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Modulation of Morphine-Induced Antinociception by Palatable Solutions in Male and Female Rats

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KANAREK, R. B. AND B. HOMOLESKI. *Modulation of morphine-induced antinociception by palatable solutions.* PHARMACOL BIOCHEM BEHAV **66**(3) 653–659, 2000.—The analgesic potency of opioid drugs varies as a function of gender, and can be modified by the intake of palatable sweet-tasting solutions. To determine if gender interacts with diet-induced changes in antinociceptive responses, male and female Long–Evans rats were fed laboratory chow and water alone, or chow, water and either a 32% w/v sucrose solution or a 0.15% w/v saccharin solution, and tested in two analgesic paradigms, the tail-flick test and the hot-plate test. For both tests, antinociceptive responses of male and female rats were tested following administration of cumulative doses (1.25, 2.5, 5.0, and 10.0 mg/kg, SC) of morphine sulfate. On the tail-flick test, morphine produced dose-related increases in antinociceptive responses. In addition, relative to both the chow only and saccharin conditions, chronic intake of the sucrose solution access significantly augmented morphine's antinociceptive properties. On the hot-plate test, when the plate was heated to 51°C, morphine led to significant dose-related increases in antinociceptive responses, but diet did not affected antinociceptive responses. When the temperature of the hot plate was increased to 53°C, there was a trend for animals given sucrose to have greater antinociceptive responses than those given either chow alone or saccharin. No differences in baseline pain sensitivity or morphine-induced analgesia were observed as a function of gender. © 2000 Elsevier Science Inc.

Morphine Antinociception Sucrose Saccharin Opioids Gender differences Rats Palatability Hot-plate test Tail-flick test

IT has been proposed that a reciprocal relationship exists between opioids and intake of palatable foods and fluids (22,30). Experiments demonstrating that administration of opioid agonists increases while administration of opioid antagonists decreases intake of palatable foods and fluids to a greater degree than intake of less palatable fare provide support for the idea that opioid peptides are important in modulating hedonic aspects of feeding behavior [(e.g., (3,10,19,28, 30,32,43,44)]. On the other hand, studies revealing that consumption of sweet and/or high-fat items modifies the behavioral consequences of morphine and other opioid drugs are evidence that intake of palatable foods and fluids alters the functioning of the endogenous opioid system [e.g., (12–14,18,23,25,31,37)]. As examples of these latter findings, a number of researchers have shown that chronic intake of palatable sucrose or Polycose solutions or dietary fat enhances the analgesic potency of opioid drugs while chronic intake of sweet-tasting, but nonnutritive saccharin solutions decreases or has minimal effects on opioid-induced analgesia [e.g., (12–14,18,23,25,31,33,37)].

Most experiments examining the effects of diet on opioid-induced analgesia have used the tail-flick test, which measures the time required for an animal to withdraw its tail from a noxious heat stimulus. The tail-flick response is a spinal reflex that can be elicited after spinal cord transection (17,20). To more fully determine the generality of the effects of chronic intake of palatable fluids on morphine's antinociceptive actions, two analgesic tests—the tail-flick test and the hot-plate test—were used in the present studies. In the hot-plate test, the animal is confined to a heated surface until it executes a behavioral response such as a hind paw lick or jump. In contrast to the tail-flick test, the hot-plate test re-

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quires that an animal perform an organized sequence of behaviors to escape the noxious stimulus. It is believed that this sequence is mediated within the brain (17,20).

With few exceptions (18), experiments assessing the effects of palatable fluids on pain sensitivity have used male rats. However, there are data that suggest that male and female rodents differ in both baseline pain sensitivity and responsiveness to analgesic drugs [e.g., (1,2,4–6,8,9,11,21,26,27, 29,35,36,38,39)]. Most researchers examining gender differences have reported that male rodents are more sensitive to the analgesic properties of opioid drugs than females [e.g., (4,8,9,11,21,26,27)]. However, others have found that opioid-induced analgesia is more pronounced in females than in males (1). It has been suggested that strain differences, and methodological considerations, including differences in the opioid agonist used, the dose of the agonist, the antinociceptive test, and whether animals were tested on an acute or chronic basis, contribute to the discrepancies in results among studies examining gender differences in pain sensitivity (5,27). To determine if gender differences exist in the effects of diet on morphine-induced analgesia, in the present experiments, antinociceptive responses were determined using the tail-flick and hot-plate tests in male and female rats given either a sucrose or saccharin solution in addition to a standard laboratory diet, or the diet alone.

