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Intake of a Palatable Sucrose Solution Modifies the Actions of Spiradoline, a Kappa Opioid Receptor Agonist, on Analgesia and Feeding Behavior in Male and Female Rats

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KANAREK, R. B., B. A. HOMOLESKI AND C. WIATR. *Intake of a palatable sucrose solution modifies the actions of spiradoline, a kappa opioid receptor agonist, on analgesia and feeding behavior in male and female rats.* PHARMACOL BIOCHEM BEHAV **65**(1) 97–104, 2000.—Previous research has shown that rats consuming a sucrose solution and chow are more sensitive to the analgesic actions of morphine, a selective mu opioid agonist, and the anorectic actions of opioid antagonists, than rats eating only chow. However, from these data, it cannot be determined if sucrose intake only modifies the behavioral consequences of drugs that act at the mu opioid receptor, or if the sugar also alters the actions of opioid drugs that act at other opioid receptor subtypes. Thus, the present experiments examined the effects of sucrose intake on the actions of spiradoline, a selective kappa opioid agonist, on analgesia and food intake in male and female Long–Evans rats. In Experiment 1, male and female rats consumed either chow, a 32% sucrose solution and water, or only chow and water. After 3 weeks, antinociceptive responses on the tail-flick test were determined after spiradoline injections (0.0, 0.3, 1.0, and 3.0 mg/kg, SC). Rats fed sucrose were more sensitive to the analgesic actions of spiradoline than rats fed only chow. In Experiment 2, drug-naive male and female rats were maintained under the same dietary conditions as in Experiment 1. Food intake was measured 1, 2, 4, and 6 h after spiradoline injections (0.0, 0.3, 1.0, and 3.0 mg/kg, SC). Spiradoline led to significant dose-related decreases in food intake for males and females in both dietary conditions. However, the anorectic effects of the drug were more pronounced in rats fed sucrose than in those eating only chow. These results support the hypothesis that intake of palatable foods and fluids alters the activity of the endogenous opioid system. © 1999 Elsevier Science Inc.

Spiradoline Kappa opioid receptors Sucrose Palatability Analgesia Antinociception Food intake Tail flick test Rats

IT has been hypothesized that an interaction exists between the endogenous opioid peptide system and the intake of palatable foods and fluids (26,39,53). Studies demonstrating that administration of opioid agonists and antagonists alters intake of palatable foods and fluids to a greater degree than intake of less palatable fare suggest that the endogenous opioid system is important in mediating the pleasurable aspects of feeding behavior [e.g., (12–14,24,34,39,56,57)]. On the other hand, experiments reporting that intake of palatable foods and fluids modifies the behavioral consequences of opioid drugs indicate that dietary variables alter the functioning of the endogenous opioid system [e.g., (15,16,20,27–31,41,42,47,54,55)].

Experiments assessing the effects of intake of palatable foods and fluids on the behavioral actions of opioid drugs primarily have used morphine, a selective mu opioid agonist, or naloxone or naltrexone, general opioid antagonists. A number of researchers have reported that chronic intake of palatable foods and fluids increases the potency of morphine on a number of analgesic tests (15,16,20,29,30,41,42,47), and enhances the anorectic potency of naloxone and naltrexone (28,54,55). From these findings, it cannot be determined if intake of palatable items only influences drugs that act at the mu opioid receptor, or also alters the actions of drugs that act at other opioid receptor subtypes. Preliminary evidence that

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the latter is the case comes from studies demonstrating that chronic intake of a sucrose solution enhances the effects of the selective kappa opioid agonist, U50,488H, on analgesia (29) and feeding behavior (Kanarek, unpublished data). For example, although U50,488H had almost no analgesic actions in male rats given only chow and water, the drug led to significant analgesic responses in males chronically consuming a sucrose solution in addition to chow and water (29). Moreover, U50,488H led to greater changes in food intake in rats fed sucrose and chow than in those fed only chow (Kanarek, unpublished manuscript). To further determine whether intake of palatable food modifies the analgesic actions of drugs acting at kappa opioid receptors, in Experiment 1, the effects of chronic intake of a sucrose solution on the actions of spiradoline mesylate (U62,066E), a selective kappa agonist (52), on antinociceptive responses on the tail-flick test were investigated. Although both U50,488H and spiradoline have analgesic actions, the analgesic potency of spiradoline has been reported to be greater than that of U50,488H on a variety of antinociceptive tests using male animals (35–37,44,45,52). No prior data are available on the analgesic actions of spiradoline in female rodents. As previous studies have indicated that gender differences exist in the analgesic actions of a number of opioid agonists (2,3,5,6,10,23,32,33,49), it was deemed important to examine dietary influences on the analgesic actions of spiradoline in both male and female rats.

