Fig. 1, %MPE varied significantly [$F(3, 39) = 4.04$, $p < 0.01$] as a function of dietary conditions. At all time points, %MPEs of rats fed chow and either sucrose or fat were greater than %MPEs of rats given either chow and the saccharin solution or chow alone. The effect of diet on nociceptive responses was most pronounced after administration of 6.0 mg/kg morphine.

EXPERIMENT 2

Experiment 2 investigated the effect of chronic sucrose availability on nociceptive responses following administration of the selective kappa opioid receptor agonist U50,488H.

Methods

Animals and diets. Fourteen adult male Long–Evans rats were used. Seven rats were fed chow alone and seven rats were fed chow and a 32% sucrose solution. Animals were given 3 weeks to adjust to dietary conditions. Nutrient intakes and body weights were measured every other day.

Procedure. After baseline tail-flick latencies were determined as described above, rats were injected with U50,488H (0.0, 5.0, 10.0, and 20.0 mg/kg) and tail-flick latencies were measured at 30, 60, and 90 min after injections. Each animal received each dose of U50,488H in a counterbalanced order. Drug injections were separated by a minimum of 5 days.

Results

Energy intake and body weight. Rats fed chow and the 32% sucrose solution consumed significantly [$t(12) = 2.86$, $p < 0.05$] more calories per day (100.6 kcal) than rats fed only

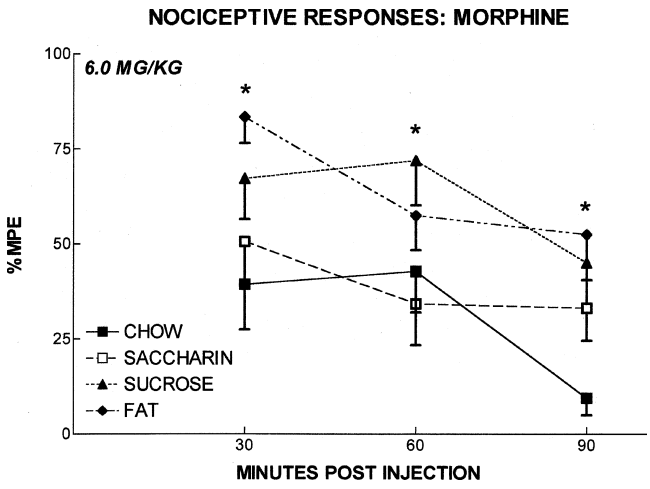

FIG. 1. Nociceptive responses (%MPEs) 30, 60, and 90 min after injections of 6.0 mg/kg morphine. *Responses (%MPEs) of animals fed sucrose or fat significantly ($ps < 0.05$) greater than those of rats consuming chow alone or chow and saccharin.

chow (89.6 kcal). Rats given the sucrose solution consumed 53.8% of their calories from chow and 46.2% from sucrose.

Although average weight gain across the experiment was greater for rats given sucrose and chow (121 g) than for rats fed only chow (109 g), this difference was not significant.

Nociceptive responses. No significant differences in baseline tail-flick latencies were observed as a function of diet (chow only, 2.7 s; chow plus 32% sucrose, 2.6 s).

Nociceptive responses differed significantly [$F(3, 36) = 13.53$, $p < 0.01$] as a function of dose of U50,488H (Fig. 2). However, in contrast to morphine, nociceptive responses did not increase directly as a function of the dose of U50,488H. %MPEs were greater after injections of 10.0 mg/kg than after injections of 20.0 mg/kg U50,488H. Additionally, in contrast to morphine, nociceptive responses after U50,488H did not vary as a function of time following injections.

Although %MPE did not differ across dietary conditions, there was a significant [$F(3, 36) = 6.81$, $p < 0.01$] interaction between drug dose and dietary conditions. Following injections of 0.0 mg/kg U50,488H, there was a trend ($p < 0.08$) for %MPE to be lower in rats consuming the sucrose solution and chow than in those eating only chow. In contrast, at all times after administration of 10.0 mg/kg U50,488H, %MPEs were significantly (ps < 0.05) greater for rats given the sucrose solution than for rats fed chow alone (Fig. 2). Additionally, 30 min after injections of 20.0 mg/kg U50,488H, %MPEs were significantly ($p < 0.05$) greater for rats consuming sucrose and chow than for rats eating only chow.

EXPERIMENT 3

Experiment 3 investigated the effects of chronic saccharin or dietary fat availability on nociceptive responses following administration of the selective kappa opioid receptor agonist U50,488H.