GENERAL METHODS

Animals

Male and female Long–Evans VAF rats (Charles River Laboratories, Portage, MI) were used. Animals were individually housed in stainless steel hanging cages and maintained in a temperature-controlled room (22 ± 1°C) on a 12 L:12 D reverse lighting schedule (lights on: 2000–0800 h).

Diet Conditions

All animals were allowed ad lib access to Purina Laboratory Rodent Chow #5001 in Wahmann (Timonium, MD) LC-306A nonspill food cups, and tap water. Additionally, one-third of the animals of each sex received continuous access to a 32% sucrose solution, and one-third received access to a 0.15% sodium saccharin solution. The concentrations of the palatable solutions were chosen on the basis of previous research demonstrating that rats consumed similar amounts of these solutions during a 24-h period (13,23). Animals were allowed at least 3 weeks to acclimate to the diet conditions before analgesic testing was carried out. Body weights were measured, and food and fluids were weighed and refilled on Monday, Wednesday, and Friday.

Drugs

Morphine sulfate, generously provided by the National Institute on Drug Abuse, was dissolved in 0.9% sterile saline solution at concentrations of 1.25, 2.5, and 5 mg/ml. Drugs were administered subcutaneously in a volume of 1 ml/kg.

Nociceptive Testing

Analgesic testing was conducted between 1000 and 1600 h under dim red lighting conditions.

Hot-plate test. The hot plate apparatus (IITC Life Science, Model 39L) was heated to 51.0° (Experiment 1) or 53.0°C (Experiment 2). The rat was placed on the hot plate, and the time until the rat licked its rear paw or jumped was recorded. Two experimenters observed the rat from opposite sides of the apparatus to ensure that licks and jumps were not missed. When the animal responded, the experimenter stepped on a foot pedal that turned off an electronic timing device contained within the apparatus. Baseline latencies were determined during one initial test. Following the baseline measurement, animals were injected with 1.25 mg/kg morphine sulfate and returned to their home cages for 30 min. Animals then were tested again on the hot plate, and injected with morphine. A cumulative dosing regime was used such that the cumulative doses were 1.25, 2.5, 5, and 10 mg/kg. Thirty minutes intervened between each injection and subsequent analgesic testing. A cutoff of either 60 (Experiment 1) or 30 s (Experiment 2) was used to prevent injury to the animals.

Tail-flick test. Animals were placed on the tail-lick apparatus (Emdie Instrument Co., Montpelier, VT, Model TF6) with their tails smoothed into the tail groove. All rats were held gently in a clean cloth by the same experimenter. A light source on the tail flick apparatus was illuminated and focused on the tail until the rat moved its tail which turned off the light, or until 9 s had elapsed. The light source was adjusted to obtain baseline tail-flick latencies of between 2–4 s. A 9-s cutoff time was used to prevent damage to the tail. Three measures of baseline tail-flick latencies using different portions of the tail and separated by 15 s were conducted, and the median of the three was used for subsequent comparisons to latencies following morphine administration. Animals then were injected with 1.25 mg/kg morphine sulfate and returned to their home cages for 30 min. Animals then were tested again on the tail-flick apparatus, and injected with morphine. A cumulative dosing regime was used such that the cumulative doses were 1.25, 2.5, 5, and 10 mg/kg. Thirty minutes intervened between each injection and subsequent analgesic testing.

Data Analysis

Analgesic response latencies were compared to baseline latencies by computing the percent of the maximum possible effect (%MPE) achieved. This is calculated as follows:

$$\%\text{MPE} = \frac{\text{Test Latency} - \text{Baseline Latency}}{\text{Maximum Latency} - \text{Baseline Latency}} \times 100$$

Data intially were analyzed using a repeated-measures ANOVA, with morphine dose as the repeated measure and gender and diet as between-subject variables Data were then analyzed separately for each gender with dose as a repeated measure. Post hoc comparisons at each drug dose were conducted using Bonferroni *t*-tests.