Although kappa opioid receptor agonists serve as analgesics, they also influence other behaviors. Previous experiments have demonstrated that a number of kappa agonists can increase food intake [e.g., (13,14,24)]; however, there is a paucity of data on the actions of spiradoline on feeding behavior. Experiment 2 was designed to determine 1) the effect of spiradoline on food intake in fasted rats, 2) the impact of chronic sucrose consumption on spiradoline-induced alterations in food intake, and 3) if these effects were gender dependent.

EXPERIMENT 1

Method

Animals. Twelve male and 12 female Long–Evans rats (Charles River Laboratories, Portage, MI), weighing between 175 and 225 g at the beginning of the experiment, were used. Animals were singly housed in hanging stainless steel cages in a temperature-controlled room (22 ± 1°C) maintained on a 12–12-h reverse light–dark cycle (lights on: 2000–0800 h).

Dietary conditions. Six male and six female rats were given ad lib access to Purina #5001 laboratory chow and water. The remaining six animals of each sex were given ad lib access to a 32% (w/v) sucrose solution in addition to chow and water. Animals were maintained under these dietary conditions for three weeks before analgesic testing was initiated.

Drugs

Spiradoline mesylate (U62,055; Research Biochemicals, Natick, MA) was dissolved in 0.9% saline and administered subcutaneously in a volume of 1 ml/kg. Animals received doses of 0.0, 0.3, 1.0, and 3.0 mg/kg. Doses were chosen on the basis of previous work demonstrating the analgesic actions of spiradoline (8,52).

Procedure

The antinociceptive properties of spiradoline were assessed using the radiant-heat tail-flick test. Each animal was individually taken into the procedure room and placed on the tail-flick apparatus (Model TF6, Emdie Instrument Co, Montpelier, VT) with its tail smoothed into a 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. 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. The median of the three baseline measures was used for subsequent comparisons to tail-flick latencies following spiradoline administration. Animals then were injected with spiradoline or saline, and tail-flick latencies measured again at 15, 30, and 60 min following injections. Two measures of tail flick latencies were taken at each time point, and the mean of the two used in data analysis. The order of drug dose was counterbalanced across dietary conditions, with a minimum of 4 days intervening between drug testing days. Analgesic testing was conducted between 1000 and 1600 h under dim red lighting conditions. All procedures were approved by the Tufts University Institutional Animal Care and Use Committee.

Data analysis

Analyses were conducted on the percent maximum possible effect (%MPE), which was calculated as follows:

$$\%\text{MPE} = \frac{\text{Test latency} - \text{baseline latency}}{\text{Maximum latency} - \text{baseline latency}} \times 100$$

with the maximum latency being the cutoff time of 9 s.

The data initially were analyzed using repeated-measures ANOVAs with dose and time following injections as repeated measures and diet and gender as between-subject variables. Then, ANOVA's were conducted at each measurement time with dose as a repeated measure and diet and gender as between subjects variables. Data were then analyzed for each gender.

One male rat fed only chow and one female fed sucrose and chow were eliminated from the data analyses because their baseline tail flick latencies were two standard deviations from the mean of their respective groups.

Results

Baseline tail-flick latencies did not vary as a function of either diet or gender (males: sucrose and chow = 2.15 ± 0.18 s, chow only = 1.98 ± 0.22 s; females: sucrose and chow = 1.92 ± 0.23 s, chow only = 2.34 ± 0.23 s).

Spiradoline significantly, $F(3, 54) = 46.60$, $p < 0.001$, increased antinociceptive responses in a dose-related manner when data were analyzed with dose and time after injections as repeated measures and gender and diet as between-subject variables. No differences in drug action were observed as a function of time after injections. Across drug doses and time of measurement, %MPEs of rats fed sucrose and chow were significantly, $F(1, 18) = 6.49$, $p < 0.05$, greater than those of rats fed chow alone. Analyses at each measurement time revealed that antinociceptive responses of males and females consuming the sucrose solution were significantly, $F(1, 18) = 13.10$, $p < 0.01$, greater than those of rats eating only chow, 15 min following injections, but did not differ between dietary groups 30 and 60 min after injections.

When analyzed separately for males and females, it was found that %MPEs varied significantly as a function of the dose of spiradoline at all measurement times (males: 15 min,

$F(3, 27) = 9.30, p < 0.001$; 30 min, $F(3, 27) = 19.34, p < 0.001$; 60 min, $F(3, 27) = 13.53, p < 0.001$; females: 15 min, $F(3, 27) = 9.99, p < 0.001$; 30 min, $F(3, 27) = 13.57, p < 0.001$; 60 min, $F(3, 27) = 10.28, p < 0.001$.