Methods

Animals and diets. Twenty-four adult male Long–Evans rats were used. Eight rats were fed chow alone, eight rats received chow and dietary fat (Crisco), and eight rats were fed chow and a 0.15% saccharin solution. Animals were given 3 weeks to adjust to dietary conditions. Nutrient intakes and body weights were measured every other day.

Procedure. Because there was no effect of time following injections in the previous experiment, U50,488H was given according to a cumulative dosing procedure. After baseline tail-flick latencies were determined as described above, rats were injected with 5.0 mg/kg U50,488H every 30 min until a final cumulative dose of 20.0 mg/kg was achieved. Tail-flick latencies were measured at 30 min after each injection.

Results

Energy intake and body weight. There was a trend for rats fed chow and Crisco to eat more calories per day (114.2 ± 15.3 kcal) than rats fed only chow (104.2 ± 7.0 kcal) or chow and saccharin (101.36 ± 8.7 kcal). Rats given Crisco consumed 43.5% of their calories from chow and 56.5% from fat. There were no differences in overall weight gain as a function of diet.

Nociceptive responses. No significant differences in baseline tail-flick latencies were observed as a function of diet (chow only, 3.5 s; chow plus 0.15% saccharin, 3.9 s; chow plus Crisco, 3.5 s).

Nociceptive responses varied significantly with the dose of U50,488H [$F(3, 57) = 4.29$, $p < 0.01$]. Nociceptive responses increased from 5.0 to 10.0 mg/kg, and then decreased at doses of 15.0 and 20.0 mg/kg. However, %MPEs did not differ as a function of diet condition. Analysis of %MPEs at each dose of U50,488H revealed a trend for %MPEs to vary as a function of diet at the 5.0 mg/kg dose [$F(2, 19) = 3.11$, $p = 0.07$]. Post hoc least significant difference tests showed that rats eating fat displayed significantly ($p < 0.05$) elevated nociceptive responses in comparison with rats eating chow alone (Fig. 3).

DISCUSSION

The results of the present experiments provide further support for dietary modulation of opioid-induced analgesia. As previously observed in Sprague–Dawley rats, intake of a su-

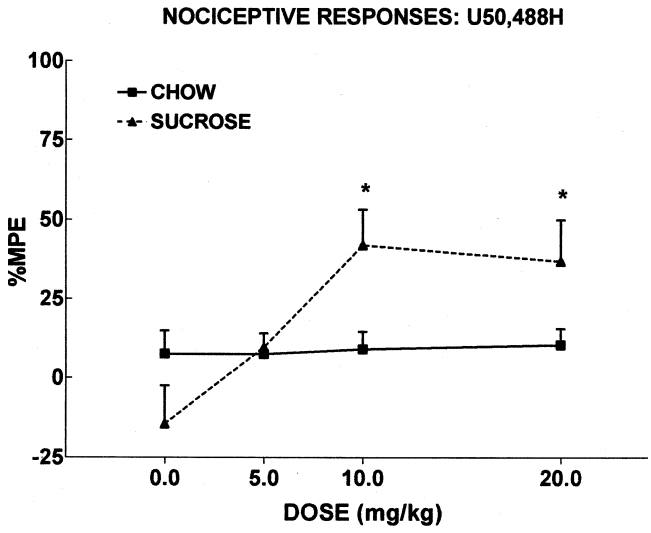

FIG. 2. Nociceptive responses (%MPEs) 30 min after injections of 0.0, 5.0, 10.0, and 20.0 mg/kg U50,488H. *Responses (%MPEs) of animals fed chow and sucrose significantly (ps < 0.05) greater than those of rats consuming chow alone.

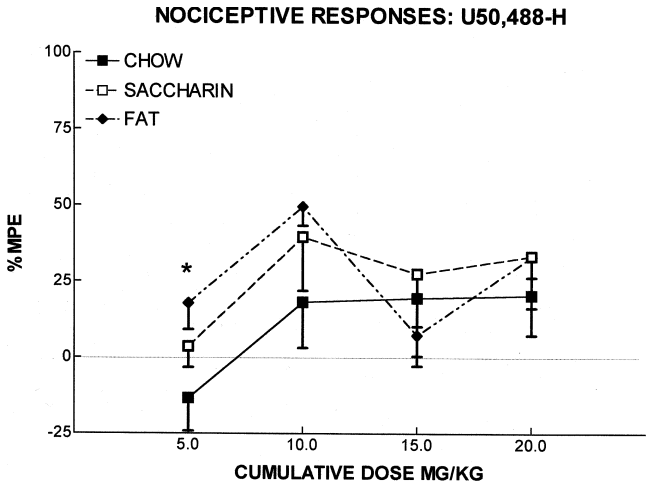

FIG. 3. Nociceptive responses (%MPEs) after cumulative injections of U50,488H. *Response (%MPE) of animals fed fat significantly (ps < 0.05) greater than those of rats consuming chow alone or chow and saccharin.