EXPERIMENT 1

Method

Twenty-seven male and 27 female Long–Evans rats, approximately 8 weeks of age at the beginning of the experiment, were used. Nine rats of each sex were given Purina Chow and water alone; nine of each sex, Purina Chow, water, and a 32% sucrose solution; and nine of each sex, Purina Chow, water, and a 0.15% saccharin solution. After 3 weeks on the diets, analgesic testing was initiated. Animals were tested first on the hot-plate apparatus with the temperature set at 51°C.

One week after testing on the hot-plate, rats were tested on the tail-flick apparatus as described in the General Methods.

TABLE 1

MEAN (±SD) FOOD INTAKE AND BODY WEIGHT IN MALE AND FEMALE RATS GIVEN EITHER CHOW AND WATER ALONE, CHOW, WATER, AND EITHER A 32% SUCROSE OR A 0.15% SACCHARIN SOLUTION

	Total Daily Caloric Intake	Body Weight (g) at Time of Analgesic Testing
Males		
Sucrose	101.6 ± 5.5 kcal*	407.0 ± 21.5 g*
Saccharin	93.1 ± 7.6 kcal	379.9 ± 27.8 g
Chow only	87.1 ± 3.7 kcal	369.2 ± 16.9 g
Females		
Sucrose	85.4 ± 7.8 kcal*	282.0 ± 29.1 g*
Saccharin	69.9 ± 5.1 kcal	241.8 ± 11.3 g
Chow only	67.7 ± 6.6 kcal	235.8 ± 22.1 g

*Indicates that mean total daily food intake and body weight of male and female rats consuming a 32% sucrose solution were significantly ($p < 0.05$) greater than those of the respective sex consuming either a 0.15% saccharin solution or chow only.

Results

Food intake and body weight. Male rats consumed significantly ($p < 0.01$) more calories per day than females (Table 1). Mean daily caloric intake varied significantly as a function of dietary conditions for both males, $F(2, 24) = 14.27$, $p < 0.01$, and females, $F(2, 24) = 19.10$, $p < 0.01$. For both sexes, total daily caloric intakes of rats given the 32% sucrose solution in addition to chow were significantly ($ps < 0.05$) greater than those of rats given chow alone or chow and the saccharin solution. Comparisons across sexes revealed that although males and females consumed equivalent amounts of sucrose per day, females consumed a significantly, $t(15) = 2.11$, $p < 0.05$, greater percent of their total daily calories from sucrose (59.0%) than males (50.6%). Additionally, females tended ($p < 0.08$) to drink more saccharin (63.9 ml/day) than males (49.6 ml/day).

TABLE 2

MEAN (±SD) BASELINE LATENCIES FOR MALE AND FEMALE RATS ON THE HOT PLATE AND TAIL FLICK TESTS AS A FUNCTION OF DIETARY CONDITIONS

	Baseline Latencies (s)
Hot Plate Test	
Males	
Sucrose	17.3 ± 5.6
Saccharin	19.5 ± 6.2
Chow only	16.6 ± 6.1
Females	
Sucrose	15.7 ± 5.0
Saccharin	19.7 ± 9.7
Chow only	20.5 ± 8.3
Tail-flick test	
Males	
Sucrose	2.8 ± 0.6
Saccharin	3.0 ± 0.6
Chow only	3.1 ± 0.4
Females	
Sucrose	2.7 ± 0.8
Saccharin	3.1 ± 0.6
Chow only	3.3 ± 0.8

Within each gender, body weight did not differ among diet groups at the beginning of the study. However, by the time of initial analgesic testing both male and female rats consuming the sucrose solution weighed significantly [males, $F(2, 24) = 6.75$, $p < 0.01$; females, $F(2, 24) = 11.68$, $p < 0.01$] more than the same-sex animals consuming either chow alone or chow and the saccharin solution (Table 1).

Antinociceptive responses on the hot-plate test. Baseline tail-flick latencies did not vary as a function of either gender or dietary conditions (Table 2).

Antinociceptive responses increased directly as a function of the dose of morphine when data were combined for males and females, $F(3, 120) = 77.55$, $p < 0.001$. Subsequent analyses revealed that dose-related response was significant for both males, $F(3, 63) = 56.02$, $p < 0.001$, and females, $F(3, 57) = 27.24$, $p < 0.001$. However, there were no differences in antinociceptive responses as a function of either diet or gender (Fig. 1).