Fifteen minutes following drug injections, antinociceptive responses of male rats fed sucrose and chow were significantly, $F(1, 9) = 14.53, p < 0.01$, greater than those of males fed only chow. Although antinociceptive responses of female rats drinking the sucrose solution were greater than those of females not given the sugar, this difference was not significant. Similarly, while with few exceptions, both male and female rats drinking the sucrose solution had higher %MPEs 30 and 60 min following spiradoline injections than rats given only chow, these differences were not significant (Fig. 1 and 2). However, 60 min following drug injections, the interaction of diet and drug dose was significant, $F(3, 27) = 4.04, p < 0.02$, in female rats. For females drinking the sucrose solution, %MPEs increased directly as a function of the dose of spiradoline, while for those eating only chow, %MPEs only increased until the 1.0 mg/kg dose of spiradoline was given.

EXPERIMENT 2

Method

Animals and dietary conditions. Twelve male and 12 female drug-naive Long–Evans rats, weighing between 175 and 225 g at the beginning of the experiment were used. Animals were housed as described in Experiment 1. Six of the animals of each sex were fed only Purina chow and water. The remaining six males and six females were given a 32% sucrose solution in addition to chow and water. Animals were maintained on these diets for 3 weeks preceding testing for the effects of spiradoline on feeding behavior.

Procedure. Rats were deprived of chow and sucrose for 18 h prior to testing. Rats then were injected with spiradoline (0.0, 0.3, 1.0, and 3.0 mg/kg, SC) in the early portion of the dark portion of the lighting cycle at 1000 h, and chow (but not sucrose) returned to the animals. Food intake was measured 1, 2, 4, and 6 h after injections. Food spillage was also recorded. The majority of animals did not spill their food. However, one male fed only chow, and two females fed sucrose and chow spilled their food at least once during the testing period. Data from these animals were not analyzed. At the end of the testing period, sucrose was returned to the appropriate animals. This procedure was repeated with a minimum of a week separating drug injections, until all animals had received each drug dose. The order in which drug doses were administered was counterbalanced across animals.

Data analysis. Data initially were analyzed using a repeated-measure analysis of variance with drug dose as the repeated measure, and diet and gender as between-group variables. Data then were analyzed separately for males and females. Post hoc comparisons were made using the Bonferroni *t*-test. All data that are reported as significant have a *p*-value of 0.05 or less.

Results

Food intake across dietary conditions and drug doses did not vary significantly as a function of gender at any measurement time. However, cumulative food intakes 4 and 6 h following saline injections were significantly greater in rats that had only consumed chow than in those that had also drunk the sucrose solution [4 h, $F(1, 17) = 6.11, p < 0.05$; 6 h, $F(1, 17) = 6.65, p < 0.05$]. When data were analyzed separately for males and females, food intake following saline injections did not differ as a function of diet in female rats, but in males, food intake was significantly ($p < 0.05$) greater 4 and 6 h after saline injections in animals fed only chow throughout