crose solution or dietary fat potentiated the antinociceptive actions of the classic mu opioid receptor agonist morphine in Long–Evans rats (35,41,49). Intake of the sucrose solution also enhanced the analgesic effects of the kappa opioid receptor agonist U50,488H. These results indicate that intake of palatable foods and fluids alters both mu and kappa opioid systems.

Although antinociception was elicited by both morphine and U50,488H, antinociceptive responses to the two drugs were not identical. First, antinociceptive responses were more pronounced after administration of morphine than after injections of U50,488H. Additionally, %MPEs for rats in all dietary conditions increased in a dose-related manner following morphine injections. In comparison, no differences in antinociception were observed as a function of dose of U50,488H for rats fed chow alone. However, for rats fed chow and the 32% sucrose solution, %MPEs increased directly as a function of dose of U50,488H from 0.0 to 10.0 mg/kg and then decreased slightly at 20.0 mg/kg. Finally, antinociceptive responses decreased as a function of time after morphine injections but not did not differ as a function of time after injections of U50,488H.

Following morphine administration, chronic intake of either sucrose or fat equally enhanced analgesia. In comparison, although chronic intake of both sucrose and dietary fat increased the analgesic actions of U50,488H, the effect of sucrose was more pronounced. Nociceptive responses of rats fed sucrose and chow were greater than those of rats fed chow alone after administration of 10.0 and 20.0 mg/kg U50,488H. In contrast, chronic intake of dietary fat only slightly increased antinociception at 5.0 mg/kg U50,488H. Moreover, the analgesic potency of U50,488H in rats eating Crisco decreased after the 15.0 mg/kg dose. In contrast, pilot data suggest that, following a similar cumulative dosing procedure, rats fed chow and sucrose show a dose response to U50,488H (D'Anci, unpublished findings). These results suggest that sucrose may alter activity at both the mu and kappa receptors, whereas fat more selectively alters activity at the mu receptor.

The differences between morphine and U50,488H with respect to maximal and dose-related antinociceptive responses are similar to previously reported data (9,42). For example, Calcagnetti and colleagues (9) found that U50,488H produced less pronounced antinociceptive responses than morphine and other mu agonists. These researchers also reported that U50,488H did not induce dose-related increases in antinociception in control rats not subjected to restraint stress, although the drug did result in dose-related increases in analgesic responses in rats that were restrained (9). These results are very reminiscent of those of the present study in that dose-related increases in analgesic responses were not observed in rats fed chow alone but were seen in rats fed chow and sucrose. Additionally, in a preliminary study using a cumulative dosing regime, we again observed that rats fed only chow did not display a strong dose response to U50,488H in comparison with rats fed chow and carbohydrate solution (D'Anci, unpublished findings).

The temperature and intensity of the thermal stimulus used in the tail-flick procedure also may have contributed to the differences in nociceptive responses observed after morphine and U50,488H injections. Recent work has indicated that drugs which act at kappa receptors are more effective in reducing the noxious effects of cold than heat (1,2,12). The actions of kappa opioid agonists against noxious heat stimuli are intensity dependent (42,43). Kappa agonists, including U50,488H and U69,593, are most effective against low-intensity and least effective against high-intensity thermal stimuli (42). In contrast, the actions of the mu agonist morphine do not depend on the intensity of the thermal stimuli (42). In the present experiments, relatively high intensities of heat were used in the tail-flick test, as evidenced by mean baseline tail-flick latencies of 2.2–2.7 s. Previous work has shown that with a stimulus of more moderate intensity (mean baseline tail-flick latency 3.52 ± 0.08 s), morphine and U50,488 are equipotent against heat stimuli (42). If a cold-water tail-flick test (1,2,12) or less intense heat stimuli had been used in the present experiments, the differences in the responses observed following injections of morphine and U50,488H might have been reduced.