Antinociceptive responses on the tail-flick test. Baseline tail-flick latencies did not differ as a function of either gender or dietary conditions (Table 2).

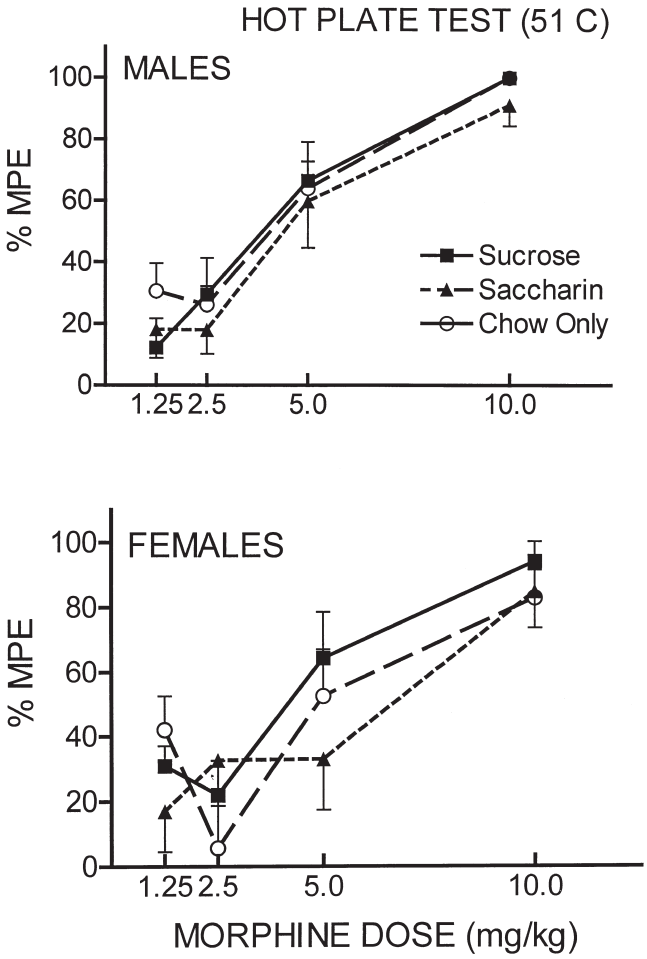

FIG. 1. Antinociceptive responses as measured by the percent maximal possible effect (%MPE) on the hot plate test (51°C) following morphine administration for male (top) and female (bottom) rats consuming either a 32% sucrose solution, chow and water, a 0.15% saccharin solution, chow and water, or only chow and water.

Antinociceptive responses increased in a dose-related manner when data were analyzed for males and females together, $F(3, 132) = 25.38$, $p < 0.001$. Similar dose-related responses were observed when data were analyzed separately for males, $F(3, 63) = 9.34$, $p < 0.001$, and females, $F(3, 69) = 17.46$, $p < 0.001$ (Fig. 2). As on the hot plate, antinociceptive responses to morphine did not differ as a function of gender. Across all animals, %MPEs varied, $F(2, 44) = 7.04$, $p < 0.01$, as a function of dietary conditions, with rats consuming sucrose and chow having significantly greater %MPEs than rats consuming saccharin and chow or chow alone. When data were analyzed separately for each sex it was found that %MPEs differed significantly as a function of diet for females, $F(2, 23) = 5.83$, $p < 0.01$, but not for males.

EXPERIMENT 2

In Experiment 1, diet altered antinociceptive responses to morphine on the tail-flick test, but not on the hot-plate test.