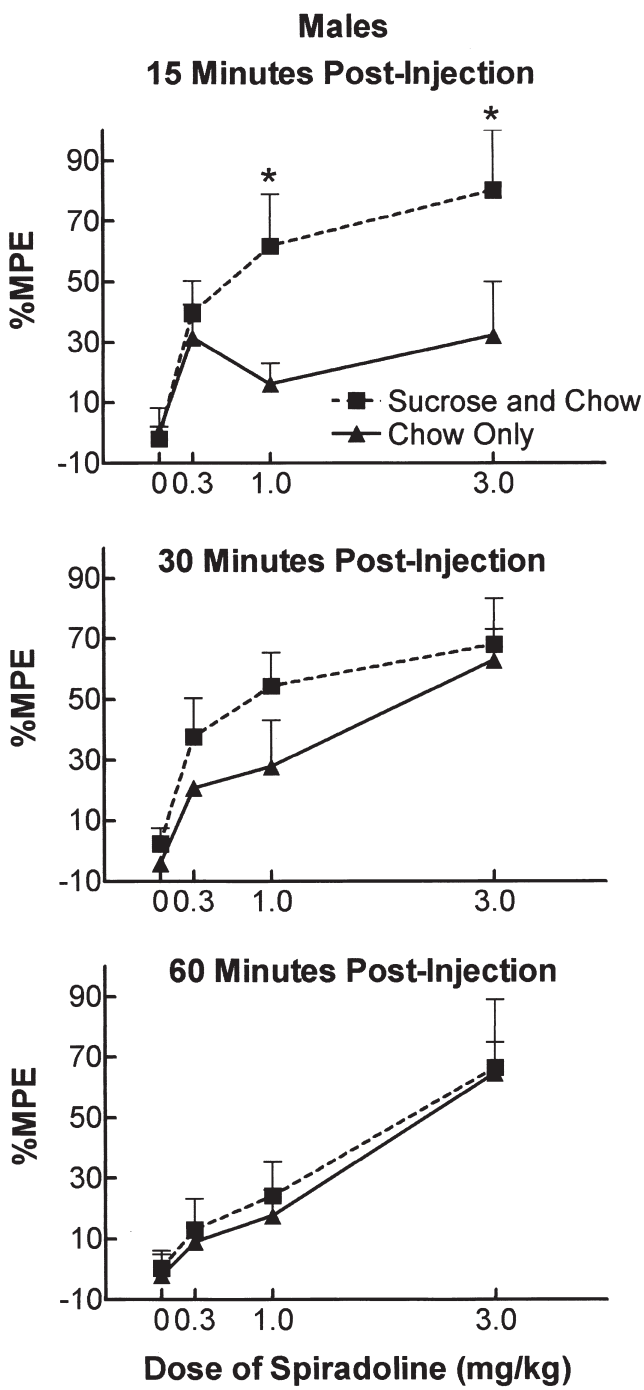

FIG. 1. Effects of spiradoline on antinociceptive responses on a tail flick test 15, 30, and 60 min following injections in male rats consuming either laboratory chow and water, or a 32% sucrose solution, laboratory chow and water. *%MPEs of rats consuming the 32% sucrose solution significantly ($p < 0.05$) greater than those of rats consuming only chow.

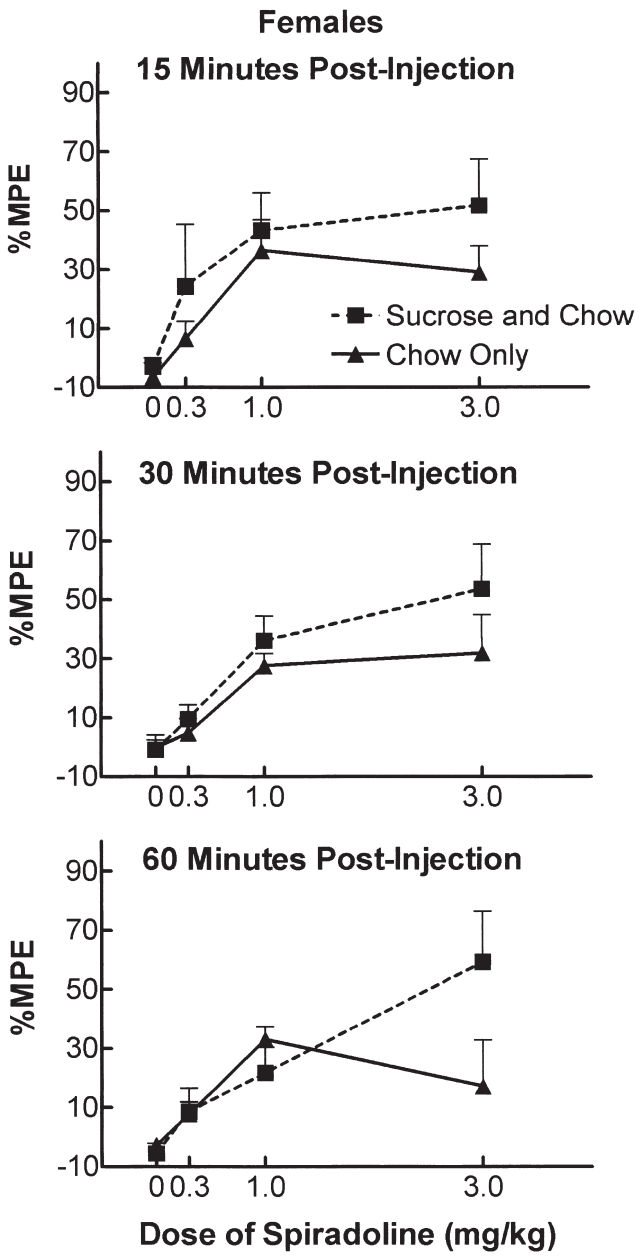

FIG. 2. Effects of spiradoline on antinociceptive responses on a tail flick test 15, 30, and 60 min following injections in female rats consuming either laboratory chow and water, or a 32% sucrose solution, laboratory chow and water.

the experiment than in those fed sucrose and chow. Because of the differences in intake following saline injections, in males, food intake data following spiradoline administration were also analyzed as percent change from saline injections.