Finally, Millan (42) reported that U50,488H failed to induce maximal antinociception and yielded shallower dose–response curves than did morphine. This author suggested that kappa agonists may be simultaneously, but differentially, activating analgesic and hyperalgesic mechanisms. Lower doses of U50,488H may predominantly affect analgesic mechanisms, whereas higher doses may stimulate hyperalgesic as well as analgesic subsystems, resulting in a decrease in nociceptive responses.

Despite the differences in nociceptive responses following morphine and U50,488H administration, intake of palatable nutritive substances accentuated the antinociceptive potency of both drugs. Intake of both sucrose and dietary fat increased the antinociceptive properties of morphine. However, as previously observed in Sprague–Dawley rats (41), intake of a sweet but nonnutritive saccharin solution failed to augment responses to morphine in Long–Evans rats. One explanation is that the rats did not find the saccharin solution to be palatable. This seems unlikely, however, because the Long–Evans rats consumed more of the saccharin solution than of the 32% sucrose solution. Comparison of the present study with previous work also suggests that sweet-tasting nutritive and nonnutritive fluids differentially affect pain sensitivity and morphine-induced analgesia. A number of studies have shown that chronic intake of sucrose potentiates the antinociceptive actions of morphine (25,41,49), whereas chronic intake of saccharin or a relatively low-calorie saccharin–glucose solution attenuates the analgesic potency of morphine (5,10,28,39). Whether nutritive and nonnutritive substances differentially affect kappa-induced analgesia remains to be determined. However, research showing that U50,488H stimulates and that the kappa antagonist nor-BNI suppresses sucrose but not saccharin intake suggests that nutritive quality may also affect kappa-induced analgesia (3,26).

Although the specific mechanisms for dietary potentiation of opioid-induced analgesia are not known, there are several possible alternatives. First, it is possible that intake of sucrose and/or dietary fat altered the body's ability to metabolize opioid drugs, resulting in higher levels of plasma opioids that could thereby increase the analgesic potency of the drugs (53). Second, differences in body weight could have contributed to the variations in opioid-induced analgesia observed among rats maintained under different dietary conditions. Rats fed chow and either sucrose or fat weighed more than rats given chow alone or chow and the saccharin solution. Based on previous work [e.g., (30–32,34)], it is assumed that the increased body weight of rats fed sucrose and fat in addition to chow was accompanied by an increase in body fat. Thus, it is possible that the increase in body fat of rats fed sucrose or fat altered the distribution of opioid drugs so that more of the drugs entered the brains of these animals. Results of several studies, however, indicate that differences in metabolism or distribution of opioid drugs cannot wholly ac-

count for the effect of dietary variables on analgesia. First, increased body weight is not a necessary condition for chronic intake of sucrose or fat to increase the analgesic potency of morphine (35). Second, rats fed sucrose or fat display signficantly greater nociceptive responses after central as well as peripheral administration of morphine (Kanarek, unpublished results). Finally, uptake of radioactive morphine into the brain is not different in rats fed chow alone or those fed chow and hydrogenated vegetable fat (Kanarek and Kream, unpublished results). These results suggest that the effects of diet on nociceptive responses are mediated at the central rather than peripheral level.

Intake of palatable sweet-tasting foods can lead to the release and/or breakdown of endogenous opioid peptides. Dum and colleagues (22,23) reported that intake of palatable sucrose-containing foods resulted in an increase in the amount of beta-endorphin occupying hypothalamic receptors in rats. Intake of sucrose solutions and dietary fat also can alter opiate receptor binding. Opiate receptor binding affinity was significantly greater in the brains of genetically obese mice and normal rats fed sucrose than in animals fed only Purina chow (40). Additionally, in some strains of mice, dietary fat increases opiate receptor binding affinity (38). It is interesting to note that although sucrose intake is associated with an increase in opioid receptor binding, saccharin intake is actually accompanied by a decrease in opiate receptor binding (20). On the basis of these data, it is hypothesized that chronic intake of sucrose or fat (but not saccharin) increases opioid receptor binding, which in turn modifies the behavioral actions of exogenously administered opioids.

In conclusion, the results of these studies demonstrate that dietary modulation of opioid-induced analgesia: a) is not limited to Sprague–Dawley rats, and b) occurs with drugs acting at both the mu and kappa receptors. Further research is needed to determine whether dietary variables would alter responses to other types of painful stimuli or to other behaviors believed to mediated by the endogenous opioid system.

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