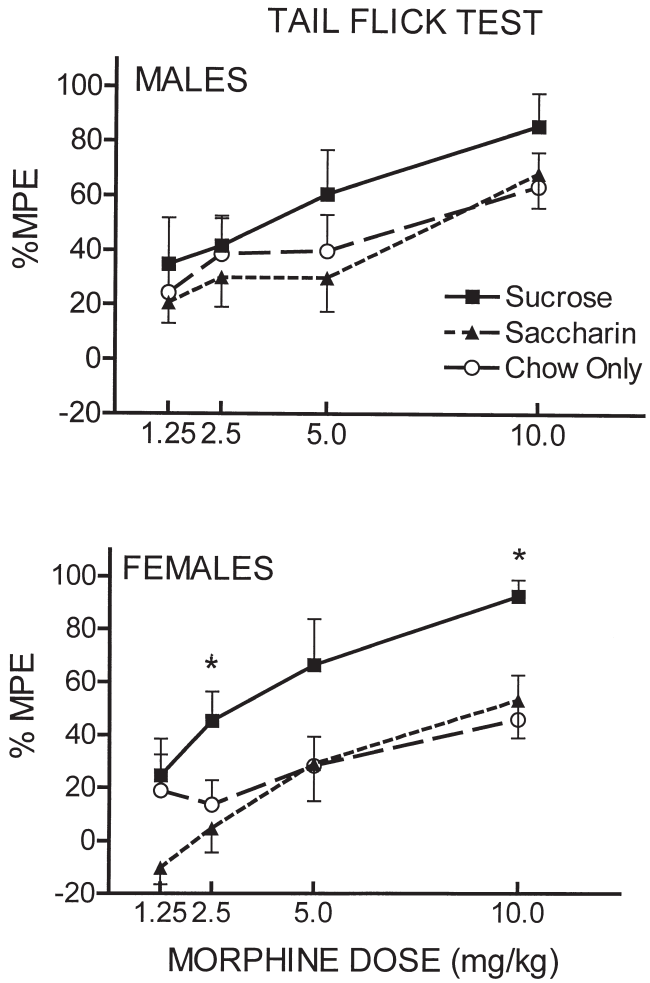

FIG. 2. Antinociceptive responses as measured by the percent maximal possible effect (%MPE) on the tail-flick test following morphine administration for male (top) and female (bottom) rats consuming either a 32% sucrose solution, chow and water, a 0.15% saccharin solution, chow and water, or only chow and water. *%MPEs of rats given the sucrose solution significantly ($p < 0.05$) greater than those of rats given the saccharin solution or chow alone.

One possible explanation for this difference is that the intensity of the noxious stimulus was greater for the tail-flick test than for the hot-plate test. Previous research has demonstrated that the intensity of the noxious stimulus can affect both baseline pain sensitivity and the antinociceptive efficacy of opioid drugs (7,16,32). To determine if the intensity of the hot plate could influence dietary modulation of morphine-induced analgesia, in Experiment 2, the temperature of the hot plate was increased to 53°C.

Methods

Twenty-four male and 24 female Long–Evans rats were used. Eight males and eight females were maintained on Purina chow and water; eight males and eight females, on chow, water and a 32% sucrose solution; and eight males and eight females, on chow, water and a 0.15% saccharin solution.

After animals had been on the diets for a minimum of 4 weeks, analgesic testing was initiated. Testing was similar to that described in the General Methods and Experiment 1 with the exceptions that the hot-plate temperature was maintained at 53°C, and that to prevent damage to the paws animals were removed from the hot plate if they did not respond within 30 s.

A box-plot analysis was conducted on baseline latencies to eliminate outliers. One male rat in the chow group, one male in the saccharin group, and two males in the sucrose group were thus eliminated from the statistical analysis.

Results

Food intake and body weight. Although daily mean caloric intakes of males and females given sucrose were greater than those of their counterparts given chow and saccharin or chow alone, caloric intake did not vary as a function of diet (Table 3). As in Experiment 1, mean daily sucrose intake did not vary in males and females, but the percent of total daily calories consumed as sucrose was significantly, $t(11) = 2.70$, $p < 0.05$, greater in females (79%) than in males (59%). In contrast to Experiment 1, males consumed significantly, $t(13) = 2.28$, $p < 0.05$, more saccharin per day (47.4 ml) than females (27.8 ml).