When data were analyzed for all animals, cumulative food intake was significantly altered as a function of spiradoline administration at all measurement times [1 h, $F(3, 45) = 29.95$, $p < 0.001$; 2 h, $F(3, 48) = 44.22$, $p < 0.001$; 4 h, $F(3, 48) = 9.03$, $p < 0.001$; 6 h, $F(3, 48) = 8.21$, $p < 0.001$]. Additionally, there was a significant interaction between diet and drug dose 1 h, $F(3, 45) = 2.71$, $p < 0.05$, and 2 h, $F(3, 48) = 8.71$, $p < 0.001$, after injections. These interactions reflect the observation that spiradoline decreased food intake in a dose-related manner in rats fed sucrose and chow, while the lowest of the drug increased food intake in rats fed only chow.

In male rats fed sucrose and chow, spiradoline led to significant dose-related reductions in cumulative food intake at all measurement times [1 h, $F(3, 15) = 15.12$, $p < 0.001$; 2 h, $F(3, 15) = 14.97$, $p < 0.001$; 4 h, $F(3, 15) = 15.61$, $p < 0.001$; and 6 h, $F(3, 15) = 4.46$, $p < 0.05$] (Fig. 3, top). Post hoc tests showed that 1, 2, and 4 h after injections, food intake was significantly ($p < 0.05$) suppressed by 1.0 and 3.0 mg/kg spiradoline, while 6 h after injections food intake was significantly ($p < 0.05$) decreased by 3.0 mg/kg of the drug. In comparison, in males fed only chow, spiradoline significantly altered food intake only 1 h, $F(3, 9) = 8.53$, $p < 0.01$, and 2 h, $F(3, 9) = 11.51$, $p < 0.01$, after injections (Fig. 3, bottom). These differences were the result of significant ($p < 0.05$) reductions in food intake following the administration of 3.0 mg/kg spiradoline in comparison to injections of saline and 0.3 mg/kg of the drug. Because food intake differed in the two dietary groups when they were injected with saline, percent change from saline intake was determined for all animals. Spiradoline led to significantly ($p < 0.05$) greater reductions in percent change from

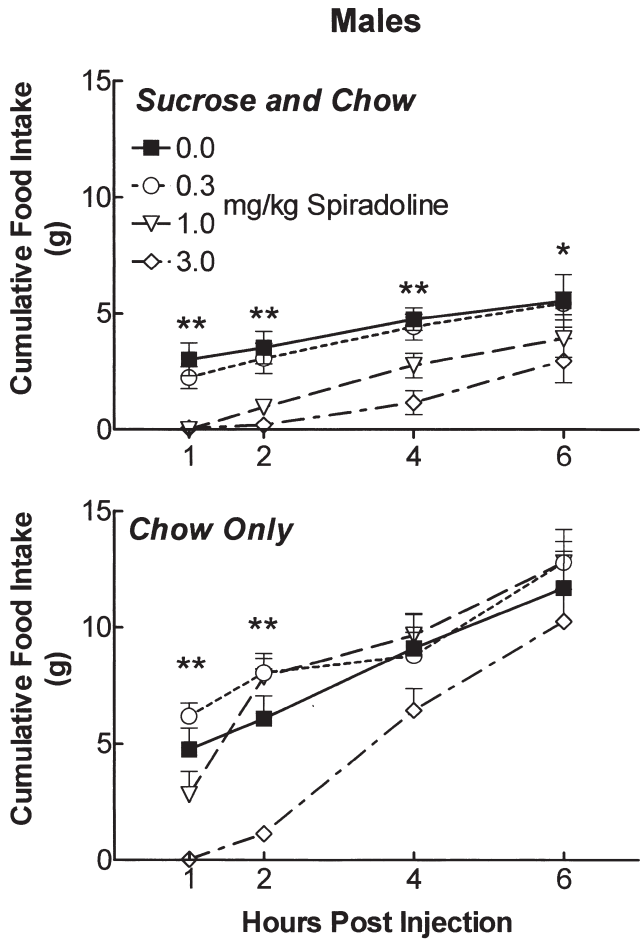

FIG. 3. Effects of spiradoline on food intake in male rats consuming either laboratory chow and water, or a 32% sucrose solution, laboratory chow and water. Food intake was significantly (**$p < 0.01$; *$p < 0.05$) altered as a function of spiradoline injections.

saline intake, 1 h after injections of 1.0 mg/kg, 2 h after injections of 0.3, 1.0, and 3.0 mg/kg, 4 h after injections of 1.0 and 3.0 mg/kg, and 6 h after injections of 3.0 mg/kg in males fed sucrose and chow than in males maintained on only chow.

In female rats fed sucrose and chow, spiradoline led to significant dose-related decreases in cumulative food intake 2 h, $F(3, 9) = 9.09$, $p < 0.01$, 4 h, $F(3, 9) = 4.60$, $p < 0.05$, and 6 h, $F(3, 9) = 8.96$, $p < 0.01$, after injections (Fig. 4, top). Post hoc tests demonstrated that at all of these times, food intake was significantly ($p < 0.05$) reduced following administration of 3.0 mg/kg spiradoline. In females fed chow only, spiradoline significantly altered food intake at 1 h, $F(3, 12) = 9.22$, $p < 0.01$, and 2 h, $F(3, 12) = 16.59$, $p < 0.01$, after injections (Fig. 4, bottom). These differences were the result of significant ($p < 0.05$) reductions in food intake after administration of 3.0 mg/kg spiradoline in comparison to injections of saline and 0.3 mg/kg of the drug.

GENERAL DISCUSSION

The results of these experiments provide further evidence that chronic intake of palatable sucrose solutions alters the behavioral effects of opioid drugs. Rats fed sucrose and chow were more sensitive to the effects of spiradoline, a selective kappa opioid receptor agonist, on analgesia and food intake than rats fed only chow. These data are consistent with those of previous studies, which found that chronic intake of sweet-tasting fluids enhanced the analgesic properties of kappa, as well as mu receptor agonists (15,16,20,22,29–31,41,42,47), and augmented the anorectic actions of opioid antagonists (28,50, 54,55). Although some minor differences were observed, in general, spiradoline affected analgesia and food intake similarly in male and female rats.

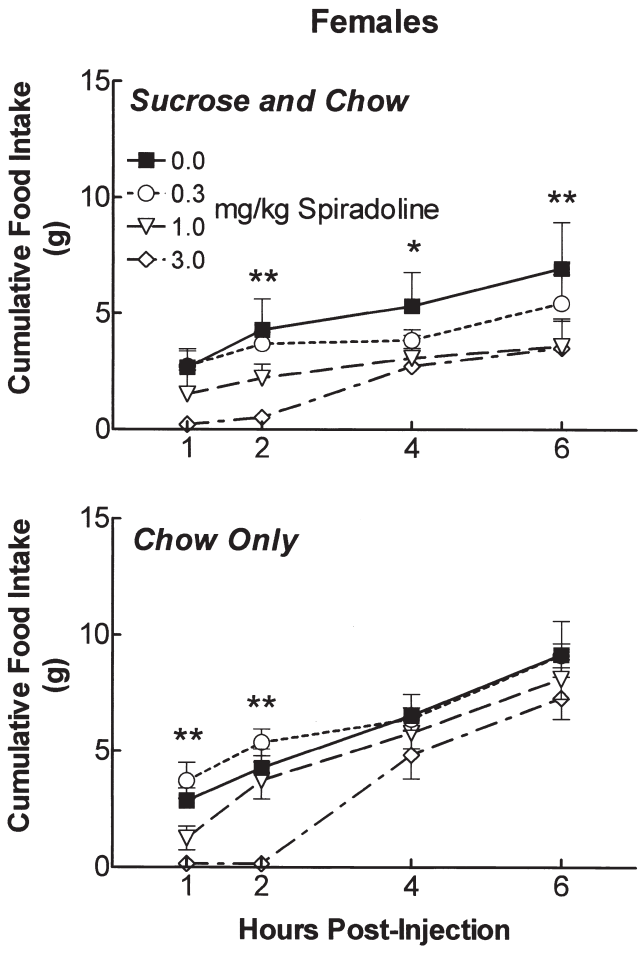

FIG. 4. Effects of spiradoline on food intake in female rats consuming either laboratory chow and water, or a 32% sucrose solution, laboratory chow and water. Food intake was significantly (**$p < 0.01$; *$p < 0.05$) altered as a function of spiradoline injections.