TABLE 3

MEAN (±SD) FOOD INTAKE AND BODY WEIGHT IN MALE AND FEMALE RATS IN EXPERIMENT 2 GIVEN EITHER CHOW AND WATER ALONE, OR CHOW, WATER, AND EITHER A 32% SUCROSE OR A 0.15% SACCHARIN SOLUTION

	Total Daily Caloric Intake	Body Weight (g) at Time of Analgesic Testing
Males		
Sucrose	95.8 ± 4.6 kcal	579.1 ± 26.4 g*
Saccharin	88.6 ± 14.4 kcal	499.1 ± 46.1 g
Chow only	89.6 ± 11.6 kcal	495.7 ± 29.4 g
Females		
Sucrose	75.5 ± 25.2 kcal	287.8 ± 36.0 g
Saccharin	65.2 ± 19.2 kcal	266.2 ± 15.6 g
Chow only	62.5 ± 7.5 kcal	256.9 ± 19.3 g

*Indicates that mean total daily food intake and body weight of male and female rats consuming a 32% sucrose solution were significantly ($p < 0.05$) greater than those of the respective sex consuming either a 0.15% saccharin solution or chow only.

Mean body weight at the time of analgesic testing was significantly greater in male rats fed sucrose than in those given saccharin or chow alone $F(2, 17) = 11.14$. However, although mean body weight of females fed sucrose was greater than that of females in the other groups, this difference was not significant (Table 3).

Antinociceptive responses. Baseline latencies on the hot plate did not differ as a function of either gender or dietary conditions (males: sucrose = 10.8 ± 2.8 s; saccharin = 10.0 ± 2.4 s; chow only = 8.2 ± 4.3 s; females: sucrose = 6.7 ± 2.0 s; saccharin = 10.1 ± 4.3 s; and chow only = 8.5 ± 2.5 s). However, comparison with Experiment 1 revealed that baseline latencies were significantly shorter $F(1, 76) = 59.35$, $p < 0.001$, when the temperature of the hot plate was 53°C than when it was 51°C.

Antinociceptive responses on the hot plate increased directly as a function of drug dose when data for males and females were analyzed together, $F(3, 108) = 62.79$, $p < 0.001$, and when data were analyzed separately for males, $F(3, 48) = 30.51$, $p < 0.001$, and females, $F(3, 60) = 33.75$, $p < 0.001$. Antinociceptive responses did not differ as a function of gender. Animals given sucrose displayed a trend toward greater %MPEs than animals given either chow alone or saccharin and chow. This trend was more notable in female than in male rats (Fig. 3).

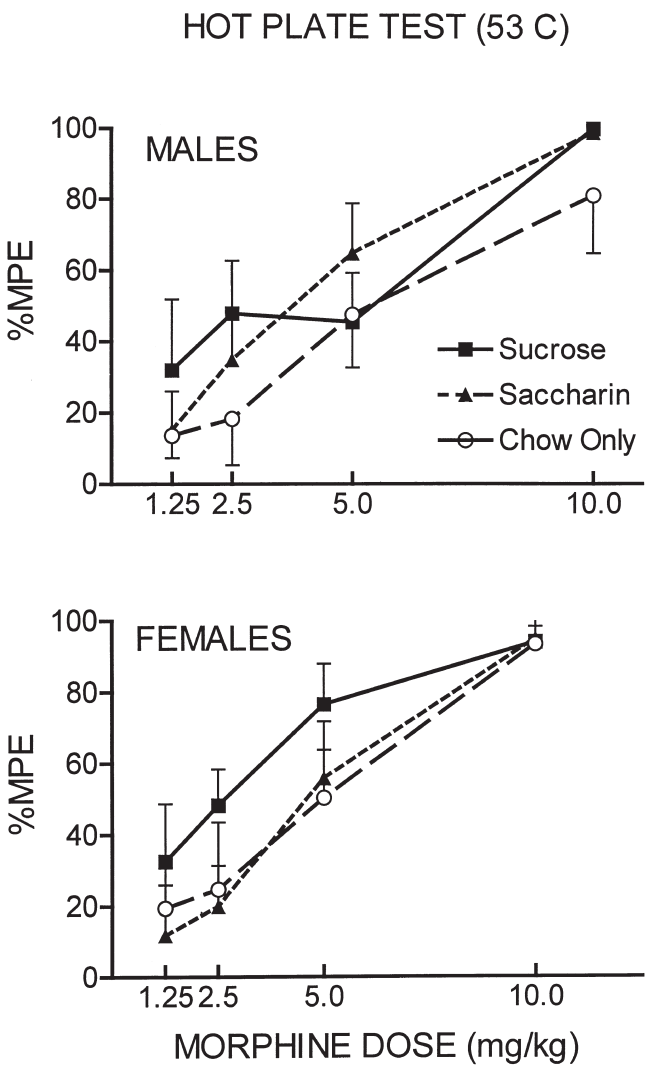

FIG. 3. Antinociceptive responses as measured by the percent maximal possible effect (%MPE) on the hot plate test (53°C) following morphine administration for male (top) and female (bottom) rats consuming either a 32% sucrose solution, chow and water, a 0.15% saccharin solution, chow and water, or only chow and water.