In Experiment 1, spiradoline led to dose-related increases in antinociceptive responses in female rats, as well as in male rats as previously reported (8,44,45,52). Comparison of antinociceptive responses in males and females revealed no gender differences in the analgesic actions of spiradoline. These results can be contrasted with those of previous studies demonstrating that male rodents are more sensitive to the analgesic actions of morphine and other opioids than females (5,10,11,23,32,33). Cicero and colleagues (10,11), for example, found that while there were no gender differences in baseline latencies on either the hot plate or tail-flick test, male rats were more sensitive to the analgesic actions of morphine, and the mu opioid receptor agonist, alfentanil, than females. These researchers additionally reported that neither peak levels nor the half-life of morphine in the blood or brain differed as a function of gender (11). From these results, they concluded that differences in responses to opioid-induced analgesia between males and females do not reflect gender differences in the pharmacokinetics of the drug. They suggest that the differences in opioid-induced analgesia more likely arise from inherent differences in the sensitivity of the brain to opioids in male and female rodents (10,11). Other researchers have reported that female rats displayed less analgesia following both continuous and intermittent cold water swims (49), and after acute restraint (3) than male rats. In contrast to these findings, results of other studies indicate that females are more sensitive to morphine's antinociceptive actions (2), or that males and females do not differ in their antinociceptive responses to opioid drugs (6,31). It has been suggested that these discrepant findings may be the result of a number of factors including the type and dose of opioid drug, the analgesic test used, the time of analgesic testing following drug administration, and the strain of animal tested (6).

The analgesic action of spiradoline was greater in rats consuming sucrose and chow than in those fed only chow. These findings are in agreement with the results of previous studies demonstrating that the analgesic actions of morphine and the kappa opioid receptor agonist, U50,488H, are more pronounced in rats and mice consuming nutritive palatable fluids than in those eating only a standard laboratory diet (15,16, 19,29–31,41,42,47). The majority of experiments assessing dietary effects on antinociception have used the tail-flick test to measure pain sensitivity [e.g., 15,16,19,29–31,47)]. Several investigators have reported that responses on the tail flick test vary as a function of tail skin temperature (7,18,48). Thus, it is possible that changes in tail temperature could mediate antinociceptive responses on the tail-flick test between rats consuming sucrose and those not eating the sugar. However, while this is possible, it does not seem likely for several reasons. First, we have observed no differences in baseline body temperature or temperature changes in response to morphine between rats fed sucrose and those not given the sugar (D'Anci and Kanarek, unpublished findings). Additionally, recent studies using several different nociceptive tests indicate

that changes in tail temperature alone do not account for enhanced opioid-induced analgesia in sucrose-fed animals. For example, using a new nociceptive test that measures the time required for rats to withdraw their hind paws from a cold solution (−6°C), we found that the antinociceptive actions of spiradoline were greater in rats fed a 32% sucrose solution than in rats fed only chow (22). Additionally, two recent studies demonstrate that intakes of palatable fluids also modify morphine-induced antinociception on the formalin test in mice (41,42). In this test, formalin is injected into the dorsal surface of the hind paw, and the time spent licking and biting the injected paw over a 30-min period measured as the indicator of pain (1). Using this test, it was found that intake of either a sucrose or aspartame solution increased, while intake of a saccharin solution had minimal effects on the analgesic potency of morphine (41,42).

The mechanisms by which intake of nutritive palatable fluids influence opioid-induced antinociception remain to be elucidated. One possibility is that the increase observed in the potency of opioid drugs in rats drinking palatable solutions is the result of alterations in nutrient intakes. When rats are maintained on water, chow, and a 32% sucrose solution, they take in approximately 50% of their calories from the solution and 50% from chow (9,25). Thus, in this situation, rats consume approximately one-half as much protein, vitamins, and minerals as rats fed only chow. Therefore, the elevation in opioid-induced antinociception seen in rats drinking a sucrose solution may be related to a reduction in intake of other nutrients. To test this possibility, we recently examined the effects of decreasing the protein or vitamin and mineral content on the morphine-induced antinociception (27). In these experiments, no differences were observed in the analgesic potency of morphine as a function of reductions in either the protein or micronutrient content of the diet (27). These findings indicate that the enhancement in opioid-induced antinociception observed in rats consuming a sucrose solution is not due to reductions in the intake of other nutrients.

Previous research has shown that drug metabolizing enzymes in the liver can vary as a function of carbohydrate intake (4,51). For example, Sonawane and colleagues (51) reported that male rats fed a high-sucrose diet had significantly lower levels of microsomal cytochrome P-450 levels than rats fed a low-sucrose diet. Thus, the rate of metabolism of spiradoline and other opioids could be altered as a function of sucrose intake. If this is the case, the concentration of these drugs, which reach sites of action within the central nervous system, could vary in rats fed sucrose and those not consuming the sugar. At this time, there are no direct data to support or refute this possibility. However, research demonstrating that chronic intake of palatable sucrose solutions increases the analgesic actions of centrally, as well as peripherally administered opioids [(19); Kanarek and Homoleski, unpublished results], suggest that differences in peripheral metabolism of opioids are not a primary factor in mediating the effects of sucrose on opioid-induced analgesia. Further evidence that intake of palatable nutrients directly alter opioid systems within the brain is provided by studies demonstrating that intake of palatable foods and fluids increase 1) beta-endorphin levels in the hypothalamus (17), 2) whole-brain opiate receptor binding affinity in rats and mice (26,40), and 3) proDynorphin mRNA levels in the arcuate nucleus and Dynorphin A_{1-17} levels in the paraventricular nucleus of rats (54).