GENERAL DISCUSSION

As in previous studies, in the present experiments, intake of a sweet-tasting nutritive sucrose solution, but not intake of a sweet-tasting but nonnutritive saccharin solution, increased the analgesic potency of morphine in the tail flick test (12–14,23,25,37). These findings, taken in conjunction with data demonstrating that prior intake of palatable foods and fluids 1) enhances the anorectic potency of opioid antagonists (24,40,42); 2) increases opioid receptor binding in the brains of rats and mice (22); and 3) leads to the release of beta-endorphin in the hypothalamus, proDynorphin mRNA levels in arcuate nucleus and dynorphin A1—17 in the paraventricular nucleus of rats (15,41) have led to the hypothesis that intake of palatable sweet-tasting nutritive solutions alters the functioning of the endogenous opioid system.

Although substantial evidence has accumulated to support the preceding hypothesis using the tail-flick apparatus, the present results using the hot-plate test do not appear to confirm the hypothesis. On the hot-plate test, no significant differences in antinociceptive responses were observed as a function of dietary variables. It has been hypothesized that the tail-flick response is mediated primarily at the level of the spinal cord, while responses on the hot plate are mediated within the brain (17,20). Thus, it is possible that intake of sweet ingesta influences opioid mechanisms within the spinal cord, but not within the brain. This possibility seems unlikely, however, because rats drinking a sucrose solution have significantly greater antinociceptive responses on the tail-flick test following morhpine injections into the lateral ventricle (34), or the periaqueductal gray (Homoleski and Kanarek, unpublished results) than rats obtaining all of their calories from chow. The differences observed in the effects of dietary variables on antinociceptive responses in the tail flick and hot plate tests may be more a function of factors of the tests than of diet differentially affecting spinal and brain opioid systems. For example, on the tail-flick test, the tail-flick response is discrete and easily measured. Additionally, because different portions of the tail can be used, it is possible to make multiple baseline determinations of tail-flick latency. These measures tend to be relatively consistent both within and among animals, and thus indicate a stable nondrug level of pain sensitivity on the tail-flick test. In comparison to responses on the tail-flick test animals' responses on the hot-plate test are more variable (16). At the lower temperature (51°C), most animals responded by licking a hind paw. However, at the higher temperature (53°C), some rats licked a hind paw, while others jumped up from the heated surface of the hot plate. Although an individual animal tended to display the same type of response on each test, variability among animals was greater on the hot-plate test than on the tail-flick test.

Another factor that could have contributed to lack of dietary effects on the hot-plate test is the intensity of the nociceptive stimulus (7,16,32). Previous work using the tail-flick test suggests that sucrose intake has a greater effect on morphine-induced analgesia when higher rather than lower stim-

ulus intensities are used (Mathes and Kanarek, unpublished results). In support of this suggestion, in Experiment 2, when the temperature of the hot plate was increased, there was a trend for female rats consuming sucrose to have elevated antinociceptive responses relative to females eating only chow. The logical way to test this suggestion would be to increase the temperature of the hot plate. However, the possibility of damage to the rats' paws makes this test not feasible.

An additional factor to consider with respect to the difference in the effects of diet on antinociceptive responses on the hot-plate and tail-flick test is the order in which the tests were completed. In Experiment 1, rats were tested on the hot plate prior to being tested on the tail-flick apparatus. We recognize that repeated testing of the animals could confound the results of the study, as it introduces two additional variables, length of exposure to the diets, and whether animals were drug naive or not. With respect to the first variable, length of exposure to the diet, we and others have found that acute intake (less than 24 h) of palatable solutions decreases morphine's antinociceptive actions, while chronic intake (greater than 3 weeks) to the same solutions increases the antinociceptive potency of morphine (14). Allowing rats to consume sucrose solutions for more than 3 weeks does not further enhance morphine-induced antinociception. For example, in experiments in which after 3 weeks of intake of palatable sucrose solution, each rat received multiple doses of morphine across several weeks, antinociceptive responses on the tail-flick test did not vary as a function of time consuming the sucrose solution (23,25). Recent studies have shown that sucrose intake not only increases sensitivity to morphine-induced analgesia, but also impairs the development of tolerance to the drug's antinociceptive actions (12). Thus, it is possible that tolerance to morphine's analgesic actions was not as great in rats that had consumed sucrose than in those given saccharin or chow alone. This lack of tolerance could have accentuated the effects of sucrose on morphine-induced analgesia on the tail-flick test.

In the present studies, no differences in baseline latencies were observed between males and females on either the tail-flick or hot-plate tests. Moreover, males and females displayed comparable dose–response curves following morphine administration. These results can be contrasted with those of previous studies demonstrating gender differences in analgesic responses. A number of investigators have reported that male rodents are more sensitive to the analgesic actions of morphine and other opioids than females (6,8,9,11,21,26,27,29). For example, Cicero and colleagues (8,9) found that while there were no gender differences in baseline latencies on either the tail-flick or hot-plate apparatus, male rats were consistently more sensitive to the analgesic actions of both morphine, and the mu opioid receptor agonist, alfentanil, than females. These researchers further observed that neither peak levels nor the half-life of morphine in the blood or brain varied as a function of gender (9). On the basis of these data, they concluded that differences in responses to opioid-induced analgesia between males and females does not reflect gender differences in the pharmacokinetics of the drug. They suggest that, more likely, the differences in opioid-induced analgesia are the consequence of inherent differences in the sensitivity of the brain to opioids in male and female rodents (9). Other researchers have reported that adult female rats displayed significantly less analgesia following both continuous and intermittent cold-water swims (38,39) and after acute restraint (3) than adult male rats. In contrast to the preceding reports, others have found either that females are more sensitive to morphine's antinociceptive actions (1), or no differences in antinociceptive responses as a function of gender (5). Results of a recent study suggest that genetic background plays a significant role in determining whether gender differences in morphine-induced antinociception are observed (27). In this study, which employed 11 strains of mice, males were more sensitive than females to morphine's antinociceptive actions in three strains, females were more sensitive than males in one strain, and there were no gender differences in morphine-induced antinociception in seven strains (27). Additionally, a number of other factors including the analgesic test used, the type and dose of opioid tested, and the time of analgesic testing following drug administration could play a role in determining whether gender differences in opioid-induced antinociception are observed (5,35,36).

Although no gender differences were observed in baseline pain sensitivity or antinociceptive responsiveness to morphine, female rats seemed to be more sensitive to the effects of sucrose on morphine-induced antinociception than males. In Experiment 1, %MPEs of female rats drinking the sucrose solution were significantly greater than those of females eating only chow, while %MPEs of males given sucrose were not greater than those of males eating only chow. Additionally, in Experiment 2, it appeared that sucrose intake enhanced morphine-induced analgesia on the hot plate to a greater degree in females than in males. These findings could reflect gender differences in the sensitivity of the endogenous opioid system to dietary variables, or gender differences in sucrose intake. In both experiments, although there were no gender differences in absolute sucrose intake, females consumed a larger percentage of their daily caloric intake as sucrose than males. Additionally, because females weighed less than males, their sucrose intake was greater on a body weight basis than that of males. Equating the percent of total caloric intake from sucrose in males and females might help to determine if there is an innate difference in sensitivity to the effect of the sugar on morphine-induced antinociception between the sexes, or if the differences we observed were simply the result of the female's relatively greater intake of sugar. However, equating intake would be impossible to do without experimentally restricting sucrose consumption, which could itself alter the sugar's effect on morphine's analgesic actions.

In conclusion, the present studies demonstrate that sucrose enhancement of morphine-induced analgesia is not gender specific. However, females may be more sensitive to sucrose's enhancement of morphine's analgesic activity than males. The results also suggest that variables such as stimulus intensity and prior drug history may interact with dietary variables in determining opioid drug action.

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