Spiradoline acted as an anorectic agent in both male and female rats. The drug led to significant dose-related reductions in food intake in both rats consuming sucrose and chow, or chow alone. These findings were somewhat surprising, as earlier studies had found that administration of kappa opioid receptor agonists led to increases in food intake, particularly intake of palatable foods [e.g., (13,14,24)]. Later work, however, has indicated that a number of experimental variables including drug dose, route of drug administration, measurement time, feeding condition, and type of food available influence the actions of kappa receptor agonists on food intake (21, 38,43,46,57). For example, Ramarao and Bhargava (46) found that, although low doses of the kappa agonists, U50,488H (1.0 mg/kg) and bremazocine (0.1 mg/kg) increased food intake in food-deprived rats, higher doses of the drugs (10.0 mg/kg U50,488H; and 1.0 and 10.0 mg/kg bremazocine) decreased food intake. In nondeprived rats, the kappa agonists failed to produce any effects on feeding behavior. Along similar lines, Lee and Clifton (38) reported that a low dose of U50,488H (0.5 mg/kg) enhanced individual meal size in rats; however, neither the low dose nor higher doses increased total food intake across a 12-h period. They also reported that injections of the kappa agonist, PD117302, led to dose-related reductions in food intake. The effects of kappa agonists on food intake are also influenced by whether the drugs are injected during the light or dark portion of the diurnal cycle. In a recent study, it was observed that when U50,488H was administered to rats at the beginning of the light cycle, food intakes were significantly greater after injections of 4 mg/kg, and significantly lower after injections of 8 mg/kg U50,488H than after saline injections. In contrast, when injected at the beginning of the dark cycle, both doses of U50,488H significantly suppressed feeding behavior (Kanarek, unpublished manuscript). Recent work has also shown that while mu and delta agonists lead to increased feeding behavior when injected directly into the brain, kappa agonists do not (43,57). Thus, while the results of some studies have led to the hypothesis that kappa receptors are involved in mediating the rewarding aspects of feeding behavior (13,14,24), the results of other experiments indicate that this hypothesis must be viewed within the context of the experimental situation. No previous data are available on the effects of spiradoline on food intake. It has been proposed that spiradoline acts specifically at the kappa-1 receptor (52). It is possible that drugs that act at kappa-1 receptors suppress feeding behavior, while those that act at other kappa receptor subtypes stimulate food intake. It should be noted, however, that in the present experiment, the low doses of spiradoline increased food intake slightly in rats fed only chow. Additionally, the drug was administered only during the dark portion of the 24-h cycle. Finally, the effects of the drug were only examined on chow intake, rather than on the intake of more palatable items. Thus, while spiradoline clearly had anorectic actions in the present study, more information is required before conclusions can be reached about the effects of the drug on ingestive behavior.

The anorectic effects of spiradoline were more pronounced in rats consuming palatable foods than in those eating only chow. Food intakes of males fed sucrose and chow were significantly suppressed by the two higher doses of spiradoline 2 and 4 h after injections, and by the highest dose, 6 h after injections. In contrast, food intakes of males maintained on chow alone were only reduced by the highest dose of the drug 1 and 2 h after injections. Moreover, spiradoline led to greater proportional reductions in intakes from saline levels in males consuming sucrose than in those not given the sugar. In females, food intake was decreased 2, 4, and 6 h after injections in animals that had consumed sucrose, but only was decreased 1 and 2 h after injections in animals eating chow. The

results of Experiment 2 are in agreement with those of previous studies investigating the effects of prior intake of palatable fluids on feeding behavior in response to the administration of opioid drugs [(28,54,55); Kanarek, unpublished manuscript]. For example, administration of naltrexone led to dose-related reductions in chow intake in rats that had consumed palatable fluids, but had minimal effects on intake in rats that had eaten only chow (28). Similarly, U50,488H had greater effects stimulating chow intake in the light, and suppressing intake in the dark in rats that had been drinking a sucrose solution than in those that had not had access to the sugar (Kanarek, unpublished manuscript). It should be noted that intake of palatable foods and fluids has not been found to influence the anorectic actions of nonopioid drugs. Prior intake of sweetened solutions does not alter the anorectic effects of *d*-fenfluramine (55), fluoxetine, or amphetamine (Kanarek and Homoleski, unpublished results). These results suggest that intake of palatable foods and fluids specifically alters the actions of opioid drugs.

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